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Vagus Nerve Stimulation (VNS™) for Treatment-Resistant Depression: Efficacy, Side Effects, and Predictors of Outcome

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This open pilot study of vagus nerve stimulation (VNS™) in 60 patients with treatment-resistant major depressive episodes (MDEs) aimed to: 1) define the response rate; 2) determine the profile of side effects; and, most importantly; 3) establish predictors of clinical outcome. Participants were outpatients with nonatypical, nonpsychotic, major depressive or bipolar disorder who had not responded to at least two medication trials from different antidepressant classes in the current MDE. While on stable medication regimens, the patients completed a baseline period followed by device implantation. A 2-week, single blind, recovery period (no stimulation) was followed by 10 weeks of VNS. Of 59 completers (one patient improved during the recovery period), the response rate was 30.5% for the primary $HRSD_{28}$ measure, 34.0% for the Montgomery-Äsberg Depression Rating Scale (MADRAS), and 37.3% for the Clinical Global Impression-Improvement Score (CGI-I of 1 or 2). The most common side effect was voice alteration or hoarseness, 55.0% (33/60), which was generally mild and related to output current intensity. History of treatment resistance was predictive of VNS outcome. Patients who had never received ECT (lifetime) were 3.9 times more likely to respond. Of the 13 patients who had not responded to more than seven adequate antidepressant trials in the current MDE, none responded, compared to 39.1% of the remaining 46 patients ($p = .0057$). Thus, VNS appears to be most effective in patients with low to moderate, but not extreme, antidepressant resistance. Evidence concerning VNS' long-term therapeutic benefits and tolerability will be critical in determining its role in treatment-resistant depression.

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Vagus nerve stimulation (VNS) delivered by the Neuro-Cybernetic Prosthesis (NCP®) System (VNS and NCP are registered trademarks of Cyberonics, Inc., Houston, Texas) is effective in reducing the frequency of seizures

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in patients with epilepsy and treatment-resistant partial onset seizures (Ben-Menachem et al. 1994; The Vagus Nerve Stimulation Study Group 1995; Handforth et al. 1998). With approximately 10,000 patients receiving VNS for treatment-resistant epilepsy, relatively few clinically significant adverse events have been observed (Schachter and Saper 1998). While the therapeutic action of anticonvulsant medications often decreases with time, uncontrolled long-term follow-up studies have suggested that seizure reduction with VNS does not diminish with continued treatment, and may in fact increase (George et al. 1994; Salinsky et al. 1996; Morris and Mueller 1999; Vonck et al. 1999; DeGiorgio et al. 2000).

VNS is undergoing investigation as a treatment for patients with resistant major depressive episodes (MDE) (Rush et al. 2000). The rationale for this indication is based on the utility of anticonvulsant medications as mood stabilizers and antidepressants in mood disorders (Goodwin and Jamison 1990; Post et al. 1998; Calabrese et al. 1999), the anticonvulsant properties of electroconvulsive therapy (ECT) (Sackeim et al. 1983; Sackeim 1999), reports of improved mood, independent of seizure control, in epilepsy patients receiving VNS (Elger et al. 2000; Harden et al. 2000), the evidence from animal and human research that VNS results in altered concentrations of neurotransmitters implicated in mood disorders, including serotonin, norepinephrine, gamma aminobutyric acid, and glutamate (Ben-Menachem et al. 1995; Krahl et al. 1998; Walker et al. 1999), and brain imaging findings that acute VNS results in modulation of functional activity in widespread cortical and subcortical brain regions (Henry et al. 1998; see George et al. 2000a,b for reviews).

In a multi-site, open label, pilot study of 30 patients with treatment-resistant major depressive episodes (unipolar and bipolar), Rush et al. (2000) reported that 40% of the sample achieved at least 50% symptom reduction after 10 weeks of VNS. Given the severity of the mood disturbance and the degree of resistance to prior antidepressant treatments, this result was encouraging.

This open pilot study was extended to include an additional 30 patients. One of these additional patients showed symptomatic improvement following surgical implantation of the NCP System and prior to active stimulation, and was dropped from efficacy analyses. Now with an enlarged sample of 60 patients ($n = 59$ for efficacy), we report on: 1) the efficacy of VNS in treatment-resistant depression; 2) the profile of side effects; and, perhaps most importantly; 3) the demographic and clinical predictors of response to VNS in treatment-resistant depression.

METHODS

Subjects

Patients had to have a DSM-IV diagnosis of major depressive disorder (MDD) or bipolar I or II disorder (American Psychiatric Association 1994). They also had to be in a MDE. The current MDE had to be > 2 years in duration or the patient (whether with unipolar or bipolar disorder) had to have > 4 MDEs in their lifetime.

Patients met the following additional inclusion/exclusion criteria. Men and women, 18 to 70 years old, were eligible, except for pregnant women and women not using acceptable birth control methods, which included abstinence. Patients had not responded to $\geqslant 2$ adequate antidepressant medication treatments from at least two different medication classes during the current MDE, with an adequate medication trial defined as a score > 3 on the Antidepressant Treatment History Form (ATHF) (Prudic et al. 1990, 1996; Sackeim et al. 1990, 2000; Oquendo et al. 1999). Separate criteria were used in completing ATHF ratings for unipolar and bipolar patients. Patients also had no substantial clinical improvement with psychotherapy (at least six weeks during any MDE). At study baseline, patients scored $\geqslant 20$ on the 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) (Hamilton 1967), which includes the atypical symptom features of anergia, hypersomnia, increased appetite, and rejection sensitivity. Patients also scored $\leqslant 50$ on the Global Assessment of Function (GAF) (American Psychiatric Association 1994) and had an IQ $\geqslant 70$ by investigator judgment. Those with bipolar disorder had to be either resistant, intolerant, or have a medical contraindication to lithium.

Patients were excluded if they: (1) met DSM-IV criteria for atypical or psychotic depression; (2) had a history of schizophrenia, schizoaffective disorder, or other nonmood disorder psychosis; (3) currently had rapid cycling bipolar disorder; or (4) had a current secondary diagnosis (or signs) of delirium, dementia, amnestic, or other cognitive disorder (by DSM-IV criteria). Also excluded were patients with clinically significant, current suicidal intent, and those with certain risks related to the surgical implantation and VNS stimulation. Patients with atypical features were excluded to enhance diagnostic homogeneity and concerns about treatment specificity given the evidence that this subgroup has a preferential response to particular antidepressant treatments (i.e., MAOIs) and limited response to other classes of medication (Liebowitz et al. 1988; Quitkin et al. 1988; Stewart et al. 1997; McGrath et al. 2000).

The study was conducted at four sites: Baylor College of Medicine; Columbia University/New York State Psychiatric Institute; Medical University of South Carolina; and the University of Texas Southwestern Medical Center. The Institutional Review Boards at each site approved the study, which was performed under an Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA).

Study Overview

Following written informed consent, patients completed a pre-implantation *baseline period* (up to four

weeks) during which clinical assessments were performed on two separate occasions. To qualify for device implantation, patients had to score ⩾ 20 on the $HDRS_{28}$ during both baseline visits. In this treatment-resistant sample, patients were not withdrawn from psychotropic medications. Rather, patients receiving medication treatment had to maintain a stable medication regimen for at least four weeks prior to the initial baseline visit.

