Vagus Nerve Stimulation for Treatment-Resistant Depression

Assessment Program
Volume 21, No. 7
August 2006

Executive Summary

Background

Depression is a serious psychiatric condition that sometimes does not respond to standard treatments such as medication and/or psychotherapy. Vagus nerve stimulation (VNS) therapy is administered through an implanted pulse generator and bipolar lead and has been studied in patients with treatment-resistant depression. VNS was previously evaluated by the Technology Evaluation Center (TEC) for this indication in 2005 and did not meet TEC criteria. Since the last TEC Assessment, the same studies evaluated in the prior Assessment have now been published in peer-reviewed journals, and there have been some reanalyses of the same data also published.

Objective

This Assessment will review the available evidence to determine if VNS therapy is effective for treatment-resistant depression. This Assessment updates the prior TEC Assessment of VNS for the same indication.

Search Strategy

A search of the MEDLINE® database was completed for the period up through June 2006. The search strategy used the terms "depression" and "vagus [or "vagal"] nerve stimulator/stimulation" as text words or subject terms. Articles were limited to those published in the English language and enrolling human subjects. The MEDLINE® search was supplemented by an examination of article bibliographies and relevant review articles, which were searched for citations.

Selection Criteria

Articles were case series, randomized trials, or observational studies evaluating clinical outcomes of VNS therapy. In the prior TEC Assessment, results were available only from documents posted to the U.S. Food and Drug Administration (FDA) Web site. At this time, the same studies have now been published in peer-reviewed journals, almost unchanged from the FDA documents. New publications analyze the same data in various ways examining duration of benefit.

Main Results

The relevant clinical evidence evaluating VNS consists of a case series of 60 patients receiving VNS, a short-term (i.e., 3-month) randomized, sham-controlled clinical trial (RCT) of 221 patients, and an observational study comparing 205 of the RCT patients on VNS therapy to 124 patients receiving usual treatment for depression. Patients who responded to sham treatment in the short-term randomized, controlled trial (approximately 10%) were excluded from the long-term observational study.

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Patient selection was a concern for all studies. VNS is intended for treatment-refractory depression, but the entry criteria of failure of 2 drugs and a 6-week trial of therapy may not be a strict enough definition of treatment resistance. Treatment-refractory depression should be defined by thorough psychiatric evaluation and comprehensive management. It has been documented that apparent treatment resistance is common due to inadequate medication or trial durations and that, for clinical trial purposes, treatment resistance should be established prospectively, not historically. Patients with clinically significant suicide risk were excluded from all VNS studies.

The case series data show rates of improvement, as measured by a 50% improvement in depression score of 31% at 10 weeks to greater than 40% at 1 to 2 years, but there are some losses to follow-up. Natural history, placebo effects, and patient and provider expectations make it difficult to infer efficacy from case series data.

The randomized study that compared VNS therapy to a sham control (implanted but inactivated VNS) did not show a statistically significant result for the principal outcome (50% reduction in depression score or Hamilton Rating Scale for Depression) at 3 months. Fifteen percent of VNS subjects responded, versus 10% of control subjects (p=0.25). Two of 3 secondary outcome measures were also nonsignificant.

An observational study comparing patients participating in the randomized clinical trial and a separately recruited control group evaluated VNS therapy out to 1 year. This observational study showed a statistically significant difference in the rate of change of depression score. However, issues such as unmeasured differences between patients and nonconcurrent controls, differences in sites of care between VNS therapy patients and controls, and differences on concomitant therapy changes raise concern about this observational study. Analyses performed on subsets of patients cared for in the same sites, and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness of VNS and almost no statistically significant differences. Given these concerns about the quality of the observational data, these results are insufficient to support the effectiveness of VNS therapy.

Additional reanalyses of these same data to evaluate persistence of response show that among those who achieve a response at 3 or 12 months, 60–75% of such patients are judged to remain a responder at 1 year later. In the context of relatively low overall response rates, these data do not provide evidence of efficacy.

Adverse effects of VNS therapy include voice alteration, headache, neck pain, and cough, which are known from prior experience with VNS therapy for seizures. Regarding specific concerns for depressed patients such as mania, hypomania, suicide, and worsening depression, there does not appear to be a greater risk of these events during VNS therapy.

Author's Conclusions and Comments

Since the last TEC Assessment, there have been no studies reporting clinical outcomes on any new or different patients. Data from the case series and clinical trials have been reanalyzed to show what proportions of patients who respond at one time are still responders at a subsequent time point. However, this information by itself does not provide evidence of the efficacy of VNS beyond that provided by the original observational comparison of VNS versus treatment as usual.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether vagus nerve stimulation (VNS) for the indication of treatment-resistant depression meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. **The technology must have final approval from the appropriate governmental regulatory bodies.**

The NeuroCybernetic Prosthesis System (NCP®, Cyberonics, Inc.) received approval of its Premarket Application (PMA) to market from the U.S. Food and Drug Administration (FDA) on

July 16, 1997, for treatment-refractory seizures. The device was approved for use in conjunction with drugs or surgery "as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures."

On July 15, 2005, the VNS Therapy System received final PMA approval by the FDA for "adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments."

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The clinical trials reviewed above report weak evidence that does not demonstrate efficacy.

3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.

The available evidence does not permit conclusions regarding the effect of VNS therapy on health outcomes or its effect compared with alternative therapies.

5. The improvement must be attainable outside the investigational settings.

Whether VNS therapy for treatment-related depression improves health outcomes has not yet been determined in the investigational setting.

For the above reasons, VNS therapy for the indication of treatment-resistant depression does not meet the TEC criteria.

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Published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group.

Assessment Objective

Depression is a serious psychiatric condition that sometimes does not respond to standard treatments such as medication and/or psychotherapy. Vagus nerve stimulation (VNS) therapy is administered through an implanted pulse generator and bipolar lead and has been studied in patients with treatment-resistant depression. VNS was previously evaluated by the Technology Evaluation Center (TEC) for this indication in 2005 and did not meet TEC criteria. Since the last TEC Assessment, the same studies evaluated in the prior Assessment have now been published in peer-reviewed journals, and there have been some reanalyses of the same data also published.

