Vagus Nerve Stimulation (VNS) for Treatment-Resistant Depressions: A Multicenter Study*

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Background: *Vagus Nerve Stimulation (VNS) delivered by the NeuroCybernetic Prosthesis (NCP) System was examined for its potential antidepressant effects.*

Methods: *Adult outpatients (*n *= 30) with nonpsychotic, treatment-resistant major depressive (*n *= 21) or bipolar I (*n *= 4) or II (*n *= 5; depressed phase) disorders who had failed at least two robust medication trials in the current major depressive episode (MDE) while on stable medication regimens completed a baseline period followed by NCP System implantation. A 2-week, single-blind recovery period (no stimulation) was followed by 10 weeks of VNS.*

Results: *In the current MDE (median length = 4.7 years), patients had not adequately responded to two (*n *= 9), three (*n *= 2), four (*n *= 6), or five or more (*n *= 13) robust antidepressant medication trials or electroconvulsive therapy (*n *= 17). Baseline 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) scores averaged 38.0. Response rates (≥50% reduction in baseline scores) were 40% for both the $HDRS_{28}$ and the Clinical Global Impressions—Improvement index (score of 1 or 2) and 50% for the Montgomery–Åsberg Depression Rating Scale. Symptomatic responses (accompanied by substantial functional improvement) have been largely sustained during long-term follow-up to date.*

Conclusions: *These open trial results suggest that VNS has antidepressant effects in treatment-resistant depressions.* Biol Psychiatry 2000;47:276–286 © *2000 Society of Biological Psychiatry*

Key Words: Vagus Nerve Stimulation (VNS), treatment-resistant depression, bipolar disorder, electrical stimulation

*See accompanying Editorial, in this issue.

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Introduction

Depression is a prevalent, disabling, and often chronic or recurrent psychiatric condition costing the United States economy more than $40 billion per year, of which $12.4 billion are direct treatment costs (Greenberg et al 1993). The 6-month prevalence of depression in the general population is about 5% (Depression Guideline Panel 1993a). Three hundred forty million people worldwide, 18 million of them in the United States, suffer from depression at any one time. Further, depressive episodes usually recur over time, with the risk for further episodes proportional to the number of prior episodes. From 5% to 15% of major depressive episodes last longer than 2 years. Up to 1.5% of the general population suffer chronic or severe depressions (Depression Guideline Panel 1993a; Lopez and Murray 1998). Up to 15% of all people with severe depressions requiring hospitalization eventually commit suicide (Depression Guideline Panel 1993b; Guze and Robins 1970).

Treatment for depression aims at achieving complete symptom remission and complete restoration of day-to-day function, as well as prevention of relapses (return of current episode) and recurrences (new episodes). Numerous antidepressant medications and several forms of empirically documented, time-limited psychotherapies are available. Depression is typically treated with medication, psychotherapy, or a combination of both. Different patients appear to respond to different treatments. A patient who does not respond to one treatment may well respond to another (Crismon et al 1999; Depression Guideline Panel 1993b; Thase and Rush 1995).

At least 10% to 20% of all depressed patients do not have satisfactory sustained responses to present treatments.[1] Treatment resistance may increase with increasing numbers of episodes or increasing episode duration (Depression Guideline Panel 1993b; Thase and Rush 1995). About 100,000 patients annually, most of whom have treatment-resistant depression, receive a course of electro-

[1]Perhaps 1–4% of patients with major depressive episodes attain the level of treatment resistance required of this research sample.

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convulsive therapy (ECT; American Psychiatric Association Committee on ECT, in press; Olfson et al 1998).

Depression is now being recognized as a chronic or recurrent, disabling lifelong illness, rather than an isolated single episode from which lasting recovery can be expected. A well-tolerated treatment that provides both acute symptom relief and longer term benefits for this lifelong illness is needed (Glass 1999).

Vagus Nerve Stimulation (VNS), delivered by the NCP System (Cyberonics, Houston) for treatment-resistant partial-onset seizures in epilepsy, has been commercially available in Europe since 1994 and in the United States since 1997. The idea of using VNS as a treatment for clinical depression was initially based on 1) clinical observations of improved cognition and mood during studies of patients with epilepsy (Handforth et al 1998; Vagus Nerve Stimulation Study Group 1995) and 2) the fact that several anticonvulsant medications, including carbamazepine (Ballenger and Post 1978; Okuma et al 1973), gabapentin (Harden et al 1999a; Letterman and Markowitz 1999), lamotrigine (Calabrese et al 1999; Fatemi et al 1997), and valproate (Swann et al 1997), are used to treat mood disorders. Whereas decreased seizure frequency may have accounted for some mood improvement in patients with epilepsy who were treated with VNS, even some of those with little or no seizure improvement also reported substantial mood improvements (Harden et al 1999b; G. Elger et al, unpublished data, 1999). A detailed rationale for the use of VNS in the treatment of depression is provided in another article in this issue (George et al 2000).