There was a single-blind *recovery period* for two weeks after device implantation. The NCP System remained OFF to allow for surgical recovery. Patients were told that "stimulation may or may not be turned ON immediately after surgery." Many patients experience no sensations when the device is operated at low stimulus intensity, and this is also true of some patients at higher intensity. This was communicated to patients to help preserve the single blind.

Clinical assessments were performed weekly. During this *recovery period*, patients had to score ⩾ 18 on the $HDRS_{28}$ for two consecutive visits (7 and 14 days post-implantation) before initiating stimulation. As indicated, one of the 60 patients had a decrease in $HRSD_{28}$ scores below this threshold which was maintained over several extended visits, and thus did not receive active stimulation during the time frame of the *acute study.* This patient was excluded from efficacy analyses, but included in the tabulations of adverse events. This patient, with recurrent major depressive disorder, had the shortest duration of current MD in the study (0.3 years). At Visit 1 and Visit 2, the patient had $HRSD_{28}$ scores of 39 and 37, respectively (pre-implantation). At Visit 4 and Visit 5, during the recovery period, these scores decreased to 20 and 2, respectively. The patient failed to meet the criterion for starting active stimulation ($HRSD_{28}$ ⩾ 18) throughout the 12-week post-implantation period. At enrollment and during the *acute study* period the patient was treated with venlafaxine 900 mg/d, sertraline (100 mg/d) and trazodone (150 mg/d). Other medications taken during the *acute study* period included clonazepam (1.5 mg/d), zolpidem (10 mg/d), and SAM-E (1200 mg/d). At Visit 4 (12/21/99), during the *recovery period*, the patient met criteria for hypomania [Young Mania Rating Scale (YMRS) score = 23]. The dose of clonazepam was increased from 1.5 to 3 mg/d. The hypomania resolved by 3/25/00. During the long-term follow-up, (22.1 weeks after implantation, 5/5/00), the patient was determined to meet criteria for MDE and was significantly depressed. Stimulation was started for the first time. At the patient's last follow-up visit on 6/27/00 (Visit 15) the depression was unremitted with a $HRSD_{28}$ score of 32.

Whether during the *recovery period* or *active stimulation*, there was no need for restrictions on the use of electronic or x-ray devices, including cell phones and microwave ovens. The only potential restriction was that a special head coil be used if an MRI of the brain was obtained. This restriction applied to both the *recovery* and *acute study* periods due to the implantation of a metallic stimulator in the chest wall.

After the *recovery period*, the NCP System was turned ON and the output current (mA setting) was progressively increased to the maximal, comfortably tolerated level over the next two weeks (*stimulation adjustment period*), with clinical assessments performed weekly.

At four weeks post-implantation (i.e., after two weeks of VNS), stimulation parameters were set and fixed for the remaining eight weeks. (A decrease in stimulation parameters was permitted if intolerable side effects developed, but no patient required decreased stimulation.) Patients were seen weekly for the next two weeks and then every other week over the ensuing six weeks. This *fixed dose stimulation period* lasted eight weeks, and the total duration of stimulation was 10 weeks.

After completion of the acute study, patients continued to receive VNS. All patients are being followed clinically after the acute study exit. During this long-term *follow-up period*, either NCP stimulation parameters and/or concomitant medications can be changed based on physician judgment. Findings regarding longer-term outcomes during follow-up are the subject of a separate report.

VNS Treatment

All aspects of device implantation and treatment delivery used in this study were identical to those in the studies of treatment-resistant epilepsy (Ben-Menachem et al. 1994; The Vagus Nerve Stimulation Study Group 1995; Handforth et al. 1998). The implantation of one patient was performed without complications using a combination of local and regional anesthesia as opposed to general anesthesia. The NCP System includes a multi-programmable Pulse Generator that was implanted in the chest wall. The generator delivered electrical signals to the left vagus nerve (10^{th} cranial nerve) via bipolar leads tunneled under the skin, with electrodes attached to the left vagus nerve in the neck. A programming wand attached to a portable computer, which adjusted stimulation parameters, regulated the generator. At each clinic visit, accuracy of stimulation parameters was verified and the pulse-by-pulse stimulation delivered since the last visit downloaded into the computer database.

After the two-week, post-implantation, single-blind *recovery period*, the device was turned ON with initial stimulation at a current intensity of 0.25 mA, a pulse frequency of 20 or 30 Hz, and a pulse width of 500 μs with stimulation ON for 30 s every 5 min. At this visit, the output current was increased gradually (in 0.25 mA increments) until a comfortable level was reached. Af-

ter tolerable output current level was attained, patients left the clinic at these settings.

Additional increases (in 0.25 mA steps) in output current were made anytime during the *stimulation adjustment period* over the next two weeks. The protocol allowed a range of frequency (e.g., 20–30 Hz), pulse width (e.g., 250–500 μs), and ON/OFF cycle parameters (e.g., OFF 3 or 5 min). However, in almost all cases, the stimulation parameters commonly used for epilepsy were employed in this study (500 μs pulse width, 20 Hz, 0.5–1.5 mA, and an ON/OFF cycle of 30 s ON and 5 min OFF).

Concomitant Therapy

Concomitant ECT, investigational drugs, or treatment with another investigational device was not permitted. Patients could receive antidepressant, mood stabilizer, or other psychotropic medications (e.g., atypical antipsychotics), as long as the same medication types and doses were maintained during the *baseline period* and for twelve weeks following implantation. In other words, medication regimens were kept stable, except that medication dosages could be decreased, but not increased, during the acute study. The only psychotropic medication that could be added during the trial was lorazepam (up to 3 mg/day), for anxiety and/or insomnia, as needed. Other medications (i.e., antibiotics, decongestants, analgesics, and over-the-counter medications) were allowed (although investigators attempted to either limit or discourage over-the-counter medications during the study). Concomitant medications were recorded at each visit.

Evaluations and Outcome Measurements

Baseline evaluations included a medical and psychiatric history, physical and neurological exams, and pre-surgical laboratory tests. Efficacy and safety data were gathered at the two *baseline* visits and at Weeks 1 and 2 (*recovery period*), 3 and 4 (*stimulation adjustment period*), and weeks 5, 6, 8, 10, and 12 (*fixed dose stimulation period*) after implantation. Clinical assessments of depressive symptoms included the 28-item HRSD and the 10-item Montgomery-Äsberg Depression Rating Scale (MADRS) (Montgomery and Äsberg 1979). Manic/hypomanic symptoms were rated by the Young Mania Rating Scale (YMRS) (Young et al. 1978). Overall symptom severity and change were assessed by the Clinical Global Impressions-Improvement (CGI-I) and Severity Index (CGI-SI) (Guy 1976). The Global Assessment of Function (GAF) (American Psychiatric Association 1994) provided an assessment of functional status. Functional outcomes (or quality of life) were also assessed using the Medical Outcomes Study Short Form-36 (MOS SF-36) (Ware and Sherbourne 1992).

The ATHF was used to characterize the extent of medication-resistance evidenced during the current MDE and the potency of antidepressant treatments received during the acute study (Prudic et al. 1990, 1996; Sackeim et al. 1990, 2000). Information to complete the ATHF was obtained from patient and family interviews, reports from treating physicians, medical records, and pharmacy logs. The ATHF rates each psychotropic medication trial on a score from 0 to 5, with a score of "3" or greater indicating a failed adequate trial. In making these ratings, compliance, blood levels, and clinical outcome were taken into account. For all medication trials, a score of "3" or greater required a minimum of four weeks at specific threshold dosage levels. For example, the dosage of fluoxetine at level "3" corresponded to 20–39 mg/day, whereas for imipramine the threshold range was 200–299 mg/day.