This Assessment will review the available evidence to determine if VNS therapy is effective for treatment-resistant depression. This Assessment updates the prior TEC Assessment of VNS for the same indication.

Background

Depression

Depression is a very common disorder that is most often chronic or recurrent in nature. In the U.S., the lifetime prevalence of major depressive disorder (MDD) is approximately 16%, and the 12-month period prevalence of MDD is approximately 7% (Kessler et al. 2003). Depression is associated with significant morbidity for the patient, patient's family, and society. Among the consequences of depression are functional impairment, impaired family and social relationships, and increased mortality from suicide and comorbid medical disorders.

Although there are many effective treatments for depression, it has been estimated that 10% to 20% of patients do not respond to treatment (Thase and Rush 1995). Furthermore, many responders do not respond completely. Such partial responders remain at substantial risk for worsening depression. There is little published evidence for any treatment strategy producing effective long-term control of depression in patients who fail to respond to initial antidepressant treatment (Stimpson et al. 2002).

There is no exact definition of treatment-resistant depression, but in general, the term refers to patients who have not responded to adequate trials of several treatment strategies. Souery et al. (1999) point out that a lack of consensus regarding the definition of treatment resistant depression limits comparisons across clinical trials and evaluation of treatment efficacy. Cadieux (1998) outlined 5 strategies for treating partial response or nonresponse to antidepressant therapy: 1) optimizing current therapy by dosage and duration; 2) substitution with different classes of pharmaceutical agents; 3) combining drugs; 4) electroconvulsive therapy; and 5) augmentation with drugs not routinely regarded as antidepressants such as lithium, thyroid hormone, or pindolol.

Vagus Nerve Stimulation

Traditionally the vagus nerve has been considered a parasympathetic efferent nerve controlling functions such as heart rate and gastric tone. However, it is actually a mixed nerve composed of about 80% afferent fibers carrying information to the brain from the head, neck, thorax, and abdomen. These fibers connect to many brain regions implicated in neuropsychiatric disorders (George et al. 2000).

For treatment of various illnesses, vagus nerve stimulation refers to stimulation of the left cervical vagus nerve using a commercial device, the NeuroCybernetic Prosthesis® (NCP®) System, manufactured by Cyberonics. This device has been used for the treatment of resistant seizure disorders in Europe since 1994 and in the U.S. since 1997. According to company documents, VNS devices have been implanted in more than 22,000 patients.

In addition to anatomic considerations that suggest that VNS therapy might have antidepressant effects, other types of evidence led to experimentation with this treatment for depression (George et al. 2000). Several studies have noted mood improvements in patients who had VNS devices implanted for seizure disorder. Elger et al. (2000) conducted a small study evaluating mood changes in patients receiving VNS for seizure disorder, showing improvements in mood score after VNS implantation. Imaging studies of patients who received VNS therapy showed changes in blood flow in several areas of the brain implicated in depression. Also, anticonvulsant medications have antidepressant effects and electroconvulsive therapy (ECT), a potent treatment for depression, is known to have anticonvulsant effects.

VNS Implantation Procedure and Treatment
Surgery for implantation of the device is done under either general anesthesia or regional cervical block. Since right vagus nerve stimulation produces bradycardia, implantation is limited to left-sided unilateral implantations. The carotid sheath is opened and 2 spiral electrodes are wrapped around the vagus and connected to an infraclavicular generator pack. In experienced hands, the entire procedure requires less than 2 hours. The programmable stimulator may be programmed in advance to stimulate at regular times or upon demand by patients or family by placing a magnet against the subclavicular implant site. Stimulator settings are programmed to deliver intermittent stimulation with current of 0.25–3.0 mA, frequency of 20–50 Hz, and pulse width of 500 nanoseconds for 30–90 seconds every 5–10 minutes.

Adverse effects, such as injuries to the vagus nerve, are rare. Hoarseness, throat pain, and cough are common during stimulation, but are not life threatening (Fisher et al. 1997). Infection necessitating removal of the device was reported in 1% of investigational device exemption (IDE) clinical trials for the epilepsy indication and has been reported in 1% of commercial implants (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a). The most common nerve injuries are left vocal cord paralysis or left facial paralysis. The rate of nerve injuries reported in IDE clinical trials was 1% and 0.5% in clinical use.

The physician's manual for the device cites the following potential risks:

- the potential for human tissue damage if diathermy or full body magnetic resonance imaging is performed in a patient implanted with the VNS Therapy System
- the potential for degenerative nerve damage to the vagus nerve if it is stimulated excessively (i.e., if stimulation on time exceeds off time)
- aspiration related to stimulation-induced impairment of swallowing, especially in the presence of predisposing factors
- painful stimulation if the device malfunctions
- increased apneic events in patients with obstructive sleep apnea
- dyspnea, especially in the presence of obstructive airway disease
- transient bradycardia or asystole, especially during initial intraoperative lead testing
- surgical risks associated with the implant procedure, principally infection, vocal cord dysfunction due to manipulation of the vagus nerve, and other nerve damage
- a variety of nonserious side effects associated with stimulation, most commonly neck pain, dyspepsia, dysphagia, vomiting, paresthesia, increased cough, dyspnea, laryngismus, and voice alteration.

FDA Status. The NeuroCybernetic Prosthesis System (NCP®, Cyberonics, Inc.), a vagus nerve stimulation device, received approval of its Premarket Application (PMA) to market from the U.S. Food and Drug Administration (FDA) on July 16, 1997, for treatment-refractory seizures. The device was approved for use in conjunction with drugs or surgery "as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures." At that time, the FDA asked the company to provide detailed information about any deaths, especially unexpected, sudden deaths, in patients with the device; FDA also requested that the company further evaluate its study data to find out whether any factors predict which patients are most likely and/or least likely to benefit from use of the device (U.S. Food and Drug Administration 1997).

On July 15, 2005, the VNS Therapy System received final PMA approval by the FDA for "adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments" (U.S. Food and Drug Administration Center for Devices and Radiological Health 2005).

