



VAGAL NERVE STIMULATION FOR TREATMENT RESISTANT DEPRESSION

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum has been asked to review the scientific literature on the safety and efficacy of vagal nerve stimulation (VNS) for treatment resistant depression.

BACKGROUND

Major Depression

Major depressive disorder (MDD) is of major public health and clinical concern. A recent epidemiologic study in the United States found that lifetime prevalence of MDD was 13% and 12-month prevalence was 5%.¹ Among those who have suffered one major depressive episode (MDE), approximately three-quarters will have a recurrent episode and many will not achieve complete remission.²

Treatment Resistant Depression

Approximately one-third of patients with MDD will have an inadequate response to a first trial of antidepressants; this is considered an early stage of treatment resistant depression (TRD).³ There are many treatment options for treatment resistant depression, including augmentation therapy with a non-antidepressant drug (e.g. lithium, buspirone, triiodothyronine, lamotrigine, or atypical antipsychotics), combination therapy with two or more anti-depressants, switching therapy from one anti-depressant to another, psychotherapy (cognitive, behavioral or interpersonal) and electroconvulsive therapy (ECT).³

Non-Pharmacologic Therapies for Treatment Resistant Depression

ECT has been shown to achieve responses in approximately 50% of people with TRD (compared to 86% of inadequately treated patients with a MDE). However, only 40% of those with TRD who respond to ECT appear to have a sustained response at one-year.⁴ Because ECT requires multiple visits over time, with the use of anesthesia at each visit and presents some concerns about postictal confusion² there has been an effort to find other non-pharmacologic therapies for TRD. Transcranial magnetic stimulation has shown promise as a less-invasive treatment than ECT, but the studies to date have been hindered by small sample sizes.⁵ VNS has shown promise as a treatment requiring only one invasive procedure and less frequent subsequent visits than ECT, while allowing for long-term treatment.

Vagal Nerve Stimulation

VNS for the treatment of epilepsy was first proposed in 1883; however, a VNS device was first implanted for medication-resistant epilepsy in 1988.⁶ According to the device manufacturer, more than 32,000 patients worldwide have had the device implanted for treatment of epilepsy.⁷ Implantation of the device involves the following: 1) a subcutaneous, programmable generator implanted in the left chest wall (similar in size and placement to a cardiac pacemaker); 2) bipolar electrode coils wrapped around the left vagus nerve near the carotid artery; and 3) leads tunneled under the skin to connect with the generator.^{7, 8}

Studies of epilepsy patients with VNS devices have shown improvement in mood,⁹⁻¹¹ leading investigators and the manufacturer to hypothesize that VNS may be an effective therapy for treatment resistant depression.

Technology Assessment (TA)

TA Criterion 1: The technology must have the appropriate regulatory approval.

The VNS Therapy System (Cyberonics, Houston, TX) received FDA Pre-market Approval on July 15, 2005 for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key word depression. These were cross-referenced with the keyword vagal nerve stimulation. The bibliographies of reviews and key articles were manually searched for additional references. The search was performed for the period from 1966 through November 2005. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

The search identified seven studies with data specifically on VNS and treatment resistant depression. Of the seven studies, four were observational pilot studies, two of which examined the same 30 patients; and two of which examined those same 30 patients plus an additional 29 patients.¹²⁻¹⁵ Of the three larger, most recent studies, the first was a randomized controlled trial (RCT),¹⁶ the second was an observational cohort utilizing all of the patients originally in the RCT¹⁷ and the third was a non-randomized comparison cohort comparing the VNS cohort from the second study to a similar group not receiving VNS.¹⁸

Level of evidence: 1, 3, 4.

TA Criterion 2 is met.

TA Criterion 3: The technology must improve the net health outcomes.

Benefit

As noted above, although there are seven published manuscripts examining the effect of VNS therapy for patients with treatment resistant depression, these publications represent only two different groups of patients with implanted VNS devices. A detailed description of four of these studies, their designs and their outcomes, is presented in Table 1.