Exposure to psychotropic medications (regardless of trial adequacy) and specifically the number of failed adequate trials during the index episode were determined, both within and across medication classes. Potency of ongoing antidepressant medication treatment at the outset of the acute VNS trial was calculated by summing the ATHF score for each psychotropic medication received during the baseline period. For both unipolar and bipolar patients the categories of antidepressant treatments considered in determining the adequacy of trials included heterocyclics/tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, bupropion, mirtazapine, nefazodone, trazodone, venlafaxine and ECT. In addition, for bipolar patients sufficient dose or blood levels and trial duration of carbamazepine and lithium could constitute an adequate trial. Thus, across unipolar and bipolar patients there were 11 categories of possibly adequate mood disorder treatment.

Adverse events and concomitant medications were coded using the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) (U.S. Department of Health and Human Services, Center for Drug Evaluation and Research, 1995) and WHO (World Health Organization) dictionaries, respectively. Holter monitoring data for at least twelve hours were collected at baseline (between baseline Visits 1 and 2) and at the end of acute study (12 weeks post-implantation) for the first 30 patients. No changes were detected in Holter results. There was no difference in the frequency of atrioventricular block, premature ventricular contractions, atrial fibrillation, or junctional rhythm and no significant change in heart rate variability.

Statistical Methods

Cyberonics, Inc. conducted clinical monitoring visits at the four sites. Data were entered, verified, and analyzed using procedures that ensured the quality of the data

and results. Response was defined *a priori* as a ⩾ 50% reduction at exit in the mean $HDRS_{28}$ score obtained at the two baseline (pre-implantation) visits (or, for secondary analyses, a ⩾ 50% reduction in baseline MADRS scores or an exit CGI-I score of 1 or 2). The clinical outcome results for the first 30 patients and the second set of 29 patients were compared using the Fisher's Exact test. The two samples were then compared in demographic and clinical features using t-tests and Fisher's Exact tests, as appropriate. Given an outlying response rate at one site, site differences in patient characteristics were examined with t-tests and Fisher's Exact tests, as appropriate. To examine predictors of response (⩾ 50% reduction in exit $HDRS_{28}$ score), a series of univariate logistic regression analyses were conducted, with a priori predictors (listed in Table 8). To produce a final set of predictors, those variables with p-values $< .20$ were entered into a multivariate logistic regression analysis.

RESULTS

Enrollment

In the initial pilot study, 30 patients completed the acute study. This included all patients who were implanted with the NCP System. In the study extension, 29 of 30 patients completed the acute study. In addition to these 60 patients, an additional 11 patients consented to trial participation but were not implanted. Six patients withdrew consent and five patients were found not to meet inclusion/exclusion criteria.

Sample Characteristics

Table 1 presents demographic and clinical characteristics for the sample of 60 patients. Baseline $HRSD_{28}$ and GAF scores indicated a level of symptomatic severity and functional impairment typically seen only in inpatient samples, although this was exclusively an outpatient study. All but 16 patients (27%) had prior affective episodes. The median duration of the current MDE was 6.6 years, indicating marked chronicity. There was a low representation of minorities. While unexplained, this low representation may have to do with the fact that insufficient response to serial adequate treatment trials was a requirement for trial entry. Access to adequate care during the index episode may have influenced the demographics of the sample.

Table 2 summarizes the antidepressant treatments received by the sample during the current MDE. On average, patients had received approximately 16 different interventions aimed at treating the current MDE, of which nine were traditional antidepressant medications and seven were other mood disorder treatments (anticonvulsant medications, atypical antipsychotics, ECT, repetitive Transcranial Magnetic Stimulation, etc.). By ATHF criteria, on average patients had not responded satisfactorily to 4.8 ± 2.7 adequate antidepressant trials during the index episode. Indeed, 16 patients (26.7%) had not responded to seven or more adequate medication trials during the index episode. As also indicated in Table 2, on average patients had not responded to trials within 3.8 ± 1.7 *categories* of antidepressant treatment [out of the possible 11 categories (nine available for unipolar patients and 11 for bipolar patients)]. One patient in Table 2 is listed as having not responded to one antidepressant medication. This was a bipolar patient who also did not respond to an adequate trial of carbamazepine during the current episode. A different patient in Table 2 had a current episode duration of 0.3 years (four months). This patient (described earlier) had recurrent unipolar MDE and during the current episode had not responded to adequate trials venlafaxine and sertraline, while receiving subthreshold doses of trazodone, as well as clonazepam, zolpidem, and SAM-E.

Table 1. Demographic and Clinical Characteristics of the Sample ($n = 60$)

	Mean ± SD	Median	Range
Age at implant (yr)	46.8 ± 8.7	47.9	20.7–63.1
Gender (*N*, % female)	39 (65)		
Caucasian (*N*, %)	59 (98)		
Hispanic (*N*, %)	1 (2)		
Weight (lb)	195.2 ± 53.0	183.0	108–350
Unipolar, recurrent (*N*, %)	28 (47)		
Unipolar, single episode (*N*, %)	16 (27)		
Bipolar I disorder (*N*, %)	6 (10)		
Bipolar II disorder (*N*, %)	10 (17)		
Baseline $HRSD_{28}$	36.8 ± 5.8	37.0	23.5–51.5
Baseline GAF	40.6 ± 6.0	42.0	21.0–50.0
Length of current episode (yr)	9.9 ± 10.8	6.6	0.3–49.5
Age at onset of current episode (yr)	36.9 ± 12.6	37.8	8.0–57.6
Total length of affective illness (yr)	18.1 ± 10.9	17.6	2.2–49.5
Age at onset of affective illness (yr)	28.7 ± 12.2	28.1	8.0–53.3

Table 2. Mood Disorder Treatments During the Current MDE ($n = 60$)

	Mean ± SD	Median	Range
Total mood disorder treatments	15.7 ± 7.9	15	3–44
Antidepressant medications	8.6 ± 4.0	8	1–21
Other mood disorder treatments	4.8 ± 3.5	4	0–16
Anxiolytics	1.9 ± 1.4	2	0–6
Nonatypical antipsychotics	0.5 ± 0.9	0	0–4
ATHF Adequacy Ratings			
Unsuccessful adequate medications trials, current MDE	4.8 ± 2.7	4	2–14
Unsuccessful categories of antidepressant treatments, current MDE	3.8 ± 1.7	4	2–9

Lifetime exposure and response to the most recent course of ECT were examined. Only 20 (33.3%) patients had never received ECT. Of the remaining 40 patients, one (2.5%) had a full response, 12 (30.0%) had responses to ECT that were not sustained, 11 (27.5%) showed partial improvement with ECT, 15 (37.5%) had no response to ECT, and for one patient (2.5%) clinical outcome with ECT could not be determined. Of these 40 patients who received ECT in their lifetime, 34 (85.0%) had received ECT treatment during the current episode. The one patient with a history of full response was unwilling to receive this treatment modality in the current MDE. The history of unsuccessful treatment attempts with medications and ECT indicates that in general the sample was highly treatment-resistant.