In addition to other postapproval requirements, the FDA is requiring two specific postapproval studies "to further characterize the optimal stimulation dosing and patient selection criteria" (U.S. Food and Drug Administration Center for Devices and Radiological Health 2005). The first study is a "prospective, multicenter, randomized, double-blind comparison of different output currents in 450 new subjects with [treatment-resistant depression]." Effectiveness responses to differing output currents will be assessed 16 weeks after a 4- to 6-week titration period, during which, concomitant therapies will not be changed. Study participants

will be followed up for at least 1 year after implantation to "further characterize duration of response as well as safety parameters at … higher doses." The second study is a "prospective, observation registry study of 1000 implanted subjects with [treatment-resistant depression] with follow-up extending to 5 years after implantation." Postapproval study results and progress reports will be filed every 6 months. The FDA Center for Devices and Radiological Health may request panel review of the postapproval data and, as necessary, will incorporate the results into supplemental labeling (U.S. Food and Drug Administration Center for Devices and Radiological Health 2005).

Outcome Assessment in Depression

There are several reasons to measure depressive symptoms in clinical practice or research. Most important for the purposes of this Assessment is to assess treatment outcome. In the research evaluating VNS therapy, the 4 most common instruments used are shown in Table 1. Except for the Clinical Global Impression (CGI) scale, the other instruments all involve answering specific inquires regarding patient symptoms such as mood, affect, energy, appetite, sleep, and suicidal or paranoid ideation. Scale scores have been calibrated with clinical evaluation to correlate to severity levels of depression and changes in scores consistent with good treatment response or remission of depression. A typical threshold for categorizing clinically significant improvement is a 50% reduction from baseline score for any of the scales. The other method for categorizing treatment response is for the final value of the test to be below a particular value, indicating very few depressive symptoms. Studies have shown reasonable concordance between the Inventory of Depressive Symptomatology (IDS) and the Hamilton Rating Scale for Depression (HRSD) in categorizing patients as treatment responders (Rush et al. 2003).

Except for the self-administered version of the Inventory of Depressive Symptomatology (IDS-SR), the depression rating scales discussed here are designed to be administered by a health care clinician. The CGI scale is the most inherently subjective scale, as it is simply a categorical 7-point scale asking whether, in the judgment of the clinician, the patient is very much improved (CGI=1) to very much worse (CGI=7). The CGI also requires an in-depth knowledge of the patient over the course of the treatment period.

Methods

Search Methods

A search of the MEDLINE® database (via PubMed) was completed for the period up through June 2006. The search strategy used the terms "depression" and "vagus [or "vagal"] nerve stimulator/stimulation" as text words or subject terms. Articles were limited to those published in English language and enrolling human subjects. The MEDLINE® search was supplemented by an examination of article bibliographies and relevant review articles, which were searched for citations.

In addition, documents were sought from the FDA Web site using the terms "Cyberonics," "vagus nerve" or "vagal nerve." Extracts of documents were reviewed if they

Table 1. Depression Rating Scales Used in Evaluating VNS

Scale	Brief Description	Common Thresholds or Cutoffs for Treatment Response
Hamilton Rating Scale For Depression (HRSD)	Observer-rated scoring of 28, 24, 21, or 17 two- to four-point items	50% reduction from baseline final rating of ≤9
Clinical Global Impression (CGI)	Observer-rated 7-point scale 1) Severity of Illness (CGI-S) 2) Global Improvement (CGI-I)	Global Improvement=1 or 2
Montgomery and Asberg Depression Rating Scale (MADRS)	Observer-rated scoring of 10 six-point items	50% reduction from baseline
Inventory of Depressive Symptomatology (IDS)	Observer-rated (IDS-C) or self-rated (IDS-SR) 30 three-point items	50% reduction from baseline

concerned VNS therapy for the indication of depression. Finally, materials received from the manufacturer were also reviewed for relevance. Table A in the Appendix reviews excluded materials with reasons for exclusion.

Study Selection

All the published and unpublished data concerning clinical outcomes of VNS therapy for the indication of treatment-resistant depression come from company-sponsored clinical studies. This Assessment attempts to summarize the major findings from all of these studies. Different analyses are reported in various publications. Using the study names that the company used in their documents for FDA review (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a), the study groups assembled for the clinical studies will first be described, followed by a description of the analyses in each of the available publications (Table 2).

Study D-01 was an open-label study of VNS therapy in 60 subjects. Short-term (i.e., 3-month) results for the first 30 patients and the whole group were published in peer-review journals, as were as 1-year outcomes in the first 30 patients. Long-term results of the whole group are published in the Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a).

Study D-02 was a randomized sham-controlled study of 233 subjects allocated to either active VNS therapy or sham (i.e., VNS implanted but not turned on). This study was planned to evaluate outcomes at 3 months, and results are available in the Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a) and a peer-reviewed publication by Rush et al. (2005).

Study D-04 is an observational study of subjects not receiving VNS. This study was created to form a comparison group to a long-term extension of Study D-02, in which study subjects in both active and sham groups were followed up for 1 year. The subjects in the original sham group had their VNS device activated. The results of the D-02 long-term extension group versus the observational control D-04 study group comprise the most extensive

Table 2. Study Groups and Source of Results of VNS Studies

Study Group	Description	Outcomes Analyzed	Publication of Results
D-01	Open-label study of 60 subjects receiving VNS	10-week outcomes of first 30 patients	Rush et al. 2000
		10-week outcomes of 60 patients	Sackeim et al. 2001
		1-year outcomes of first 30 patients	Marangell et al. 2002
		1- and 2-year outcomes of available subset of 60 patients	U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a
D-02	Randomized sham-controlled trial of 233 subjects, VNS vs. sham	3-month outcomes of randomized sham vs. VNS groups VNS and sham groups combined and compared to D-04 study group	Rush et al. 2005
D-04	Observational group of 124 patients NOT receiving VNS	1-year outcomes of D-02 extension study versus D-04 control group	George et al. 2005
ECT control group	Matched subset of 172 from previously published observational study of ECT	1-year outcomes of D-02 extension study versus 6-month outcomes of ECT control group	U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a

analysis presented in the Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a). Results were also published in a peer-reviewed publication by George et al. (2005).

Additional analyses reporting on the duration of treatment effect reported from these same study groups have been reported in studies by George et al. (2005), Rush et al. (2005), and an unpublished draft by Sackeim et al.