Objectives

Our four-site study assessed the safety and efficacy of VNS in treating patients with treatment-resistant, chronic or recurrent, nonpsychotic, major depressive, bipolar I or bipolar II (both in the depressed phase) disorders. Vagus Nerve Stimulation was used with or without antidepressant medications. We aimed to 1) determine the degree and timing of antidepressant effects, if any, utilizing reliable, clinical assessments; 2) determine the safety and tolerability of VNS in this patient group; and 3) determine whether a randomized safety and efficacy study was warranted.

This open-label, nonrandomized, single-arm study of VNS was designed to enroll up to 45 patients to obtain a total of 30 treated patients who had implants under Investigational Device Exemptions (1980) approval from the United States Food and Drug Administration and appropriate institutional review board approvals.

Recruitment/Consent

All aspects of the protocol were managed in compliance with current United States regulations and international guidelines pertaining to good clinical practices.[2] The protocol and all amendments were reviewed and approved by each study site's institutional review board. Each patient signed a written informed consent.

We selected subjects who had prominent and definitive histories of treatment resistance, which in turn led to a sample with a very chronic prior history characterized by multiple treatment attempts in both the current and previous episodes, to ensure that the risk of an entirely untested intervention requiring surgery would be a logical and ethical consideration for every patient or participant.

Methods and Materials

Study Population

Patients had to have a DSM-IV diagnosis of major depressive disorder (MDD) or bipolar I or II disorder (American Psychiatric Association 1994). They had to be in a major depressive episode (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 his or her lifetime.

Patients also met the following 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 to 1) score ≥3 on the Antidepressant Treatment History Form (ATHF; Oquendo et al 1999; Prudic et al 1990, 1996; Sackeim et al 1990), indicating that they had failed on ≥2 antidepressant medication treatments from different medication classes during the current MDE[3]; 2) have had no substantial clinical improvement with psychotherapy (at least 6 weeks); 3) score ≥20 on the 28-item Hamilton Depression Rating Scale[4] ($HDRS_{28}$; Hamilton 1960, 1967; Williams 1988); 4) score ≤50 on the Global Assessment of Function (GAF; American Psychiatric Association 1994); and 5) have an IQ ≥70 (investigator judgment). Those with bipolar disorder had to have either resistance, intolerance, *or* a medical contraindication to lithium.

Patients were excluded if they had 1) atypical or psychotic features in the current MDE; 2) a history of schizophrenia, schizoaffective disorder, or other non–mood disorder psychosis; 3) rapid-cycling bipolar disorder; or 4) a current secondary diagnosis (or signs) of delirium, dementia, amnesia, or other cognitive disorder (by DSM-IV). Also excluded were patients with clinically significant, current suicidal intent and those with certain risks related to surgical implantation and treatment.

[2]The protocol was conducted in compliance with the *Investigational Device Exemptions Manual* (1996; IDE Number G980099) and was monitored by Cyberonics, Inc.

[3]Medication classes included selective serotonin reuptake inhibitors, heterocyclic antidepressants, monoamine oxidase inhibitors, other antidepressant medications, lithium, electroconvulsive therapy, and anticonvulsants.

[4]The 28-item Hamilton Depression Rating Scale includes atypical symptom features (anergia, hypersomnia, increased appetite, and rejection sensitivity).

Study Overview

All patients followed the same treatment schedule. Following written informed consent, patients completed a "baseline period" (up to 4 weeks) preimplantation during which clinical assessments were performed on two separate occasions. To qualify for implantation, patients had to score ≥20 on the $HDRS_{28}$ during both baseline visits. Patients on medications had to maintain a stable medication regimen for at least 4 weeks prior to the initial baseline visit.[5]

For 2 weeks following implantation, (single-blind "recovery period"), 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." Clinical assessments were performed weekly. Further, during this recovery period, patients had to score ≥18 on the $HDRS_{28}$ for two consecutive visits (7 and 14 days postimplantation) before initiating stimulation.[6]

At the end of the recovery period, the NCP System was turned on and the output current (mA setting) was progressively increased to the maximum, comfortably tolerated level over the next 2 weeks ("stimulation adjustment period"), with clinical assessments performed weekly.

At 4 weeks postimplantation (i.e., after 2 weeks of VNS), stimulation parameters were set and left unchanged for the remaining 8 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 2 weeks and then every other week for another 6 weeks. This "fixed-dose stimulation period" lasted 8 weeks; the total duration of stimulation was 10 weeks.

After completion of the acute study, patients were allowed to continue receiving VNS. All patients are being observed clinically at least 9 months after the acute study exit and for at least 12 months following implantation.[7] During this long-term "follow-up period," either NCP stimulation parameters or concomitant medications may be changed based on investigator or primary physician judgment. As such, follow-up data provide descriptive information as to longer term outcomes.

Treatment

The NCP System implantation technique and the programming sequence used in this study were identical to those used in the studies of treatment-resistant epilepsy. The NCP System includes an implantable and multiprogrammable pulse generator that delivers electrical signals to the left vagus nerve (10th cranial nerve) via the bipolar lead. The pulse generator is programmed via a programming wand attached to a computer, which sets or adjusts stimulation parameters. Additional information about the NCP System has been provided in another article in this issue (George et al 2000).