Concomitant Treatments

Table 3 presents the number of patients who continued to receive one or more interventions within the various categories of mood disorder treatments during the acute VNS trial. The sample averaged 3.6 ± 1.9 concurrent mood disorder treatments (median = 4; range = 0–10). On average, 1.4 ± 0.9 of these treatments were with traditional antidepressant medications (median = 1; range = 0–4). To estimate the potency of ongoing antidepressant pharmacology, ATHF ratings (0–5) were determined for each medication received during the baseline period and summed for a total score. For example, if a patient was receiving a lithium augmentation trial with 350 mg/day imipramine (ATHF rating = 5), paroxetine at 10 mg/day (ATHF rating = 2), and lorazepam at 3 mg/day (ATHF rating = 1), the total potency score would be 8. The mean potency score during the acute study was 5.7 ± 3.2 (median = 5; range = 0–14).

VNS Treatment

Once the stimulation parameters were determined at the end of the two-week stimulation adjustment period, no patient required stimulation parameter adjustments during the *fixed dose stimulation period*. Forty-four patients (74.6%) were stimulated with a 500 μs pulse width and 20 Hz frequency for 30 s ON and 5 min OFF. Nine patients (15.2%) had these same settings except for receiving a frequency of 30 Hz. Three patients (5.1%) were stimulated with 500 μs pulse width and 30 s ON time; however, these patients had an OFF time of 3 min, along with two of the three having a 30 Hz frequency and one with 20 Hz. The last patient was stimulated with 500 μs pulse width, 20 Hz frequency, ON time of 30 s, and OFF time of 3 min. Three patients were stimulated with 250 μs pulse width and 20 Hz frequency for 30 s ON and 5 min OFF.

The reductions in pulse width were made to lessen adverse side effects. The increases in pulse frequency and/or shortening of the OFF time were conducted in patients who well tolerated the standard settings during the adjustment period and reflected an effort to maximize efficacy by increasing the amount of stimulation. Output currents ranged from 0.25 to 3.0 mA and averaged 0.96 ± 0.54 (median = 0.75 mA).

Clinical Outcome Measures

Figure 1 presents the $HRSD_{28}$ scores at acute study exit for each patient ($n = 59$), as well as the percent reduction in $HRSD_{28}$ scores relative to the average (two visits) baseline score. The data are plotted as a function of unipolar or bipolar diagnosis. Inspection of Figure 1 indicates that there was no indication that therapeutic effects differed by diagnosis. Overall, 18 of the 59 patients (30.5%) met the criteria for response, i.e., ⩾ 50% reduction in $HRSD_{28}$ scores. This contrasts with the 40% response rate observed in the first sample of 30 patients. In the second sample of 29 patients, the response rate was 20.7% (6/29). Across the 59 patients, nine (15.3%) met the criteria for complete response, i.e., acute exit $HRSD_{28} \leqslant 10$. This rate was 16.7% (5 of 30) in the first sample and 13.8% (4 of 29) in the second sample.

Mean scores at key time points are presented in Table 4 for each of the major clinical outcome measures. The total sample averaged statistically significant im-

Table 3. Mood Disorder Treatments Received During The Acute Study by Treatment Category ($n = 60$)

Category of Treatment	N (%)
Heterocyclics/TCAs	8 (13)
SSRIs	22 (37)
MAOIs	1 (2)
Bupropion	9 (15)
Venlafaxine	14 (23)
Mirtazapine	8 (13)
Nefazodone	9 (15)
Trazodone	2 (3)
Lithium	5 (8)
Anticonvulsants—Total[a]	20 (33)
Carbamazepine, Lamotrigine, Valproic Acid	11 (18)
Other anticonvulsants: Clonazepam, Gabapentin, Topiramate, Vigabitrine	10 (17)
Stimulants	13 (22)
Atypical Antipsychotics	21 (35)
Phototherapy	1 (2)
Repetitive Transcranial Magnetic Stimulation (rTMS)	0 (0)
Thyroid Hormone	5 (8)
Anxiolytics	24 (40)
Nonatypical Antipsychotics	3 (5)
Other (e.g., flax seed oil, SAM-E, Naltrexone)	4 (7)

[a]one patient had both types of anticonvulsants.

provement in $HRSD_{28}$ [paired-t(58) = 7.93, $p < .0001$], MADRS [paired-t(58) = 6.10, $p < .0001$], GAF [paired-t(58) = 7.70, $p < .0001$], and CGI severity scores [paired-t(58) = 6.19, $p < .0001$] at acute study exit. Of the 59 patients, 37.3% (22 of 59) received a CGI-I score of 1 or 2, indicating that they were very much improved by clinician judgment, whereas only three patients were rated as minimally worse. The remainder of the patients ($n = 34$) were either unchanged or minimally improved. Across the sample, there was no significant change in YMRS scores from baseline to acute study exit.

Time Course for Clinical Response

Figure 2 presents at each study visit the average $HRSD_{28}$ score for the total sample, as well as separately for the subgroups classified as VNS responders and nonresponders. When clinical improvement occurred, it was typically gradual. As indicated, only one of 60 patients showed sufficient and sustained improvement during the recovery period after implantation so that VNS stimulation was not instituted. Of the 18 patients who met the $HRSD_{28}$ response criterion, 12 (66.7%) showed first

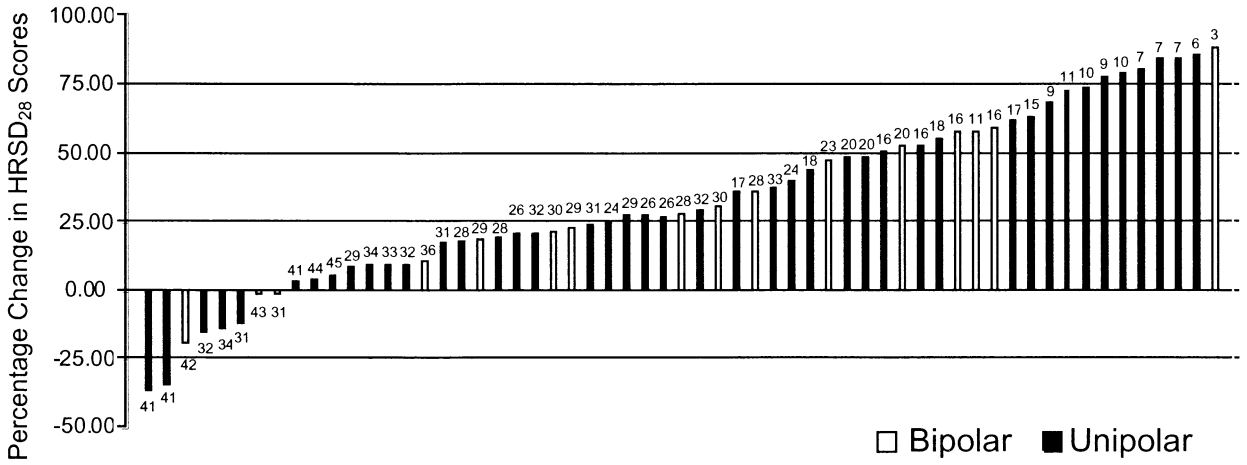

Figure 1. Percent change from baseline and acute study exit $HRSD_{28}$ scores for the 59 patients, as a function of diagnosis of unipolar or bipolar disorder. Numbers above or below each bar indicate the final $HRSD_{28}$ score at acute study exit.