Finally, a matched control group receiving ECT was recreated from a previously published observational study by Prudic et al. (2004). Six-month results from this subgroup were compared to the D-02 extension study.

Medical Advisory Panel Review

Current Assessment. This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on June 22, 2006. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Previous Assessment. A previous Assessment of vagus nerve stimulation for depression was reviewed by the MAP in June 2005. The MAP determined that vagus nerve stimulation for patients with treatment-resistant depression did not meet the TEC criteria.

An earlier Assessment of vagus nerve stimulation for treatment-refractory seizures was reviewed by the MAP in February 1998. The MAP determined that vagus nerve stimulation for patients 12 years of age and older with medically refractory partial-onset seizures, for which surgery is not recommended or for which surgery has failed, met the TEC criteria. Vagus nerve stimulation for patients with other types of seizure disorders, which are medically refractory and for which surgery is not recommended or for which surgery has failed, did not meet the TEC criteria.

Formulation of the Assessment

Patient Indications

VNS is indicated for patients with treatment-resistant depression. According to the study protocols for the D-01 and D-02 studies, patients enrolling in these studies had the following characteristics:

- current major depression
- chronicity as defined by ≥2-year duration for the current episode or ≥4 lifetime episodes
- prior failure to respond to at least 2 adequate antidepressant treatments from 2 different drug classes
- prior failure of at least 6 weeks of psychotherapy
- minimum level of depression of 20 or greater on the HRSD-24.

Prior treatment history was evaluated using the modified Antidepressant Treatment History Form. Prior treatments were evaluated for both dose and duration, and were required to meet a threshold score in order to be judged as adequate.

Exclusion criteria included patients with certain other co-existing mental disorders, patients with clinically significant current suicidal intent, and patients with certain risks associated with surgical implantation or VNS stimulation.

Technologies to be Compared

VNS treatment will be compared to continued medical management.

Health Outcomes

Potential Benefits. The primary outcome to be evaluated is relief of depression symptoms. This can usually be assessed by any one of many different depression symptom rating scales. A 50% reduction from baseline score is considered to be a reasonable measure of treatment response. An improvement in depression symptoms may allow reduction of pharmacologic therapy for depression, with a reduction in adverse effects related to that form of treatment.

Potential Harms. Harmful outcomes of VNS would include any morbidity associated with the implantation of the device or adverse effects of the VNS therapy itself. Concern has been raised whether antidepressant treatments may worsen depression or even lead to suicide attempts. This is a controversial issue, not

proven or established for any antidepressant therapy. The Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a) discusses the evidence for worsening depression and suicide in patients treated with VNS.

Specific Assessment Questions

1. What is the effect of VNS therapy on treatment-resistant depression?
2. What are the adverse effects of VNS therapy?

Review of Evidence

Overview

Evidence for the effectiveness of VNS therapy comes from the studies described in the "study selection" section described previously (Table 2). Entry criteria and selected baseline characteristics of the subjects are shown in Table 3.

D-01 Case Series

Results from the D-01 case series as extracted from several sources at different time points are presented in Table 4. After 10 weeks of active VNS therapy, 30.5% of subjects had a 50% reduction in the principal outcome of the HRSD-28. Other measures of improvement ranged from 15% to 37.3%. In reports reporting outcomes at later time points, outcomes appear to continue to improve out to 1 year, where 45% of patients now had a 50% improvement in HRSD-28. This appears to stabilize out to 2 years, but there are substantial losses to follow-up at this time (n=42 at 2 years versus original sample of 59). The last value carried forward technique of analysis was used to report results at 2 years. Outcome rates are not reported for the 42 patients that were assessed at 2 years, so it is difficult to know whether the losses to follow-up affect the results reported.

It is also difficult to make inferences of effectiveness from case series data like these because natural history, placebo effects, patient, and investigator expectations may explain some or all of the effects noted.

D-02 Randomized Trial

The randomized trial was a placebo-sham randomized trial designed to evaluate patients at 12 weeks after VNS implantation (Rush et al. 2005). The sham group received a real VNS device, which was to be turned on after this acute phase of the study. The sham group apparently received follow-up visits where therapy was "adjusted," and investigators were blinded to treatment assignment. However, VNS

Table 3. Patient Characteristics of Studies of VNS

Study	Entry Criteria	Selected Entry Characteristics (mean)		Study Restrictions on Concomitant Therapies
D-01	Major depressive disorder Duration >2 yr or >4 episodes lifetime Not responsive ≥2 medication classes Not responsive to 6 wks psychotherapy Baseline HDRS-28 ≥20	Age Female HRSD-28 Episode duration Age onset illness	46.8 65% 36.8 9.9 yr 28.7	3-month outcomes—no changes or dose increases after 3 months—any change allowed
D-02 randomized trial	Major depressive disorder Duration >2 yr or >4 episodes lifetime Not responsive ≥2 medication classes Not responsive to 6 wks psychotherapy Baseline HDRS-24 ≥20	Age Female HRSD-24 Episode duration Age onset illness	46.5 63% 29.2 4.1 yr 22.0	No changes or dose increases
D-02 extension of trial	Same as D-02 randomized trial, plus: HDRS-24 ≥18 after 3 months sham (sham nonresponders)	HRSD-24 IDS-SR Prior ECT Prior Rx failures	27.9 42.4 53% 3.5	Any change allowed
D-04 observational comparison arm	Same as D-02 randomized trial, except: no requirement for prior failed psychotherapy	HRSD-24 IDS-SR Prior ECT Prior Rx failures	27.8 43.8 26% 3.5	Any change allowed

therapy is detectable by many patients, and adequacy of blinding is not reported. Results are shown in Table 5. The principal outcome for the trial was a 50% improvement in the HRSD-24. There were 15% of patients in the VNS group that showed a 50% improvement in HRSD-24, whereas 10% of the patients in the sham control group showed 50% improvement (p=0.25). The IDS-SR was considered a secondary outcome, and showed a difference in outcome that was statistically significant in favor of VNS (17% versus 7.3%, p=0.03). All other outcomes assessed in the trial did not show statistically significant differences between groups.