After completion of the 2-week, postimplantation, single-blind "recovery period," the device was turned on with initial stimulation parameters of 0.25 mA, 20 or 30 Hz,[8] and 500 μsec, with stimulation on for 30 sec every 5 min. At this visit, the output current was increased gradually (in 0.25-mA increments) to allow accommodation to the stimulation until a comfortable tolerance level was reached. After a comfortably tolerated output current was attained, the patient 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 2 weeks. Stimulation parameter settings were determined based on patient tolerance. Investigators were allowed by protocol a range of frequency (e.g., 20–30 Hz), pulse width (e.g., 250–500 μsec), and on/off cycle parameters (e.g., off 3 or 5 min). In general, the stimulation parameters commonly used for epilepsy were used in this study.

Concomitant Therapy

No patient received concomitant ECT, investigational drugs, or treatment with another investigational device during the study. Patients were allowed (but not required) to take antidepressant and/or mood stabilizer medications, as long as the same doses and same medication types were maintained during the baseline period and for 12 weeks following implantation. Medications could be decreased, but not increased, during the acute study. Lorazepam (up to 3 mg/day) was allowed for anxiety and/or insomnia as needed. Other medications (i.e., antibiotics, decongestants, analgesics, and over-the-counter medications) were allowed (though investigators made all reasonable attempts 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 neurologic exams, and presurgical 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 5, 6, 8, 10, and 12 (fixed-dose stimulation period) after implantation. Clinical assessments of depressive symptoms included the $HDRS_{28}$ and the 10-item Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg 1979). Manic/hypomanic symptoms were rated by the Young Mania Rating Scale (Young et al 1978). Overall status and response were gauged by the Clinical Global Impressions—Improvement (CGI-I) and Severity (CGI-S) indices (Guy 1976) and the GAF (American Psychiatric Association 1994). Functional outcomes were also assessed using the Medical Outcomes Study (MOS) 36-item short form (SF-36; Ware and Sherbourne 1992).

Stimulation parameter settings were documented at each visit (and at any additional visit if stimulation parameters were

[5]Patients were allowed to continue stable medication regimen(s) rather than become medication free because 1) the medication(s) had provided some relief that could be lost if discontinued; 2) almost all patients, we believe, would have declined to stop taking even these modestly beneficial treatment(s); and 3) the medication discontinuation symptoms and possible significant clinical worsening were avoided using this scheme.

[6]If patients had scored less than 18, they would have had an extended visit and been observed weekly until the 28-item Hamilton Depression Rating Scale score was 18 or more, at which time the regular visit schedule would have been reinitiated. No patient required extended visits.

[7]After 1 year, patients can still continue to receive treatment.

[8]Standard frequency was changed from 30 Hz to 20 Hz in a protocol amendment—a change not expected to affect clinical outcome.

Table 1. Clinical and Demographic Features ($n = 30$)

	%	Mean ± SD	Median	Range
Female	67			
Caucasian	100			
MDD, recurrent	50			
MDD, single episode	20			
Bipolar I disorder	13			
Bipolar II disorder	17			
Current MDE of ≥2 years	70			
Age (years)		47.5 ± 7.5	47.9	28.6–63.1
Length of current MDE (years)		10.3 ± 12.5	4.7	0.3–49.5
Age at onset of current MDE (years)		37.2 ± 12.4	40.4	8.0–57.6
Length of illness (years)		19.3 ± 13.1	19.6	0.3–49.5

MDD, major depressive disorder; MDE, major depressive episode.

adjusted). During the fixed-dose stimulation period, parameter settings were confirmed by interrogating the pulse generator at each visit. Adverse events and concomitant medications were coded using the *Coding Symbols for Thesaurus of Adverse Reaction Terms* (1995) and *World Health Organization Drug Dictionary* (1999), respectively. Holter monitoring data for at least 12 hours were collected at baseline (between baseline visits 1 and 2) and at the end of acute study (12 weeks postimplantation).

Data Management and Analysis

Cyberonics conducted routine clinical monitoring visits at all 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 (preimplantation) visits (or, for secondary analyses, a ≥50% reduction in baseline MADRS or a CGI-I score of 1 or 2).

Results

Enrollment

A total of 38 patients were enrolled, 30 of whom had implants (Dallas, 14; Charleston, 7; Houston, 6; New York, 3). Of the eight who enrolled but did not have implants, four withdrew consent, one responded to changed medications, and three no longer met the inclusion/exclusion criteria. This report summarizes findings for the 30 patients with implants, all of whom completed the acute study, and the available postacute study (long-term follow-up) outcomes.

Sample Features

Table 1 presents the clinical and demographic features of the sample. The patient population was 67% female. Most (70%) had MDD, and nearly 50% of those with MDD had recurrent MDD. The median length of the current MDE was 4.7 years. Over two thirds (70%) of the patients had been in the current MDE for ≥2 years.