The first group of four published manuscripts report on a non-comparison cohort of patients. Two studies report the 12-week and one-year results for an initial (pilot) group of 30 patients implanted with a VNS device.^{12, 13} The other two studies report 12-week and two-year results on this same 30-patient cohort and add in results on 30 patients enrolled in a continuation of the initial pilot, giving results on 59 patients who completed the acute phase of the study.^{14, 15} The manuscript by Nahas et al., which reports on two-year outcomes, shows a positive effect of VNS on approximately one-third of participants; this effect appears to increase moderately at one-year and to be sustained at two-years. However, there was no comparison with a non-VNS group.

The other three manuscripts were published together in September 2005.¹⁶⁻¹⁸ The first of these presents results of a well-designed RCT of VNS. Participants randomly assigned to the control arm received an identical surgery to the active participants, with implantation of the actual device, but the device was not turned on after surgery. Both evaluators and participants were blinded as to which participants were receiving active VNS and which were not. There was a one-to-one randomization. Efforts were made to maintain blinding of evaluators by having a non-blinded device programmer turn off the active devices just

prior to each evaluation session; this prevented the occurrence of voice alterations during the session. Efforts were made to maintain blinding of participants by ensuring that they did not overlap in the waiting room before and after their evaluation sessions. Because the primary outcome, the 24-item Hamilton Rating Scale for Depression (HSRD-24), involves administration of a semi-structured interview, evaluators at each site underwent a certification process. The reliability of the ratings was assessed by sending a random subset of video-tapes for each evaluator to outside experts who were blinded to the treatment assignment, time point in treatment or follow-up and the scores obtained at the sites. Outcomes were assessed at 12-weeks after device implantation, which was 10-weeks after activation of the VNS device for the active group. The results of the primary outcome of this study showed no difference in the proportion of participants who experienced at least a 50% reduction in the HSRD-24 score between the active and sham VNS groups. Although there was a trend toward a positive effect of VNS on all scales measured, including the HSRD-24, the only outcome that was positive was the 30-item Inventory of Depressive Symptomatology-Self-Report (IDSR-30) ($\geq 50\%$ reduction for 17% of VNS vs. 7.3% of sham group; $p=.03$; See Table 1).

The remaining two manuscripts are cohort studies which include in the VNS cohort, participants originally randomized to VNS in the above RCT, as well as those randomized to sham control, who subsequently had their VNS devices activated after completion of the 12-week RCT. The first of these studies is a non-comparison cohort ($n=205$), which found a 27% response rate on the primary measure of greater than or equal to 50% in the HSRD-24 score. The last manuscript is a comparison of that same cohort of 205 VNS participants to a similar group of patients ($n=124$) with TRD undergoing treatment as usual (TAU) recruited over the same time period primarily from the same sites as those receiving VNS. The analysis in this non-randomized comparison study adjusted for 17 baseline characteristics, including prior treatments and depression severity, through the use of propensity scores. This method is intended to simulate randomization by accounting for the baseline propensity of participants in the two groups to receive the intervention. Adjustment for recruitment site and baseline IDSR-30 were also made. There were no significant differences between the two groups on most depression characteristics, except that the VNS group had received more prior ECT and the TAU group had a higher average number of lifetime depression episodes. Results of this comparison for the primary outcome of IDSR-30 difference per month showed the VNS scored 0.4 points per month lower than the TAU group, with greater difference in scores in each subsequent month ($P<.0001$). All of the secondary measures, including measures of remission and sustained response at 9 and 12 months were also significantly better for the VNS group (See Table 1).

Harms

In both of the groups of patients (Nahas et al., n=59; Rush et al., n=205), there were deaths and suicide attempts which appeared unrelated to device placement (See Table 2).^{15, 16} One patient had a post-surgical infection and needed the device removed. The most common side effect appears to be voice alteration when the device is actively stimulating the vagus nerve; this occurs at least initially in more than half of patients. Neck pain, dyspnea and increased cough also occur with some frequency.