The randomized trial failed to achieve statistical significance for its predetermined primary outcome. The sponsor believes that the trial was not of sufficient duration to demonstrate full efficacy, as the single-arm studies have shown further improvement in symptoms beyond 12 weeks. Other potential explanations are that the trial was not sufficiently powered to find a smaller amount of benefit, or that VNS therapy is not effective.

D-04 versus D-02 Observational Study

This study, first reported in the Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a) and then in published form by George et al. (2005), compares the outcomes of patients from the D-02 study who continued into a long-term follow-up study, compared to a control group (referred to as D-04 in FDA documents, TAU ["treatment as usual"] in George et al. 2005) that did not receive VNS. The control group was to receive quarterly assessments of depression state, but otherwise was to receive treatment as usual. However, comparison to treatment as usual is a weaker approach than comparison to optimal treatment; it is documented that apparent treat-

Table 4. Results of D-01 Case Series Study

Study	n	Follow-up Time	Outcome	Result
Sackheim et al. 2001	59	10 weeks	50% improvement HRSD-28	30.5%
			final HRSD-28≤10	15%
			50% improvement MADRS	34.0%
			final CGI-I=1 or 2	37.3%
Marangell et al. 2002 (subset of Sackheim 2001)	28	1 year	50% improvement HRSD-28	46%
			final HRSD-28≤10	29%
			50% improvement MADRS	50%
			final CGI-I=1 or 2	57%
Nahas et al. 2005	59	1 year	50% improvement HRSD-28	44%
			final HRSD-28≤10	27%
	59	2 years	50% improvement HRSD-28	42%
			final HRSD-28≤10	22%

Patients in published study of Rush et al. (2000) included in Sackheim et al. (2001)

Table 5. Results of Randomized Clinical Trial, Study D-02 (Rush et al. 2005), at 3 Months

Outcome	VNS (n=112)	Control (n=110)	p-value
50% improvement HRSD-24	15.2%	10.0%	0.25
50% improvement MADRS	15.2%	11.0%	0.378
Final CGI-I value 1 or 2 (much improved)	13.9%	11.8%	0.648
50% improvement IDS-SR	17.0%	7.3%	0.04
HRSD-24 % mean improvement	16.3	15.3	0.639
MADRS % mean improvement	17.1	12.4	0.208
IDS-SR % mean improvement	21.2	16.3	0.158

ment resistance is common due to inadequate medications or trial durations and that, for clinical trial purposes, treatment resistance should be demonstrated prospectively, not historically (Fava et al. 2003). Several other aspects of this study are also worth noting before presenting the results.

First, according to the summary minutes of the FDA panel reviewing VNS therapy (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004c), this observational study was conceived only after results of the randomized clinical trial were known. Second, several aspects of the design and analysis required additional analyses requested by the FDA. Most of the recruitment of control patients occurred after all the VNS patients had been recruited. Many control patients were recruited from sites that did not enroll VNS patients, and some VNS patients were recruited from sites that did not enroll control patients. Both patients in VNS and control groups were allowed concomitant changes in both type of and dose of antidepressant medications. This raises concern that some of the durable effects attributed to VNS may actually be due to changes in antidepressant therapy. George et al. (2005) states that the statistical analysis plan was developed before completion of the study. The disclosures accompanying the report state that Quintiles, Inc. monitored the study for the VNS patients, and Cyberonics monitored the control group.

Finally, the principal outcome assessed was different than in other prior studies of VNS. In this study, they proposed a repeated-measure analysis of IDS-SR scores, which produces a measure of effect comparing the rate of improvement over time between the two treatments, rather than comparing the proportion of subjects achieving response. Apparently, HRSD scores were only assessed at baseline and at 12 months, precluding a repeated measures analysis of this outcome measure. In order to account for differences between the groups at baseline, a propensity score analytic technique was used to attempt to balance baseline characteristics.

Note in Table 6, the numbers of patients as analyzed in various analyses. Out of 233 subjects in the original D-02 study group and 138 in the original D-04 control group, considerably fewer are reported in various analyses. Most of the patients from the D-02 randomized study who were then excluded from the observational comparison to the D-04 control group did not meet eligibility requirements for continuing in the observational study because they improved during sham therapy. Other numbers vary because some patients did not have baseline or follow-up data for a particular depression scale.

Table 7 shows the overall results of the nonrandomized study. The results abstracted here are identical in the Cyberonics Executive Summary and in the peer-reviewed publication by George et al. (2005). Analyses are presented for 2 subject populations, an evaluable population, in which no missing values are imputed, and a "last observation carried forward population," (LOCF) in which missing values are imputed from the last available value. The latter are often considered less biased in the context of a randomized clinical trial, because all participants are retained in the trial, preserving the balance between groups. Subjects who remain in a trial may be the most adherent and compliant patients, and may no longer be truly representative of the original patient population.

The rate of change in IDS-SR score over 12 months between groups was statistically significant at $p<0.001$. This result represents both the rate of change and the p-value with the propensity score incorporated into the analysis. For other outcomes, results were all statistically significant for the evaluable population. In the LOCF analysis, most outcomes were statistically significant, but in general VNS was a few percentage points less effective for most outcome measures. Citing the result that is most comparable to the other studies of VNS, 27% of VNS patients achieved a 50% improvement in HRSD versus 13% of control patients (LOCF analysis, $p=0.011$). Note that this response rate is higher than that observed for VNS patients at 3 months as reported in the randomized clinical trial, leading the authors to believe that the response to VNS therapy may be often delayed.