Table 2. Number and Percent of Patients Taking Antidepressant Treatments ($n = 30$)

	Lifetime	Current episode	Acute study
Treatment	*n* (%)	*n* (%)	*n* (%)
Selective serotonin reuptake inhibitors (total)	30 (100)	29 (97)	13 (43)
1	4 (13)	8 (27)	11 (37)
2	7 (23)	8 (27)	1 (3)
3	7 (23)	5 (17)	1 (3)
4	8 (27)	4 (13)	0 (0)
5	4 (13)	4 (13)	0 (0)
Heterocyclics/tricyclics (total)	25 (83)	20 (67)	4 (13)
1	10 (33)	9 (30)	4 (13)
2	2 (7)	2 (7)	0 (0)
3	5 (17)	5 (17)	0 (0)
4	3 (10)	3 (10)	0 (0)
≥5	5 (17)	1 (3)	0 (0)
Bupropion	24 (80)	21 (70)	3 (10)
Venlafaxine	23 (77)	22 (73)	7 (23)
Lithium	23 (77)	19 (63)	4 (13)
Electroconvulsive therapy	19 (63)	17 (57)	0 (0)
Mirtazapine	19 (63)	17 (57)	3 (10)
Monoamine oxidase inhibitors (total)	18 (60)	14 (47)	0 (0)
1	8 (27)	5 (17)	0 (0)
2	8 (27)	7 (23)	0 (0)
3	2 (7)	2 (7)	0 (0)
Trazodone[a]	13 (43)	8 (27)	2 (7)
Nefazodone	15 (50)	15 (50)	4 (13)

[a]"Counted" only if doses exceeded 200 mg/day or patient stated it was not used solely as a hypnotic.

Tables 2 and 3 present the treatment histories (lifetime, during the current episode, and during VNS) of all patients. Over their lifetimes, patients averaged 18.4 ± 7.2 (range = 6–38) antidepressant and mood disorder treatments, of which 10.3 ± 3.7 (range = 4–18) were antidepressant medication trials. Altogether, 63% had received ECT in their lifetime, whereas 57% had received ECT during the current MDE. Ten (33%) had received ECT within 2 years of study entry. Of the 19 patients who had *ever* received ECT, seven had no response (no or minimal symptom reduction), three had partial responses (only modest symptom reduction), eight had transient responses (substantial symptom reduction lasting <2 months), and one had a sustained response.

All patients met or exceeded eligibility criteria by failing at least two robust treatment trials in the current MDE according to the ATHF. To qualify, the agent had to be used at doses with established efficacy for a sufficient period (e.g., at least 4 weeks) to establish that the agent was ineffective. During the current MDE, 30% had failed

Table 3. Number and Percent of Patients Taking Other Mood Disorder Treatments ($n = 30$)

	Lifetime	Current episode	Acute Study[a]
Treatment	*n* (%)	*n* (%)	*n* (%)
Carbamazepine, lamotragine, valproate (total)	20 (67)	19 (63)	5 (17)
1	7 (23)	7 (23)	5 (17)
2	8 (27)	7 (23)	0 (0)
3	5 (17)	5 (17)	0 (0)
Other anticonvulsants (total)	21 (70)	21 (70)	11 (37)
1	13 (43)	13 (43)	10 (33)
2	5 (17)	5 (17)	0 (0)
≥3	3 (10)	3 (10)	1 (3)
Atypical antipsychotics (total)	22 (73)	22 (73)	10 (33)
1	8 (27)	8 (27)	10 (33)
2	8 (27)	8 (27)	0 (0)
3	6 (20)	6 (20)	0 (0)
Stimulants (total)	16 (53)	15 (50)	7 (23)
1	7 (23)	7 (23)	7 (23)
2	7 (23)	7 (23)	0 (0)
3	2 (7)	1 (3)	0 (0)
Repeated transcranial magnetic stimulation	3 (10)	3 (10)	0 (0)
Phototherapy	2 (7)	2 (7)	1 (3)
Thyroid augmentation	13 (43)	13 (43)	1 (3)
Nonatypical antipsychotics (total)	13 (43)	9 (30)	3 (10)
1	7 (23)	5 (17)	3 (10)
2	3 (10)	3 (10)	0 (0)
3	3 (10)	1 (3)	0 (0)
Anxiolytics (total)	26 (87)	25 (83)	15 (50)
1	9 (30)	11 (37)	13 (43)
2	10 (33)	9 (30)	1 (3)
3	6 (20)	4 (13)	1 (3)
4	1 (3)	1 (3)	0 (0)
Other[b]	4 (13)	4 (13)	1 (3)

[a]Treatments received during the period from implantation to acute study exit.
[b]Other treatments included ω3 fatty acids, flax seed oil, etc.

two treatments, 7% had failed three, 20% had failed four, and 43% had failed five or more well-documented treatments that met ATHF criteria. Tables 2 and 3 reveal, in fact, that many more treatment attempts were made, often in combinations, for the current MDE. As a group, the patients were remarkably treatment resistant—resulting in prolonged, severe, and disabling illness.

Concomitant Treatments during the Acute Study

Patients were taking from zero ($n = 5$) to four (median = 1) antidepressant medications while receiving VNS, during the acute study. They were also taking a mean of 3.5 ± 1.7 (median = 4, range = 1–8) other mood disorder treatments while receiving VNS, during the acute study.