Because VNS has been used for the treatment of epilepsy since 1989, and most of those patients who have had the device implanted have been followed long term in trials and registries, there is significantly more known about the side effects and potential harms of this device than can be learned from the studies of VNS and depression alone. Short-term (three-month follow-up) adverse events appear to include post-operative infections (3-6%) most often requiring oral antibiotics and occasionally requiring device and electrode removal; rare left cord paralysis related to older versions of the VNS device, rare lower facial weakness related to high surgical incisions connecting the electrodes to the vagus nerve and intra-operative asystole (0.1%).^{19, 20} Other side effects, such as voice alteration, hoarseness and throat pain appear to be more frequent with high stimulation than with low stimulation and appear to decrease in frequency over time.¹⁹ There does not appear to be significant long-term (one and three-year follow-up) effects on cardiac electrical conduction or pulmonary function.¹⁹ A search of the FDA's adverse event database revealed 28 reports of bradycardia or asystole, the large majority of which occurred during implantation. A few occurred during the course of treatment and may have been related to the VNS device or migration of the electrodes along the vagus nerve.²¹

Summary

Although the harms appear to be relatively small in this severely ill population, the benefits remain unclear. The best evidence of the short-term randomized control trial showed no benefit at 12-weeks. It is possible that if this trial had been continued for a full year, it would have shown benefit, however, we do not have that data. The observational cohort evidence is promising that this technology may be of significant benefit to patients with TRD over time. However, in light of the negative RCT, it is not yet convincing. A longer-term RCT showing benefit, or multiple large observational studies also showing benefit, would be more compelling.

TA Criterion 3 is not met.

Table 1 Efficacy of VNS for Treatment Resistant Depression

Study	Design	Number of Subjects	Definition of TRD Population (inclusion criteria)	Outcome Measures	Results
Nahas et al. 2005	Cohort study (open pilot + continuation) 2-year follow-up	59 – no comparison group (same patients as Sackheim 2001; also includes the 30 patients in Rush 2000 and Marangell 2002)	Meet DSM-IV criteria for non-psychotic MDD of bipolar-I or bipolar-II depressed phase; score >20 on HSRD-24 prior to implantation <i>and</i> score >18 HSRD-24 two weeks post-implantation (prior to activation of VNS) <i>and</i> current MDE ≥ 2 years or at least 4 lifetime MDE <i>and</i> unsatisfactory response to at least two adequate trials of different classes of antidepressant medication according to the modified Antidepressant Treatment History Form (ATHF)	Primary outcome: Response of ≥ 50% reduction HSRD-28 Secondary outcome: Remission by HSRD-28 ≤ 10	Last observation carry forward analysis (LOCF) Response 3 months: 30.5% Response 12 months: 44.1% Response 24 months: 42.4% LOCF analysis Remission 3 months: 15.3% Remission 12 months: 27.1% Remission 24 months: 22.0%
Rush et al. 2005	RCT double blind -- active VNS vs. sham VNS x 12 weeks (all patients on stable medication regimen x 4 weeks prior to device implantation; changes in medication during study period not allowed)	112 active VNS 110 sham VNS	Meet DSM-IV criteria for non-psychotic MDD of bipolar-I or bipolar-II depressed phase; average of 2 scores >20 on HSRD-24 prior to implantation <i>and</i> score >18 HSRD-24 two weeks post-implantation (prior to activation of VNS) <i>and</i> current MDE ≥ 2 years	<u>Primary outcome:</u> ≥50% reduction in HSRD-24 <u>Secondary outcomes:</u> MADRS ≥50% reduction IDS-SR-30	No statistically significant difference on primary outcome of >50% reduction in HSRD-24 score from baseline: 15.2% active vs. 10% sham; p=.25 MADRS: 15.2% vs. 11%; p=.38 IDS-SR-30: 17% vs. 7.3%; p=.03