Table 4. Scores on Major Clinical Outcome Measures at Baseline, Recovery Period, and Acute Study Exit ($n = 59$)

Rating Scale	Baseline Period[a] Mean ± SD	Recovery Period[b] Mean ± SD	Acute Study Exit Mean ± SD	Mean Percent Change: Baseline to Exit[c]
$HRSD_{28}$	36.8 ± 5.8	35.0 ± 6.6	24.7 ± 10.9	32.0%*
MADRS	33.4 ± 5.2	32.0 ± 6.7	22.9 ± 11.7	29.9%*
CGI-I[d]	NA	0%	37%	NA
CGI-SI	5.2 ± 0.7	5.0 ± 0.7	3.9 ± 1.3	23.0%*
GAF	40.6 ± 6.0	43.0 ± 8.6	57.4 ± 16.2	43.7%*
BDI	34.9 ± 7.7	32.6 ± 9.3	23.0 ± 11.1	32.6%*
YMRS	2.1 ± 1.5	1.8 ± 1.9	2.1 ± 3.3	−12.3%

[a]Baseline period score calculated as the average of Visit 1 and Visit 2.
[b]Recovery period score calculated as the average of Visit 4 and Visit 5.
[c]p-values determined using the paired t-test on change scores. All measures marked with * had a p-value < .0001.
[d]CGI-I reported as the percentage of patients with a score of 1 or 2.

response only at or after Visit 10 (six weeks of stimulation). In fact, the average time to first response for the 18 responders was 48.1 ± 31.7 days (median = 45.5 days).

Effects on Quality of Life

Average scores on the summary and subscales of the MOS SF-36 are presented in Table 5 at baseline and at acute study exit for the total sample and separately for the responder and nonresponder subgroups. The total sample was markedly impaired at baseline on several subscales relative to norms for both healthy individuals and depressed samples (Ware and Sherbourne 1992). Responders showed significant improvement at study exit in the mental component [paired-t(15) = 4.01, p = .001] and all subscales other than physical function and pain index (all p's < .05, paired t-test).

Non-responders showed much smaller, but statistically significant, improvement in the mental component [paired-t(36) = 3.60, p = .001), and the subscales assessing vitality improvements, social function, and mental health (all p's < .05, paired t-test), as well as borderline statistical significance in the physical component [paired-t(36) = 1.91, p = .064). Overall, response to VNS was associated with a marked improved in these functional indices with much smaller changes in nonresponders.

Adverse Events

None of the 60 patients discontinued the acute study due to adverse events (AEs). The AEs which occurred in at least 5% of patients and may have been related to surgery and/or VNS stimulation are listed in Table 6. The average start date for these AEs relative to implantation, the percentage of patients in whom the AE resolved by the end of the acute study period, and (independent of intermittence) the average time to final

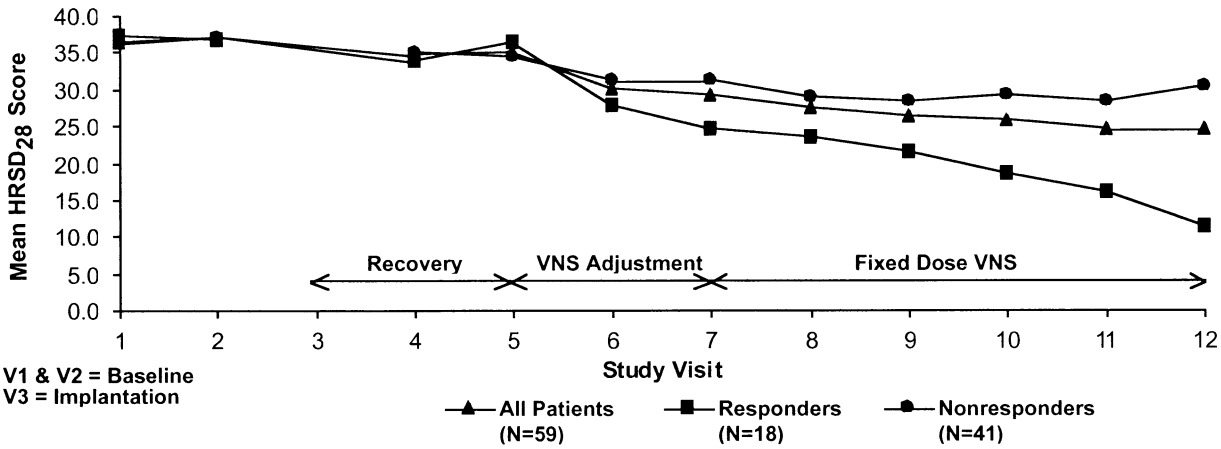

Figure 2. Mean $HRSD_{28}$ scores for the total sample and responder ($n = 18$) and nonresponder ($n = 41$) at each study visit.

Table 5. Mean Scores on the Medical Outcomes Study Short Form-36 (MOS SF-36) for the Total Sample and Responders and Nonresponders

	Total Sample (N=58)		Responders (N=17)		Nonresponders (N=41)	
Variable	**Baseline**	**Exit**	**Baseline**	**Exit**	**Baseline**	**Exit**
Mental component[a]	17.1	26.9[b]	17.1	39.3[b]	17.1	21.0[b]
Physical component[a]	49.6	46.0	46.4	44.7	50.8	46.5
Subscales[a]						
Physical function	64.2	63.6	60.3	65.9	65.9	62.6
Role function	50.0	51.3	33.8	59.7[b]	56.9	47.4
Pain index	62.3	55.9	58.5	60.7	63.9	53.7
Health perceptions	55.0	57.0[b]	49.4	61.7[b]	57.1	54.8
Vitality improvements	11.0	25.3[b]	8.8	41.1[b]	12.0	17.9[b]
Social function	22.0	37.1[b]	22.8	58.3[b]	21.6	27.2[b]
Role emotional	10.5	19.9	3.9	40.7[b]	13.3	10.3
Mental health	21.8	38.3[b]	22.1	62.2[b]	21.7	27.3[b]

[a]Some patients did not complete all of the MOS SF-36 subscales.
[b]Statistically significant percentage improvement from baseline using a p-value of $< .05$ and the paired t-test.

resolution of the AE are reported in Table 7. By far, the most common AE was voice alteration or hoarseness (33/60, 55%), which was generally mild, well tolerated, and related to the intensity of the output current. Coughing and shortness of breath (dyspnea), particularly on exercise, and were experienced by 17% and 15% of patients, respectively, and again related to output current intensity. This relationship is well established since reduction in current intensity leads to rapid and often immediate disappearance or decreased severity of these symptoms.