To determine if the overall strength of the antidepressant treatment regimen received concomitantly during the acute study was a prognostic indicator of treatment response, a modification of the Antidepressant Resistance Rating (ARR) based on the ATHF ratings was used to calculate the Total Strength of Treatment (TST) score. The individual ATHF ratings for each mood disorder treatment that a patient was taking during the acute study were added together to obtain a TST score. For example, if a patient was taking 525 mg venlafaxine (ARR = 4), 6 mg clonazepam (ARR = 0), and 2 mg risperidone (ARR = 1) during the acute study, then the TST score would equal 5. Medications (as circumstances require) were included in the calculation of the TST, if they were rated at a strength >1 on the ARR. Patients had a mean TST score of 5.8 while receiving VNS during the acute study.

VNS Treatment

All 30 patients had the stimulation parameters set at 500-μsec pulse width and 20- ($n = 25$) or 30-Hz ($n = 5$) frequency for 30 sec on and 5 min off, except for one who received a 250-μsec pulse width and for three others who received stimulation for 30 sec on and 3 min off. Output currents ranged from 0.25 to 3.0 mA depending on patient tolerance (median 0.75 mA).[9] Once the stimulation parameters were set at the end of the 2-week stimulation adjustment period, no patient required stimulation parameter adjustments during the fixed-dose stimulation period. No device malfunctions or complications were encountered.

Symptomatic Outcomes

Figure 1 presents the $HDRS_{28}$ total score at the exit visit for each patient and the percent reduction in the average (two visits) baseline $HDRS_{28}$ in relation to the diagnosis for each patient ($n = 30$). Overall, a 40% response rate was found using a ≥50% reduction in the baseline $HDRS_{28}$ total score to define response.

Table 5 presents the mean scores for each major clinical outcome variable at baseline, recovery, and acute study exit. At exit, according to the CGI-I, 3% were minimally worse, 27% were unchanged, 30% were minimally improved, 20% were much improved, and 20% were very much improved at acute study exit. When complete response is defined as exit $HDRS_{28} \leq 10$, 17% of patients responded completely. Global Assessment of Function scores improved from 40.6 at baseline to 61.9 at acute study exit.

[9]There was no experimentation with alternative stimulation parameters to optimize efficacy during the stimulation adjustment period, since onset of improvement in depressive symptoms, when it occurred, typically took longer than the 2-week stimulation adjustment period permitted by the protocol.

Table 4. Number and Percent of Patients Reporting Adverse Events Occurring in ≥7% of Patients ($n = 30$)

			Stimulation related		
		Surgery related	Possible	Probable	Definite
Body system	COSTART term	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Body as a whole	Incision site pain	9 (30)	0 (0)	0 (0)	0 (0)
	Headache	2 (7)	5 (17)	0 (0)	2 (7)
	Pain	2 (7)	0 (0)	2 (7)	3 (10)
	Chest pain	1 (3)	3 (10)	0 (0)	1 (3)
	Neck pain	0 (0)	1 (3)	2 (7)	2 (7)
	Infection	2 (7)	0 (0)	0 (0)	0 (0)
Respiratory	Voice alteration	2 (7)	1 (3)	3 (10)	12 (40)
	Pharyngitis	1 (3)	2 (7)	4 (13)	1 (3)
	Dyspnea	1 (3)	2 (7)	3 (10)	1 (3)
	Coughing	0 (0)	0 (0)	1 (3)	3 (10)
Digestive	Dysphagia	1 (3)	0 (0)	1 (3)	3 (10)
	Dyspepsia	2 (7)	0 (0)	1 (3)	0 (0)
	Nausea	1 (3)	2 (7)	0 (0)	0 (0)
Nervous	Dizziness	0 (0)	3 (10)	0 (0)	0 (0)
	Hypertonia	1 (3)	0 (0)	0 (0)	2 (7)
	Twitching	0 (0)	0 (0)	2 (7)	0 (0)
Skin and appendages	Rash	1 (3)	2 (7)	0 (0)	0 (0)
Metabolic/nutritional disorders	Abnormal healing	3 (10)	0 (0)	0 (0)	0 (0)
	Edema	2 (7)	0 (0)	0 (0)	0 (0)
Special senses	Ear pain	0 (0)	2 (7)	0 (0)	0 (0)

COSTART, *Coding Symbols for Thesaurus of Adverse Reaction Terms* (1995).

Figure 2 presents the mean $HDRS_{28}$ scores at each study visit for the whole group ($n = 30$) and for responders ($n = 12$) and nonresponders ($n = 18$; defined by the threshold of >50% reduction in the baseline $HDRS_{28}$ total). Separately, for responders ($n = 12$), early effects (i.e., during VNS dose adjustment) are suggested, but more than half of the total reduction from 39.1 (average at baseline) to 12.3 (average at exit) for responders occurred over 6 of the 8 weeks of fixed-dose VNS. No patient responded during the 2-week, postimplantation (no stimulation), single-blind recovery period, using the $HDRS_{28}$ to define response ($n = 12$), with six of the 12 patients (50%) who