			or at least 4 lifetime MDE <i>and</i> unsatisfactory response to at least two adequate trials of different classes of antidepressant medication (≤ 6 classes) according to the modified ATHF	CGI-I	CGI-I: 13.9% vs. 11.8%; $p=.65$
Rush et al. 2005	Cohort study 12 month follow-up: enrolled active VNS group from Rush et al. RCT above followed additional 9 months of active VNS; enrolled sham VNS followed for additional 12 months of active VNS; changes in medication during study period allowed	205 (same patients as Rush et al. above)	(same as above; prior sham VNS group with average of 2 scores >18 on HSRD-24 prior to activation)	Primary outcome: $\geq 50\%$ reduction in HSRD-24 Secondary outcomes: $\geq 50\%$ reduction IDS-SR-30; MADRS	LOCF primary outcome of $\geq 50\%$ reduction in HSRD-24 = 27% response rate IDS-SR-30: 20% response rate MADRS: 28% response rate
George et al. 2005	Comparison cohort (non-randomized) for 12 months: active VNS plus TAU vs. TAU only	205 VNS + TAU (same patients as Rush et al. above) 124 TAU only	VNS + TAU group same as Rush et al. above; TAU group: Same as VNS + TAU group except (1) only single measurement of baseline HSRD-24 score ≥ 20 , and (2) no exclusion for risks associated with implantation of VNS device (pregnancy, h/o MI or cardiac arrest, general anesthesia w/in 30 d	Primary outcome: IDS-SR-30 inter-group difference per month adjusted for propensity score, baseline IDS-SR-30 score and site. Secondary outcomes: $\geq 50\%$ reduction HSRD-24 $\geq 50\%$ reduction IDS-	IDS-SR-30: VNS + TAU 0.4 points per month lower score than TAU group, with greater difference in scores in each subsequent month ($P<.0001$) LOCF $\geq 50\%$ HSRD-24 response rate: VNS + TAU 26.8% vs. TAU 12.5% ($p=.011$) LOCF IDS-SR-30 response rate:

			of enrollment, potential need for whole-body MRI)	<p>SR-30</p> <p>CGI-I score= 1 or 2 (much or very much improved)</p> <p>Remission (adjusted for propensity score and baseline score): HSRD-24 \leq14 or IDS-SR-30 \leq9</p> <p>Sustained Response (adjusted for propensity score and baseline score): \geq50% reduction IDS-SR-30 at both 9 & 12 months</p>	<p>VNS + TAU 19.6% vs. TAU 12.1% (p=.108)</p> <p>LOCF CGI-I much or very much improved: VNS + TAU 34% vs. TAU 6.7% (p<.001)</p> <p>LOCF remission HSRD-24: VNS + TAU 15.6% vs. TAU 6.7% (p=.059); IDS-SR-30: VNS + TAU 13.2% vs. TAU 3.2% (p=.007)</p> <p>Sustained Response IDS-SR-30 9 & 12 months: VNS + TAU 15.5% vs. TAU 4.6% (p=.005)</p>
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Table 2 Adverse Events Associated with VNS Therapy for Treatment Resistant Depression.

	Rush et al. 2005 (1-year)* (N=232)	Nahas et al. 2005 (2-year) (N=60)
<u>Study Withdrawal</u>	24 participants (7 adverse events – inclusive of death; 17 lack of efficacy or other)	6 participants (2 death; 4 lack of efficacy) 6 additional participants turned off generator before 24 months but did not withdraw from study
<u>Serious</u> Death Suicide attempts Hospitalizations	n=3 (1 esophageal cancer, 1 suicide, 1 unknown cause) n=7 (6 participants) n=60 (30 participants)	n=2 (1 sepsis after colorectal surgery; 1 lung cancer) n=3 (3 participants) Not noted
Worsening depression (on HSRD-24)	7%	n=10
<u>Common</u> Headache Neck pain Pain Dysphagia Nausea Insomnia Paresthesia Cough increased Dyspnea Laryngismus Pharyngitis Voice alteration	5% 16% 6% 13% 6% 4% 11% 24% 14% 10% 6% 58%	22% (3 months) / 13% (24 months) 15% (3 months) / 8% (24 months) 60% (3months) / 27% (24 months)

*event rates were reported at 3, 6, 9 and 12 months. The highest number of events were at 3 months and for the common events, that is what is reported here.

For the serious events of death, suicide and hospitalization, the total number at 12 months is what is reported here, and for worsening depression, the highest event rate (at 6 months) is reported.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Although there are many treatment options for early treatment resistant depression, such as combination antidepressants or atypical neuroleptics, the main non-pharmacologic treatment of TRD is ECT. ECT has a higher rate of initial response than VNS does in the large observational study (50% vs. 27%).^{4, 18, 22} Both therapies appear to have about the same ability to achieve a sustained response (approximately 16%).^{18, 22} When ECT is followed by continuation pharmacotherapy and or continuation ECT, patients have fewer relapses.^{22, 23} Patients with longer duration of illness and those with medication resistance are the most likely to relapse after discontinuation of ECT.²² However, it is important to remember that the patients included in the observational study of VNS were just those patients: they had a very long mean duration of illness (49 months) and all had medication resistance. In addition, more than half of them had tried ECT in the past, with one-third having tried and failed it during the MDE during which they enrolled in the study. Thus, although the rate of initial response is lower than for ECT, the study population appeared to be an even more gravely ill group than those in the ECT studies.