Additional analyses were presented in the peer-reviewed published report to support an argument that confounding factors such as site differences and medication changes were not responsible for the differences observed between VNS and control groups. In an analysis comparing only patients enrolled from 12 sites where both VNS and control patients were recruited, the primary outcome of change in IDS-SR score remained statistically significant. The response rate as measured by a 50%

Table 6. Patient Flow Chart of D-02 Study Group and D-02 versus D-04 Study Group

	D-02 Study Group	D-04 Control Group
Original n	**233**	**138**
	n analyzed for specific scale outcome	
Analyzed for RCT	221 HRSD 215 IDS-SR	Not applicable
Met criteria for nonrandomized study	205	124
Analyzed in last value carried forward observational study	205 HRSD 204 IDS-SR	104 HRSD 124 IDS-SR
Analyzed in completers observational study	180	104 HRSD 112 IDS-SR

Table 7. Results of Nonrandomized Study, D-02 VNS Patients versus D-04 Control Patients, Complete Study Population

Outcome	VNS	Control	p-value
Evaluable Population	**n=180**	**n=112**	
Average change in IDS-SR over 12 months*	–9.8	–4.6	<0.001
50% improvement IDS-SR	22%	12%	0.029
Final IDS-SR≤14	15%	4%	0.006
Average change in HRSD-24 over 12 months*	–8.2	–4.9	0.006
50% improvement HRSD-24	30%	13%	0.003
Final HRSD-24≤9	17%	7%	0.031
CGI-I=1 or 2	37%	12%	<0.001
Last Value Carried Forward Population	**n=205**	**n=124**	
Average change in IDS-SR over 12 months*	–9.3	–5.0	<0.001
50% improvement IDS-SR	20%	12%	0.108
Final IDS-SR≤14	13%	3%	0.007
Average change in HRSD-24 over 12 months*	–7.4	–4.9	0.04
50% improvement HRSD-24	27%	13%	0.011
Final HRSD-24≤9	16%	7%	0.059
CGI-I=1 or 2	34%	12%	<0.001

*analysis adjusts for propensity score, p-value represents repeated-measure analysis

improvement in HRSD-24 was 25% for the VNS group and 11% for the control group (p=0.033).

Overall, VNS patients had fewer dosage increases or additional medications (71%) than the control group (81%). Patients who were considered responders to VNS at 12 months as judged by HRSD-24 scores had fewer increases or additional medications (56%) than nonresponders (77%). The authors propose that the fact of fewer patients receiving dose increases or additional medications in the VNS group that had higher response rates indicates that additional treatments were not responsible for the difference between the VNS and control groups.

FDA Response. The FDA had an opportunity to review these results at an earlier stage of analysis, and requested some additional analyses from the sponsor (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004b). Because VNS and control patients were recruited from different sites and concomitant therapy changes were allowed, the FDA requested an analysis using only patients from sites where both VNS and control patients were recruited, and to censor VNS patients at the time when concomitant therapies were changed. The Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a) includes responses to these requests, but detailed presentation of these additional analyses is not included in the document.

The FDA Statistical Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004b) presents these additional analyses in detail, which appear to be slightly different from statements given in the Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a). The Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a) states, "… the repeated measures linear regression analysis of IDS-SR scores was still marginally statistically significant (p=0.052)." The FDA findings of this same analysis, as best as can be determined, are shown in Table 8. Note that the sample size is reduced due to excluding patients from certain sites. There is now only one statistically significant finding (average change IDS-SR, evaluable population), and the magnitudes of the difference as well as the p-values for all the other analyses have changed considerably.

Table 8. Results of Nonrandomized study, D-02 VNS Patients versus D-04 Control Patients, Only from Sites Where Both VNS and Control Patients Recruited, Censoring VNS Patients with Medication Changes

Outcome	VNS	Control	p-value
Evaluable Population	**n=131**	**n=108**	
Average change in IDS-SR over 12 months*	–6.7	–4.2	0.026
50% improvement IDS-SR	16.8%	11.1%	0.26
Final IDS-SR≤14	8.4%	2.8%	0.095
Average change in HRSD-24 over 12 months*	–4.9	–4.7	0.581
50% improvement HRSD-24	18.5%	11%	0.14
Final HRSD-24≤9	7.7%	5.0%	0.59
Last Value Carried Forward Population	**n=147**	**n=120**	
Average change in IDS-SR over 12 months*	–6.1	–4.6	0.16
50% improvement IDS-SR	15.0%	11.7%	0.47
Final IDS-SR≤14	7.5%	2.5%	0.097
Average change in HRSD-24 over 12 months*	–4.3	–4.7	0.91
50% improvement HRSD-24	16.3%	11.0%	0.27
Final HRSD-24≤9	6.8%	5.0%	0.79

*analysis adjusts for propensity score, p-value represents repeated-measure analysis

Citing the result most comparable to other studies of VNS, the proportion of patients who achieved a 50% improvement in HRSD score was 16.8% for the VNS group versus 11.1% for the control group (p=0.26).

The other concerns of the FDA statistical review, briefly noted are:

1. Unmeasured differences between VNS in control groups, as in any observational study.
2. Uncertain clinical significance of principal outcome of difference in average change in IDS-SR, lack of prespecified clinically detectable difference, lack of power calculation
3. Lack of statistical adjustment for categorical outcomes such as percent with 50% improvement.
4. Poor correlation between IDS-SR and HRSD scores within patients.

In sum, although the overall observational analysis shows statistically significant results in most of the outcomes, observational studies suffer from potential confounding by unmeasured patient and provider characteristics and external influences such as other treatments. In analyses focusing on reducing the influence of provider characteristics and concomitant antidepressant treatment, treatment effects were markedly reduced and most outcomes were no longer statistically significant.

New Analyses of D-01 and D-02 Groups Addressing "Durability" of Benefit

Additional analyses reporting duration of treatment response in various subgroups of the D-01 and D-02 groups have been reported in an unpublished draft by Sackeim et al. Different subgroups of patients who were responders at various points in time were followed for persistence of response. Response in this study was defined as a 50% reduction in HRSD scores, and maintenance of response at later time points was defined as a 40% reduction from baseline in HRSD score. Thus a slight worsening of HRSD score was not considered a loss of response. The principal results are shown in Table 9. The results show that of those who responded at 3 or 12 months, between 61% and 79% maintained response at a later time point.

It is not clear how data on the maintenance of response provides evidence of effectiveness apart from evidence provided by rigorous comparative trials. The authors state "…in the absence of a long-term, sham-controlled, masked trial, one cannot conclude that the acute or sustained effects observed in the pilot or pivotal studies were attributable to VNS. The three major alternatives are that the therapeutic benefits reflected placebo effects, the action of altered medication regimens, or the natural history of the illness."