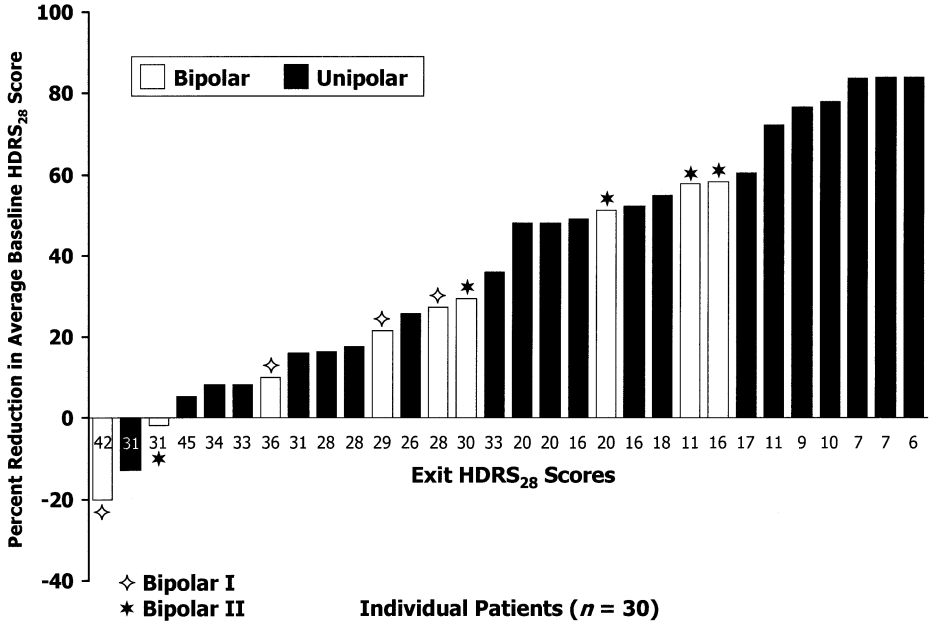

Figure 1. Response by diagnosis (unipolar and bipolar) and exit 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) score.

Table 5. Major Clinical Outcomes

Rating Scale	Baseline period[a]	Recovery period[b]	Acute study exit
$HDRS_{28}$	38.0 ± 5.5	36.6 ± 6.6	23.0 ± 10.8
MADRS	33.8 ± 5.6	32.5 ± 7.1	20.1 ± 12.2
CGI-I[c]	NA	0%	40.0%
CGI-S	5.3 ± 0.7	5.1 ± 0.7	3.7 ± 1.4
GAF	40.6 ± 6.8	43.2 ± 9.8	61.9 ± 16.8
YMRS	2.3 ± 1.3	2.2 ± 2.1	1.9 ± 3.4

Results are means ± SDs or %. $HDRS_{28}$, 28-item Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-I, Clinical Global Impressions—Improvement; CGI-S, Clinical Global Impressions—Severity of Illness; GAF, Global Assessment of Functioning; YMRS, Young Mania Rating Scale.

[a]Calculated as the average of visits 1 and 2.
[b]Calculated as the average of visits 4 and 5.
[c]Reported as the percentage of patients with a score of 1 or 2.

ultimately responded doing so by week 5 following implantation.

Effect on Function

Table 6 presents the MOS SF-36 overall and subscale results (baseline to exit) for all patients, as well as separately for responders and nonresponders (defined by ≥50% reduction in baseline $HDRS_{28}$). Note that baseline function was remarkably low (e.g., role emotional = 6.9, role function = 41.4, vitality = 9.0, social function = 22.0, etc.). Response (by $HDRS_{28}$) was associated with highly clinically significant increases in the mental component, role function, vitality, social function, role emotional function, and mental health. Nonresponders did not change (save for a statistically significant increase in social function of 10 points). Of the 12 responders, 25% achieved exit role emotional ratings that equaled or exceeded population norms, indicating that these patients achieved normal functioning.

Which Patients Respond to VNS?

A logistic regression analysis was conducted using $HDRS_{28}$ response and the following prognostic factors: $HDRS_{28}$ total baseline score, diagnosis (major depressive or bipolar disorder), length of index MDE, total length of illness, age, prior ECT response, VNS stimulation output current, and TST score. A univariate model indicated that the only potentially significant factors concerned prior ECT response and VNS stimulation output current (mA); however, the relationship between ECT response and VNS response did not reach statistical significance ($p = .10$) in a multivariate model that included both ECT response and output current. Lower levels of VNS stimulation output current were associated with better treatment response ($p = .07$) in the same multivariate model.

Of seven patients not responding at all (either partially or transiently) to ECT, only one responded to VNS. Within the five categories of ECT response, the logistic regression odds ratio was strongest when patients who had completely failed to respond acutely to ECT were compared with all other patients (i.e., those who never had ECT combined with those with transient or partial responses).