However, there has been no direct comparison of ECT and VNS for treatment resistant depression. Additionally, as stated above, the benefits of VNS remain unclear given the observational nature of the long-term studies.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Vagal nerve stimulation has not been found to improve outcomes in the context of clinical trials of treatment resistant depression, thus, improvement cannot be obtained outside of the investigational setting.

TA Criterion 5 is not met.

CONCLUSION

Two groups of patients have been studied to evaluate the efficacy of VNS on treatment resistant depression. The first group of 59 patients included 30 from a pilot study and an additional 29 as part of a two-year continuation of that pilot study. The second group of 205 patients, half of whom were initially randomized to VNS and the other half to sham VNS, were then subsequently treated with active VNS and followed together with the initial VNS group over the course of a year and compared to a very similar TAU

group of patients. The pilot-study and its continuation data showed promising results in a small group of patients, leading to the larger RCT.

On average, the patients enrolled in the larger trial were quite ill. They were very depressed, had long duration of illness, had lifetime histories of prior major depressive episodes, had multiple prior adequate medication trials and half had been treated in the past with ECT. Thus, the population being studied was very ill and in need of more treatment options.

Both the RCT and the subsequent cohort comparison trial were well designed. The initial RCT had a sham surgery control group, was double-blinded and made good efforts to maintain blinding. Thus, the negative results from this trial are quite convincing. At least in the short-term (three months), VNS is not an effective therapy for treatment resistant depression. Because the authors believed that the benefit from VNS may be most evident over time, they followed their original RCT participants as a cohort and then compared them to a similar treatment resistant trial. The analyses in this study were also carefully and expertly conducted. The authors used propensity scores, a good technique to attempt to approximate randomization in a non-randomized trial, and they controlled for baseline depression scores and study site. The positive results at one-year resulting from this cohort comparison trial are promising. It appears that VNS may benefit almost one-third of this difficult to treat group of patients and obtain a sustained response in a smaller, but clinically significant number of patients (16%).

However, given the well-designed negative RCT and the fact that this is a single group of patients in an observational trial, it is early to conclude that the new technology of VNS improves the net health outcomes as much as or more than the established alternative of TAU with medications and/or electroconvulsive therapy.

RECOMMENDATION

- It is recommended that VNS does not meet Technology Assessment Criterion 3, 4 or 5 for effectiveness and improvement in health outcomes for TRD

The California Technology Assessment Forum panel voted to approve the recommendation.

February 15, 2006

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center Medical Advisory Panel conducted a review of VNS for Treatment Refractory Depression in June 2005 and found that TEC criteria were not met.

Centers for Medicare and Medicaid Services (CMS)

CMS does not have a National Coverage Determination specific to the use of this technology for treatment refractory depression.

California Psychiatric Association (CPA)

A CPA representative was not able to attend the meeting nor did the CPA have an opinion regarding the use of this technology

California Association of Neurological Surgeons (CANS)

CANS does not have an opinion/position statement on the use of this technology and did not attend the meeting.

ABBREVIATIONS USED IN THIS ASSESSMENT

ATHF: Antidepressant Treatment History Form

HSRD-24: 24-Item Hamilton Rating Scale for Depression

HSRD-28: 28-Item Hamilton Rating Scale for Depression

IDSR-30: 30-Item Inventory of Depressive Symptomatology Self-Report

LOCF: Last Observation Carry Forward

MADRS: Montgomery-Asberg Depression Rating Scale

MDD: Major Depressive Disorder

MDE: Major Depressive Episode

RCT: Randomized Controlled Trial

CGI-I: Clinical Global Severity Improvement rating

TAU: Treatment As Usual

ECT: Electroconvulsive Therapy

TRD: Treatment Resistant Depression

VNS: Vagal Nerve Stimulation

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