An analogous but slightly different analysis with different cut-points using the IDS-SR was reported by George et al. (2005) in which similar rates of persistence of response at 12 months for 3-month responders were calculated for both VNS patients (D-02 study) and control patients (D-04 study). Of 29 VNS patients who were considered responders, 55%

Table 9. Status of Response at 12 and 24 Months of Study Group Participants Who Responded at 3 or 12 Months

Subgroup of VNS Recipients	n	12-month Maintenance of Response	24-month Maintenance of Response
Sackeim, unpublished draft			
D-01 responders at 3 months	18	72.2%	61.1%
D-01 responders at 12 months	14	–	78.8%
D-02 responders at 3 months	30	63.3%	76.7%
D-02 responders at 12 months	40	–	65.0%
George et al. 2005*			
D-02 responders at 3 months	29	55%	
D-04 (control) responders at 3 months	7	14%	

* D-02 patients the same in Sackeim unpublished draft and George et al. (2005), but criteria for response and maintenance of response are different

were also responders at 12 months. Of 7 control patients who were considered responders, only 1 was still a responder at 12 months.

ECT Observational Group versus D-02 Observational Study

The sponsor commissioned an analysis from a previously published study of ECT by Prudic et al. (2004). A subset of patients that would have qualified for the VNS trials was assembled. The VNS patients had several characteristics associated with a greater severity of treatment-resistant depression. Fifty-eight percent of patients receiving ECT achieved at least a 50% reduction in HRSD score. At 6 months following ECT, 41% of patients still had at least a 50% reduction in HRSD score. Comparing this informally to the results of the VNS patients in the D-02 versus D-04 observational study, ECT appears to be a much more effective treatment for depression. This analysis is not presented in a rigorous manner in the Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a), and does not provide rigorously presented evidence of the efficacy of VNS therapy.

Adverse Effects of VNS Therapy

Common adverse effects that occurred in greater than 10% of patients at 3 months and at 12 months from the D-01 case series are shown in Table 10, as abstracted from Sackeim et al. (2001) and Marangell et al. (2002).

Also shown in the table are rates of the same adverse effects that were reported in the D-02 randomized clinical trial (Rush et al. 2005). Of these relatively frequent short-term adverse effects, most were found to be higher in the D-02 randomized clinical trial in the VNS group than in the sham control group, indicating that they are attributable to VNS therapy. All of these events have been noted previously in the experience of VNS therapy for seizures. Voice alteration is reported by over half the subjects at 3 months, and remains at 12 months in a significant minority.

Of specific concern regarding treatments for depression is the precipitation of manic or hypomanic episodes and suicidal ideation and behavior. For the combined D-01 and D-02 groups, there was a 5% rate of mania or hypomania. Among subjects with a diagnosis of bipolar disorder, the rate of mania or hypomania was 22% (9/41) (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a). During the randomized trial, there were 2 events of mania or hypomania reported, both in the VNS group, but one event occurred prior to initiation of the therapy. It is not possible to conclude whether this represents an increased or decreased rate of events.

For all VNS therapy studies combined, the suicide rate was 0.4% per patient-year (3 events/689 patient-years) and the suicide

Table 10. Percent of Patients from D-01 Case Series and the D-02 Randomized Trial Reporting Adverse Events

	D-01 Case Series		D-02 Randomized Clinical Trial at 3 months	
Adverse Event	% at 3 months (n=60)	% at 12 months (n=30)	VNS (n=119)	Sham (n=116)
Voice alteration	55	21	68	38
Incision site pain	30 (post-op only)	–		
Headache	22	3		
Neck pain	17	7	21	10
Coughing	17	0	29	9
Dyspnea	15	7	23	14
Dysphagia	13	3	21	11
Pain	13	0		
Pharyngitis	13	0		
Dyspepsia	10	–	10	5

attempt rate was 3.5% per patient-year (24 events/689 patient-years). These do not appear to be elevated compared to historical controls cited in the Cyberonics Executive Summary (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004a).

An additional concern is whether VNS may worsen depression in certain patients. Using hospitalizations as a surrogate measure for worsening depression, VNS subjects in the D-02 study had a hospitalization rate of 0.293 per patient-year, and control subjects from the D-04 study had a hospitalization rate of 0.237 per patient-year. Among subjects who reported low levels of depressed mood on the HRSD (0 or 1) at baseline, rates of worsening (to a score of 3 or 4) were reported in approximately equal proportions in the 2 groups (24% for VNS patients, 25% for the control group).

In sum, the adverse effects of VNS therapy as used in depression reflect the known adverse effects of the device as used for seizure disorders. Regarding specific adverse effects of concern for use in depression, such events as mania, hypomania, suicide, suicide attempts, and worsening depression do occur, but it cannot be determined if the rate of such events is higher than for other treatments. Rates seem to be similar to the D-04 control group, but numbers of events are small.

Summary

The selected evidence of efficacy consists of a case series of 60 patients receiving VNS, a short-term (i.e., 3-month) randomized, sham-controlled clinical trial of 221 patients, and an observational study comparing 205 patients on VNS therapy compared to 124 patients receiving ongoing treatment for depression.

The case series data show rates of improvement, as measured by a 50% improvement in depression score, of 31% at 10 weeks to greater than 40% at 1 to 2 years. Natural history, placebo effects, and patient and provider expectations make it difficult to infer efficacy from case series data.

The randomized study that compared VNS therapy to a sham control (implanted but inactivated VNS) showed a non-statistically significant result for the principal outcome at 3 months. Fifteen percent of VNS subjects responded, versus 10% of control subjects (p=0.25).

The observational study comparing patients participating in the randomized clinical trial and a separately recruited control group evaluated VNS therapy out to 1 year. This observational study showed a statistically significant difference in the rate of change of depression score. However, issues such as unmeasured differences between patients and non-concurrent controls, differences in sites of care between VNS therapy patients and controls, and differences on concomitant therapy changes, raise concern about this observational study. Analyses performed on subsets of patients cared for in the same sites, and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness of VNS and almost no statistically significant results. Given these concerns about the quality of the observational data, these results are insufficient to support the effectiveness of VNS therapy.

Additional reanalyses of these same data to evaluate persistence of response show that among those who achieve a response at 3 or 12 months, 60–75% of such patients are judged to remain a responder at 1 year later. In the context of relatively low overall response rates, these data do not provide additional evidence of efficacy.