Adverse Events

No patient discontinued the acute study due to adverse events. Reported adverse events were similar to those in

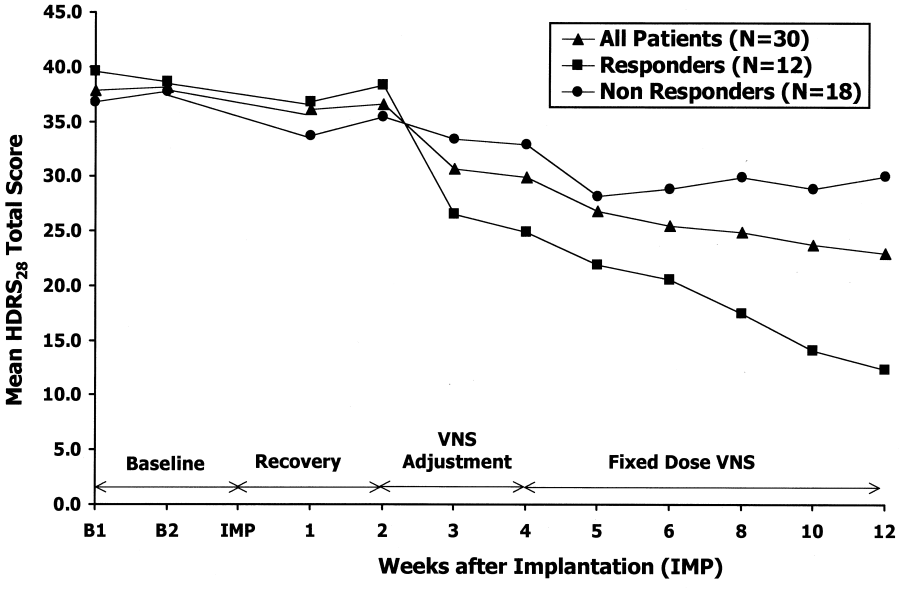

Figure 2. Mean 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) score during acute study.

Table 6. Mean Scores on the Medical Outcomes Study 36-Item Short Form

	Overall (n = 29)		Responders (n = 12)		Nonresponders (n = 17)	
Variable	Baseline	Exit	Baseline	Exit	Baseline	Exit
Mental component[a]	18.8	29.5[b]	17.2	39.9[b]	19.9	22.5
Physical component[a]	44.6	44.1	46.2	46.0	44.1	42.7
Subscales						
Physical function	55.0	61.1[b]	56.7	68.0	55.3	56.2
Role function	41.4	48.3	31.3	66.7[b]	51.4	35.3
Pain index	51.9	54.8	56.4	61.8	47.7	49.8
Health perceptions[a]	49.4	54.0	56.3	63.1	46.5	47.6
Vitality improvements	9.0	25.3[b]	7.1	43.3[b]	12.5	14.7
Social function	22.0	42.7[b]	24.0	61.5[b]	19.4	29.4[b]
Role emotional	6.9	26.4	5.6	47.2[b]	11.1	11.8
Mental health	24.7	42.0[b]	20.7	60.9[b]	26.2	28.7

[a]One patient did not fully complete the questionnaire.
[b]Statistically significant percent change from baseline using $p < .05$ and paired t test.

previous studies of epilepsy (Table 4). Some adverse events were related to implantation and stimulation, with most of the treatment-related adverse events being stimulation related. Nine patients (30%) reported pain at the incision site, which typically dissipated over 1 to 2 weeks. The most common events reported as possibly, probably, or definitely related to stimulation were hoarseness (60%), throat pain (27%), headache (30%), shortness of breath (23%), general pain (23%), and neck pain (17%). All events had been reported with VNS in previous epilepsy studies (Handforth et al 1998; Vagus Nerve Stimulation Study Group 1995)—although headaches were not as commonly associated with stimulation in the epilepsy trials. In general, stimulation-related adverse events (including hoarseness and throat pain) were mild and well tolerated, and they occurred only when stimulation was on. One patient developed hypomania, which subsided with stimulation reduction.

Additionally, three patients (10%) reported abnormal wound healing, which involved a longer time for implant incisions to heal. All patients' wounds healed without significant intervention. These events all occurred at one site; the surgeon has since modified his incision closure technique. After implantation, two patients (7%) at one site experienced rashes, which eventually subsided.

Six clinically significant adverse events occurred, five during the acute study and one during the long-term follow-up. One event, infection, was related to implantation. Two separate events of leg pain reported by one patient may have been related to implantation. Two events (agitation/panic during the acute study and agitation/irritability/dysphoria in the long-term follow-up) were reported as possibly related to stimulation. One event of worsened depression due to benzodiazepine withdrawal was reported as not related to stimulation.

Safety Testing and Post–Acute Study Follow-Up

Twenty-four-hour Holter monitor results revealed no significant cardiac changes when comparing baseline with acute study exit recordings. Nearly all patients (29/30, 97%) have continued to receive VNS treatment after exiting the acute study. One patient had the NCP generator explanted after 10.8 months of follow-up, due to an inability to sustain antidepressant effects at levels of stimulation that were comfortable. To date, all 10 patients who responded acutely and for whom follow-up data are available have maintained response (Table 7), though two patients experienced a transient worsening on one follow-up occasion. Recall that changes to stimulation parameters and mood-stabilizing medications were both permitted and made during follow-up. At their most recent follow-up visits, seven of these 10 acute study responders demonstrated a complete response ($HDRS_{28} \leq 10$).

Discussion

This is the first report of VNS in adult outpatients with severe, nonpsychotic, treatment-resistant MDEs. Response rates of 40% (by $HDRS_{28}$ and by CGI) or 50% (MADRS), as well as the 17% complete response (remission) rate (exit $HDRS_{28} \leq 10$), suggest efficacy in this very treatment-resistant population. Responses occurred between 1 and 10 weeks following the initiation of stimulation.