The other most frequent AEs ($\geq$ 15% of the sample) were headache (22%), neck pain (17%), dysphagia (20%), and pain (15%). The most common adverse event related to surgery was pain at the incision site (30%, 18 of 60), which typically resolved over 1 to 2 weeks. In general,

Table 6. Number and Percent of Patients Reporting Adverse Events That Were Reported As Possibly, Probable, or Definitely Related to the Implant Surgery or Stimulation, Occurring in $\geq$ 5% of Patients (n = 60)

Body System	**COSTART Term**	**Possibly, Probably, or Definitely Related to Implantation or Stimulation N (%)**
Body as a whole	Incision site pain	18 (30)
	Headache	13 (22)
	Neck pain	10 (17)
	Pain	9 (13)
	Chest pain	4 (7)
	Wound abnormality	4 (7)
	Infection	3 (5)
Digestive system	Dysphagia	8 (13)
	Dyspepsia	6 (10)
	Nausea	4 (7)
	Tooth disorder	3 (5)
Nervous system	Dizziness	3 (5)
	Paresthesia	4 (7)
	Twitching	3 (5)
	Insomnia	3 (5)
Respiratory system	Voice alteration	33 (55)
	Dyspnea	9 (15)
	Coughing	10 (17)
	Pharyngitis	8 (13)
Metabolic/Nutritional	Healing Abnormal	3 (5)
Cardiovascular	Palpitation	3 (5)
Skin and appendages	Rash	4 (7)
Musculoskeletal	Generalized spasms	0 (0)

Table 7. Onset Time, Number and Percent of Patients Resolved, and Time to Resolution for Adverse Events That Were Reported as Possibly, Probably, or Definitely Related to the Implant Surgery or Stimulation, Occurring in ⩾ 5% of Patients ($n = 60$)

Body System	COSTART Term (Number of patients reporting event during Acute Study)	Onset Time (days)				Number Resolved (%)	Resolution Time (days)			
		Mean	S.D.	Min	Max		Mean	S.D.	Min	Max
Body as a whole	Incision site pain (18)	1.2	2.5	0	8	15 (83.3)	9.8	8.5	1	32
	Headache (13)	19.8	19.9	−1	73	9 (69.2)	9.3	13.4	0	43
	Neck pain (10)	37.7	26.1	8	82	7 (70.0)	9.0	7.4	0	18
	Pain (9)	14.3	16.4	0	49	7 (77.8)	29.9	27.4	4	73
	Chest pain (4)	124.5	133.4	16	316	4 (100.0)	16.8	24.6	0	53
	Infection (3)	18.0	18.4	5	39	3 (100.0)	15.7	10.4	4	24
Digestive system	Dysphagia (8)	11.3	10.0	0	26	7 (87.5)	44.6	30.1	7	97
	Dyspepsia (6)	20.8	18.3	1	50	6 (100.0)	34.5	31.4	0	83
	Nausea (4)	19.8	19.3	0	40	4 (100.0)	8.8	7.8	0	19
	Tooth disorder (3)	54.0	45.6	17	105	2 (66.7)	30.0	17.0	18	42
Nervous system	Dizziness (3)	9.7	11.2	0	22	3 (100.0)	3.3	5.8	0	10
	Paresthesia (4)	3.0	6.7	−1	13	3 (75.0)	28.7	30.7	0	61
	Twitching (3)	27.0	10.5	16	37	3 (100.0)	21.7	21.5	0	43
	Insomnia (3)	46.7	28.7	20	77	0 (0.0)	—	—	—	—
Respiratory system	Voice alteration (33)	15.9	14.0	0	56	12 (36.4)	54.2	19.9	12	75
	Dyspnea (10)	37.9	24.3	0	66	4 (44.4)	18.0	24.3	1	53
	Coughing (10)	17.9	7.5	12	38	7 (70.0)	28.6	33.7	6	102
	Pharyngitis (8)	19.5	11.9	3	38	5 (62.5)	14.4	12.2	3	33
Metabolic/nutritional	Healing Abnormal (3)	16.7	2.5	14	19	3 (100.0)	23.0	6.6	17	30
Cardiovascular	Palpitation (3)	24.0	11.4	16	37	2 (66.7)	9.5	13.4	0	19
Skin and appendages	Rash (4)	11.8	9.5	0	20	4 (100.0)	17.5	10.2	8	32

the profile of adverse events matched that observed in the previous VNS trials in epilepsy (Ben-Menachem et al. 1994; The Vagus Nerve Stimulation Study Group 1995; Ben-Menachem 1998; Handforth et al. 1998).

Table 7 reports the time to onset, percent resolution, and duration of the adverse events experienced by 5% or more of the patients and thought to be at least possibly related to surgery or stimulation. The vast majority of AEs resolved by the end of the acute study period. The major exceptions were respiratory AEs, particularly voice alteration and dyspnea, for which resolution was achieved in 36.4% (voice alteration) and 44.4% (dyspnea) of the patients who experienced these AEs. The ongoing stimulation through the trial, in some patients at high levels, was responsible for these continuing AEs. To date, all but one of the 60 implanted patients have elected to continue with VNS. This exceptional patient requested explantation due to lack of efficacy.

Of note, two patients (3.3%), one with a diagnosis of unipolar disorder and one with bipolar disorder, developed significant hypomanic symptoms during the acute study, with peak YMRS scores ranging from 18–27. Details of the first case were described earlier and the hypomanic episode occurred during a period without active stimulation. In second case, at time of implant (1/28/2000), the patient's medications were trazodone (150 mg/d), topiramate (400 mg/d), sertraline (200 mg/d), clonazepam (0.5 mg/d), dexedrine (5 mg/d), and lithium (900 mg/d). VNS parameters were gradually increased to 0.5 mA (current), 500 μs (pulse width), 20 Hz (frequency), and 30 s ON and 5 min OFF (duty cycle). The hypomania (YMRS = 18) was noted to have started on 2/27/2000. The dexedrine was stopped, the lithium increased to 1,200 mg/d and the VNS output current reduced to 0.25 mA. The episode of hypomania resolved by 3/14/2000. Subsequently, VNS was increased back to its original intensity level with the return of depressive symptoms.

There were 10 serious or clinically significant adverse events during the acute study. These included an infection related to the implantation. Two separate instances of leg pain were reported by one patient that possibly could have been related to the implantation. Two patients experienced worsening depression considered as possibly related to stimulation. An instance of agitation/panic was also reported as possibly related to stimulation. Three instances of worsened depressive symptoms (one of suicidal intent) were reported as not related to the stimulation or the implant. One other serious adverse event reported in the acute study was vomiting/diarrhea, which was reported as not related to the implant surgery or stimulation. One patient experienced a myocardial infarction (MI) considered possibly related to stimulation. The MI occurred in a 52-year old, moderately obese female, who had hypertension, hy-

percholesteremia, hypothyroidism, and was a heavy smoker. The MI occurred on 2/19/00, two days after starting VNS stimulation. Heart catheterization done on 2/22/2000 revealed a 40-50% blockage of her left anterior descending coronary vessel, and the patient underwent percutaneous transluminal coronary angioplasty and stent placement. After discussion with the investigator about potential risks and benefits, the patient opted to continue in the study. No cardiac changes were noted at the time that VNS was restarted. With respect to cardiac status, the patient remained nonsymptomatic through the acute study.

Comparison of the Two Pilot Samples

The response rate in the first sample of 30 patients was 40.0% (12 of 30 patients), compared to 20.7% (six of 29 patients) in the second sample. This difference was not statistically significant ($p = .158$, Fisher's Exact). Similarly, the average percent change in $HRSD_{28}$ scores from baseline to acute exit were not significantly different, with 38.2 ± 29.9 in the first sample compared to 25.7 ± 31.4 in the second sample, $t(57) = 1.57$, $p = .12$).

Despite the lack of statistically significant differences, it appeared that therapeutic effects were less robust in the second sample. Therefore, the two samples were compared in the demographic, clinical and treatment history features listed in Tables 1 and 2, as well as in history of ever having receiving ECT, outcome of most recent ECT treatment, potency of antidepressant treatment during the baseline period, and VNS output current. These analyses indicated that there were no statistically significant differences between the first and second groups for these factors.