Adverse effects of VNS therapy include voice alteration, headache, neck pain, and cough, which are known from prior experience with VNS therapy for seizures. Regarding specific concerns for depressed patients such as mania, hypomania, suicide, and worsening depression, there does not appear to be a greater risk of these events during VNS therapy.

Discussion

Overall, the evidence supporting efficacy of VNS is not strong. The single randomized clinical trial did not show statistically significant results in favor of VNS for the primary outcome. Treatment response in the randomized clinical trial was much lower than had been observed in case series studies, raising concerns about placebo effects and observer bias. The nonrandomized observational study had numerous methodological problems. Alternative analyses showed diminished or no efficacy of VNS therapy. Although the FDA voted to approve VNS therapy, a poll of committee members showed that approval was based on the safety of VNS therapy rather than

strong evidence of efficacy (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004d).

Patient selection was a concern for all studies. VNS is intended for treatment-refractory depression, but the entry criteria of failure of 2 drugs from 2 drug classes and a 6-week trial of therapy may not be a strict enough definition of treatment resistance. Treatment-refractory depression should be defined by thorough psychiatric evaluation and comprehensive management before an invasive surgical procedure of limited efficacy is performed. Patients with clinically significant suicidal intent have been excluded from trials of VNS, so its effectiveness in these patients is unknown.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether vagus nerve stimulation (VNS) for the indication of treatment-resistant depression meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. **The technology must have final approval from the appropriate governmental regulatory bodies.**

The NeuroCybernetic Prosthesis System (NCP®, Cyberonics, Inc.) received approval of its Premarket Application (PMA) to market from the U.S. Food and Drug Administration (FDA) on July 16, 1997, for treatment-refractory seizures. The device was approved for use in conjunction with drugs or surgery "as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures."

On July 15, 2005, the VNS Therapy System received final PMA approval by the FDA for "adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments."

2. **The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

The clinical trials reviewed above report weak evidence that does not demonstrate efficacy.

3. **The technology must improve the net health outcome; and**
4. **The technology must be as beneficial as any established alternatives.**

The available evidence does not permit conclusions regarding the effect of VNS therapy on health outcomes or its effect compared with alternative therapies.

5. **The improvement must be attainable outside the investigational settings.**

Whether VNS therapy for treatment-related depression improves health outcomes has not yet been determined in the investigational setting.

For the above reasons, VNS therapy for the indication of treatment-resistant depression does not meet the TEC criteria.

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Appendix

Table A. Materials Received from Cyberonics with Reasons for Exclusion from TEC Assessment

Document	Comment
Meeting Abstracts on VNS	
Suicidality in Treatment-Resistant Depression: Results from a 24-month trial of Vagus Nerve Stimulation (Burke and Moreno, meeting poster)	Original VNS subjects in D-02 study, suicidal ideation followed over time, case series only
Durability of Antidepressant Response to Vagus Nerve Stimulation (Brannan et al. meeting poster)	Similar data and same patients as reported in other studies in TEC review of evidence
Subacute and Chronic Brain Metabolic Change with Vagus Nerve Stimulation in Depression (Conway et al. *Psychiatry Res*, 2006)	PET scan study with no clinical outcomes
Concomitant Use of Vagus Nerve Stimulation and Electroconvulsive Therapy for Treatment-Resistant Depression (Burke and Husain, meeting poster)	Addresses efficacy of ECT in patients who already have VNS implanted
Cerebral Blood Flow Changes During Vagus Nerve Stimulation for Depression (Conway et al. *Psychiatry Res*, 2006)	PET scan study with no clinical outcomes
Prospective, Long-Term, Multicenter Study of the Naturalistic Outcomes of Patients with Treatment-Resistant Depression (Dunner et al. *J Clin Psychiatry*, 2006)	Evaluation of the D-04 control group only out to 2 years
Long-Term Antidepressant Effects of Vagus Nerve Stimulation (VNS) in Treatment-Resistant Depression (Sackeim et al.) (in reference list)	Data included in TEC assessment
Articles on VNS	
Vagus Nerve Stimulation (VNS) and Treatment of Depression: To the Brainstem and Beyond (O'Reardon et al. *Psychiatry*, 2006)	Review article
VNS Therapy in Treatment-Resistant Depression: Clinical Evidence and Putative Neurobiological Mechanisms (Nemeroff et al. *Neuropsychopharmacology*, 2006)	Review article
Effect of Vagus Nerve Stimulation on Serotonergic and Noradrenergic Transmission (Dorr and Debonnel, *J Pharmacol Exp Ther*, 2006)	Animal experiment
Background and Rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study (Fava et al. 2003) (in reference list)	Describes the STAR*D trial, a study of pharmacologic treatments of depression
Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications in Clinical Practice (Trivedi et al. *Am J Psychiatry*, 2006)	STAR*D trial study

Table A. Materials Received from Cyberonics with Reasons for Exclusion from TEC Assessment (cont'd)

Document	Comment
Bupropion-SR, Sertraline, or Venlafaxine-XR after Failure of SSRIs for Depression (Rush et al. *N Engl J Med*, 2006)	STAR*D trial study
Treatment Strategies after SSRI Failure-Good News and Bad News (Rubinow, *N Engl J Med*, 2006)	Editorial
Materials on Economics of Depression	
Medicare Cost Analysis	Analysis of Medicare data from Moran Company, unpublished
The Impact of Treatment-Resistant Depression on Health Care Utilization and Costs (Crown et al. *J Clin Psychiatry*, 2002)	Claims-based analysis of pharmacologic treatment of depression
The Cost Consequences of Treatment-Resistant Depression (Russell et al. *J Clin Psychiatry*, 2004)	Claims-based analysis of pharmacologic treatment of depression, same data as study by Crown et al.
Letters	
Letter to Aetna regarding VNS Therapy (Sackeim)	No primary data.
Letter to BCBS TEC regarding VNS Therapy (Dunner)	No primary data.
Letter to Aetna (Nemeroff)	No primary data.
Center Guidelines for VNS Therapy for Treatment Resistant Depression (TRD) Massachusetts General Hospital	No primary data.
Evidence-Based Medicine Review of VNS Therapy for TRD Letter to BCBS TEC (Rudolph and Leon)	No primary data.
Letter to BCBS TEC regarding VNS Therapy and STAR*D (Rush)	No primary data.

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