To date, all of the 10 responders for whom we have follow-up visit data after acute study exit have basically sustained the response status over the 4–9 months following implantation. Additionally, as of the most recent follow-up visit, seven of these 10 acute-phase responders have attained or remained in remission ($HDRS_{28} \leq 10$). No significant correlates of VNS response were found, though a larger sample is needed to evaluate both prior

Table 7. Summary of the 28-Item Hamilton Depression Rating Scale Scores during Long-Term Follow-Up for Responders ($n = 10$)

Baseline average	Acute exit	Follow-up (months)					
		1	2	3	4	5	6
41	20 (51)	—	13 (68)				
43	7 (84)	—	—	4 (91)	—	—	1 (98)
40	18 (55)	—	—	16 (60)			
38.5	9 (77)	—	—	2 (95)	9 (77)		
37.5	6 (84)	—	—	14 (63)	8 (79)		
45.5	10 (78)	—	—	26 (43)	5 (89)		
43	17 (61)	21 (51)					
33.5	16 (52)	8 (76)	2 (94)				
26	11 (58)	24 (8)	6 (77)				
43.5	7 (84)	1 (98)					

Percent improvement from baseline is shown in parentheses. Dash (—) indicates that visit was not performed.

ECT response and output current (mA) settings as potential predictors. Studies of VNS in epilepsy have found no relationship between response and output current. Failure to respond at all (i.e., not even partially or transiently) to prior ECT may be a possible predictor of nonresponse to VNS, as might higher stimulation currents. A larger sample is needed.

Adverse events were no different than those previously noted with VNS in patients with epilepsy. No patients discontinued VNS due to adverse events. Most typically occurred only while stimulation was on. No serious, unanticipated adverse events occurred during the study. One patient developed hypomania that resolved with a reduction in stimulation.

Given the small sample size, these findings are preliminary. Furthermore, ratings were not blinded. However, symptomatic responses were accompanied by very substantial improvements in overall function based on the MOS SF-36, which corroborates the symptomatic ratings.

In addition, there was no control group. Without a randomized, sham-control group, one cannot draw definite conclusions about effectiveness in this patient population. However, the severe, chronic, disabling, and treatment-resistant nature of the depressive episodes in this patient sample suggests that only 5–10% of these patients would have been expected to improve spontaneously or to respond to any established treatment during the 3 months following implantation (Sackeim et al 1993; Thase and Rush 1995). The response rate that was found (i.e., 40%) substantially exceeds these expectations.

Although neither spontaneous improvement nor a placebo response can be absolutely excluded without a control group, several points argue against such effects in this study. First, no patient responded in the 2-week, postimplantation, single-blind recovery period. In fact, no change in $HDRS_{28}$ average scores between baseline (preimplantation) and recovery was found. This finding suggests that the responses obtained were due neither to the passage of time nor to the nonspecific effects of the treatment process. Second, the nature of the sample itself, with prolonged, index MDEs aggressively treated before study entry, argues against nonspecific effects causing these results.

Third, the follow-up data suggest that patients who initially improved retained that improvement after acute study exit. A pattern of sustained benefit is unlikely to be a "placebo response" (Quitkin et al 1991; Shea et al 1992; Thase and Rush 1995). Underlying chronic depression and three or more previous affective episodes predict a statistically significant increase in the rate of relapse (Keller et al 1982), so significant relapse would be expected for this population. Since all responders to date have sustained the acute improvements in the longer term, VNS appears to provide ongoing benefit for those who do respond. In fact, relapse rates of 20–30% have commonly been reported in patients with far less severe, nonresistant major depression while in continuation or maintenance medication treatment studies (Doogan and Caillard 1992; Feiger et al 1999; Montgomery et al 1988, 1993; Montgomery and Dunbar 1993; Versiani et al 1999). Relapse rates were even higher (up to 50%) among patients who receive ECT (Sackeim 1994; Sackeim et al 1990; Shapira et al 1995). For patients who are medication resistant but who respond to ECT, relapse rates are even higher than for those who are less medication resistant (Devanand et al 1991; Prudic et al 1990; Sackeim et al 1990).

Other findings suggestive of antidepressant activity include 1) the onset of hypomania in one patient, 2) the fact that two of the five (40%) patients taking no antidepressants responded (equivalent to the overall response rate), and 3) that the trend suggesting lower rather than higher current settings may be associated with a better response (nonblinded investigators would be biased toward expecting higher settings to be more effective).

This study of VNS delivered by the NCP System in the treatment of patients with severe treatment-resistant depression encourages further investigation of the safety and efficacy of VNS in treatment-resistant depression, especially because the acute benefits of VNS seem to persist. Further studies are needed to determine if, as in epilepsy, benefits beyond those obtained acutely accrue over time.

Future studies should likely give consideration to the following questions:

1. Can nonresponders to VNS during the acute study become responders after long-term treatment with changes in stimulation parameters?
2. Does VNS continue to provide ongoing, sustained symptom relief over months or years following acute phase response?
3. Are there "predictors" or "correlates" of response or of time to response?
4. Can medication amounts or types be reduced or eliminated once a stable, sustained response to VNS is obtained?
5. Where does VNS fit into treatment algorithms for managing major depressive or bipolar disorder?

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