Site Differences

Across the 59 completers, the response rates at the four sites were: four of 11 patients (36.4%) at the Baylor College of Medicine; one of 12 patients (8.3%) at Columbia University; four of 13 patients (30.8%) at the Medical University of South Carolina; and nine of 23 patients (39.1%) at the University of Texas at the Southwestern Medical Center. An analysis contrasting all the sites did not support a difference in rates of response ($p = .282$, Fisher's Exact). Nonetheless, inspection of the response rates indicated that clinical outcome was substantially poorer at Columbia University than the other sites. A contrast of the response rate at Columbia University and all other sites yielded a trend for a difference ($p = .08$, Fisher's Exact). Of note, Columbia University contributed 9 of the 29 completing patients (31.0%) in the second sample, but only three of the 30 completing patients (10.0%) in the first sample.

The demographic, clinical, and treatment characteristics of the 12 patients at the Columbia University site were compared to the remaining 47 completing patients at the other three sites. Patients at Columbia University differed from the combined group of patients from the other three sites in the following variables: receiving ECT in lifetime, response to the most recent ECT, DSM-IV diagnostic code, and the number of unsuccessful antidepressant trials and the number of unsuccessful antidepressant trial categories during the current episode. All 12 patients at the Columbia site had received ECT in their lifetime, whereas only 57% (27/47) of the other patients had received ECT ($p = .005$, Fisher's Exact). Moreover, the patients at Columbia did not respond as well to the ECT as the other group of patients. The other major difference between the two groups was the number of unsuccessful antidepressant trials received in the current episode. The Columbia patients did not respond to an average of 6.7 ± 2.5 adequate treatments compared to 4.4 ± 2.6 treatments in the other group of patients, $t(57) = 2.76$, $p = .0078$.

At Columbia the diagnostic distributions were 25.0%, for recurrent, unipolar major depression, 58.3% for single episode unipolar major depression, 8.3% for bipolar I disorder, and 8.3% for bipolar II disorder. At the other sites, the distributions of these diagnoses were 52.1%, 18.8%, 10.4%, and 18.8%, respectively. Relative to the other sites, patients with chronic, single episode unipolar depression had greater representation at Columbia, and patients with recurrent, unipolar depression were less common ($p = .0225$, Fisher's Exact).

It is unlikely that inter-site differences in the reliability of clinical ratings contributed to the site differences. A common set of videotaped $HRSD_{28}$ interviews were scored by the raters at Columbia, who achieved an intraclass coefficient scores of 0.98.

Predictors of Clinical Outcome

The preceding analyses suggested that the somewhat inferior clinical outcome in the second sample may have been related to the fact that the second group of patients had a nearly statistically significant higher proportion of Columbia patients than the first 30 patients ($p = 0.057$, Fisher's Exact). Furthermore, the poorer rate of response observed at Columbia University may have been related to the fact that the patients at this site were characterized by all receiving ECT, the majority not having a positive response to ECT, as well as a significantly higher number of unsuccessful antidepressant trials during the current episode. These factors suggest that the Columbia patients were more resistant to antidepressant treatment than the rest of the sample.

To test these possibilities more broadly, a series of univariate logistic regression analyses were conducted using all 59 patients and the set of demographic, clinical, and treatment factors as predictors of VNS response (≥ 50% reduction in $HRSD_{28}$ scores). As in the analyses of sample and site differences these included all the

variables listed in Tables 1 and 2, as well as history of ever having receiving ECT, outcome of most recent ECT treatment, potency of antidepressant treatment at the outset of the acute study, and VNS output current. Table 8 shows that the following variables were significant in univariate analysis: receiving ECT in lifetime, response to most recent ECT, number of unsuccessful antidepressant trials in the current MDE, and the number of unsuccessful antidepressant trial categories in the current MDE. This analyses suggested that patients who had not responded to a larger number of adequate trials were less likely to respond to VNS. Also, patients who had ECT in their lifetime and/or did not respond well to ECT were less likely to respond to VNS. Indeed, patients who had never received ECT (lifetime) were 3.9 times more likely to respond to VNS.

Those variables, which obtained a p-value $\leqslant .20$ in the univariate analyses were entered into a simultaneous logistic regression analysis, again predicting response. A stepwise approach was used to eliminate potential predictors from the logistic regression model at each step. Using this method, no clear multivariate model emerged to predict response. Therefore, significant effects were only found with the univariate factors mentioned above. To ensure whether these effects were not unduly influenced by the poor efficacy at the Columbia University site and the differences in patients' characteristics at this site, the simultaneous logistic regression was repeated excluding the patients from Columbia University ($n = 47$). In this patient population, none of the tested predictors were statistically significant ($p > .05$) in a univariate model. However, in building the multivariate model using the previously described stepwise method, a multivariate model including baseline weight and ongoing antidepressant medication score were simultaneously significant predictors of clinical outcome ($p = .0129$ and $p = .0189$, respectively). We have no explanation for why baseline weight was a predictor (greater weight was associated with better outcome). The strength of ongoing antidepressant medication is highly correlated with the adequacy of previous treatment trials, and likely reflects the degree of medication resistance of the patient.

It was evident from these analyses that the number of unsuccessful adequate antidepressant treatment trials during the index episode had a powerful relation to VNS outcome. Figure 3 plots the response and remission rates to VNS in the sample of 59 patients as a function of the number of failed trials during the index episode. Among the 13 patients who had not responded to more than seven adequate antidepressant trials, none met response or remitter criteria. On the other hand, the response rate (39.1%) was substantial among patients who showed less profound evidence of treatment resistance ($p = .0057$, Fisher's Exact). Consequently, it appears that VNS is most effective in patients with moderate, but not extreme, levels of resistance to conventional antidepressant treatments.

DISCUSSION

This study found that a substantial proportion of adult outpatients with severe, nonatypical, nonpsychotic, treatment-resistant major depressive episodes responded to VNS. Across the 59 patients the primary measure, a $\geqslant$50% reduction $HRSD_{28}$ scores, yielded a 30.5% response rate. Response rates were 33.9% by

Table 8. Prognostic Factors Investigated in Logistic Regression on $HRSD_{28}$ Response Status ($N = 59$)

Predictor Variable	*p*-value
Investigational site	0.6972
Diagnosis (unipolar/bipolar)	0.9399
Age at implant	0.8369
Gender	0.8102
Baseline weight	0.1399
Length of total Illness	0.3137
Age at onset of current episode	0.3207
Length of current episode[a]	0.3451
Received ECT in lifetime	0.0234
Classification of response to most current ECT	0.0394
Baseline $HRSD_{28}$	0.7946
Baseline GAF	0.2587
Number of mood disorder medications in current episode	0.1015
Number of failed adequate antidepressant trials	0.0125
Number of failed categories of antidepressants	0.0273
Concurrent medication potency score	0.1411
Output current during acute study	0.1301

[a]Natural log of length of current episode used in the analysis to achieve normal distribution.

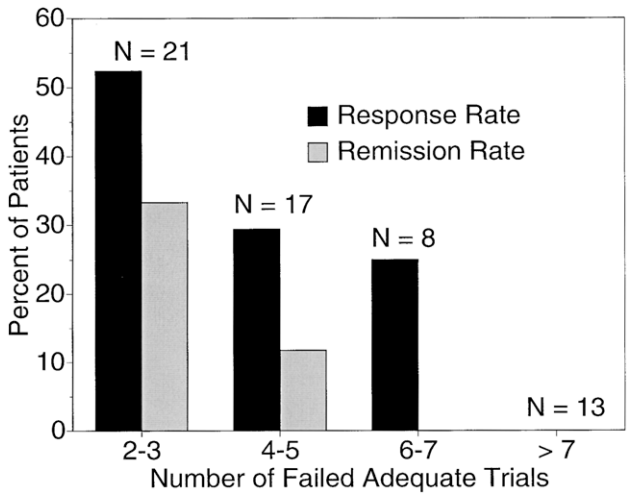

Figure 3. Percent response and remission status (based on $HRSD_{28}$ score criteria) as a function of the number of failed adequate antidepressant treatment trials during the current episode of major depression.

MADRAS criteria and 37.3% by the CGI-I. Full remission ($HRSD_{28} \leqslant 10$) was achieved by 15.3% of the sample. Response was associated with substantial improvements in functional and quality of life indices.

VNS was well tolerated. The overall pattern of side effects during the trial was highly similar to those reported in the studies of epilepsy (Ben-Menachem et al. 1994; Schachter and Saper 1998). The most common side effect was voice alteration during stimulation. The incidence and intensity of this side effect, as well as coughing and pharyngitis, are related to the intensity of the output current. There was no indication in this study that higher output current (the primary electrical parameter manipulated) was related to superior efficacy. Indeed, although not statistically significant, responders (0.81 ± 0.38 mA) tended to receive lower intensity stimulation than nonresponders (1.04 ± 0.59 mA), $t(49) = 1.84$, $p = .07$. Further evidence of tolerability is the fact that only one of 60 patients has elected so far to have the NCP System removed. As seen in Table 7, tolerance developed to many of the side effects of VNS during the acute study, with most adverse events resolving by the end of the acute study period. This is particularly consequential since VNS is intended to be a long-term treatment.

Depending on the measure, between 30–37% of patients showed significant clinical improvement and met response criteria. Since this was an open label, uncontrolled study, it is conceivable that much or all of the improvement reflected a placebo response or spontaneous remission. While this issue can only be definitively settled with a randomized, sham-controlled or multiple dosage design, several considerations strongly argue against this possibility. First, the sample was selected for treatment resistance and, on average, had received approximately 16 different mood disorder treatments during the current episode, thus having had many prior opportunities to manifest a placebo response. Second, the sample was selected in part for chronicity (e.g., current MDE ⩾ two year or ⩾ four MDEs lifetime), with an average episode duration of approximately 10 years. The likelihood of spontaneous remission during the 12 weeks following implantation would seem remote. In addition, unlike the pattern seen with placebo response in MDE (Quitkin et al. 1993, 1998), when symptomatic improvement occurred with VNS it was usually gradual, taking approximately 48 days for patients to meet response criteria. Finally, one bipolar patient on active VNS hypomanic symptoms, leading to alteration of VNS parameters, which also suggests active antidepressant properties.

Patients varied considerably in the type and intensity of concurrent pharmacological treatment they received during the acute VNS trial. It might be argued that the concurrent pharmacotherapy was responsible for much of the clinical improvement. Again, a controlled trial is necessary to rule out this possibility. However, it should be noted that pharmacological regimens had been kept stable for a minimum of 4 weeks prior to the start of the baseline period, which in turn averaged 33.9 ± 17.8 days prior to implantation, and was then followed by a two-week recovery period. Throughout this time, patients had to maintain threshold symptom severity scores to be eligible for implantation and active stimulation. Only one patient fell below this threshold. Thus, it appears that VNS exerts antidepressant effects in some treatment-resistant patients in a MDE.

Perhaps most importantly, this study identified factors that predict VNS clinical outcome. Key among these factors is the degree of treatment resistance manifested during the index episode. One site (Columbia University/New York State Psychiatric Institute) was an outlier with an unusually low rate of response. Patients at this site clearly evidenced the greatest degree of treatment resistance, having both a higher percentage of patients who had both received and failed to benefit from ECT, and the average number of unsuccessful adequate antidepressant trials was highest at this site. More critically, univariate analyses across the sample revealed that predictors of poor VNS outcome were having received ECT (lifetime), the outcome of the most recent treatment with ECT, the number of unsuccessful antidepressant trials in the current episode, and the number of unsuccessful antidepressant trial categories in the current episode (Table 8). Some of these factors were correlated with each other. It would have been useful to also examine psychiatric co-morbidity (especially Axis II) and number of previous episodes as potential predictors of outcome. Data on personality

disorders were not collected, and would, in any case, have been likely distorted by the severity of depressive illness at baseline. It was felt that the information on number of previous episodes was not reliable, since the chronicity and high degree of recurrence in this sample made determination of discrete episodes difficult.

Of the patients who had not responded to two or three adequate antidepressant trials, 50.0% were responders. Of the patients who had not responded to between four and seven trials, 29.1% were responders. In contrast, of the patients who had not responded to more than seven adequate trials in the current MDE, none were responders. This suggests that probability of response to VNS in MDE, at the device settings used in this study, is highly contingent on and graded by degree of resistance manifested in previous antidepressant treatment trials. This relationship is probably not unique to VNS. For instance, it has been repeatedly shown that response to ECT is poorer in patients with established medication resistance relative to patients who come to ECT without having failed an adequate medication trial (Prudic et al. 1990, 1996; Sackeim et al. 2000).

Our findings suggest that VNS may be most appropriate in patients with low-to-moderate, but not extreme, levels of treatment resistance. Except in cases of intolerance to multiple antidepressant strategies, patients with low-to-moderate levels of treatment resistance usually have pharmacological and/or other somatic treatment (e.g., ECT) strategies that have yet to be attempted. Given the finding that VNS is unlikely to be successful as a "last resort" treatment, its role in the care of patients with low-to-moderate levels of treatment resistance will require careful consideration. Foremost is the issue of long-term benefit. Since it involves a surgical procedure, it use is not likely to be attractive if the clinical benefits are short-lived. On the other hand, the naturalistic findings in epilepsy suggest that the therapeutic properties of VNS become more potent with time (George et al. 1994; Salinsky et al. 1996; Morris and Mueller 1999; Vonck et al. 1999; DeGiorgio et al. 2000). The early evidence from the first 30 patients in this trial, although constrained by changes in VNS and pharmacological regimens, suggested a similar phenomenon, with additional patients converting to both responder and remitter status and maintenance of response once achieved (Rush et al. 2000). Now with a longer follow-up period and an enlarged sample, information on the long-term therapeutic effects of VNS will be critical in evaluating its potential. One advantage of VNS in short- and long-term treatment is that adherence is guaranteed, while this is often a problem in pharmacotherapy, particularly with complicated medication regimens.

Another consideration will be differential side effect profiles. The side effects associated with VNS are largely distinct from those of traditional antidepressant and mood stabilizing medications. VNS does not result in sexual dysfunction, dry mouth, urinary retention, weight gain, or other common side effects of psychotropics. Unlike ECT, VNS does not appear to have adverse cognitive effects, with recent evidence demonstrating improvement in some cognitive domains, in concert with symptomatic reduction in depressed patients (Sackeim et al. 2001). The most common side effects of VNS are voice alteration and hoarseness during the period of active stimulation. The experience to date has been that most patients with MDE readily accommodate to the VNS side effects and do not find them bothersome. In some cases, this may also suggest use of VNS relative to other treatment alternatives.

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