Effectiveness and Safety of Vagus Nerve Stimulation for Severe Treatment-Resistant Major Depression in Clinical Practice After FDA Approval: Outcomes at 1 Year

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ABSTRACT

Objective: To describe the outcomes of a consecutive series of depressed patients treated with vagus nerve stimulation (VNS) following US Food and Drug Administration (FDA) approval of this intervention.

Method: We implanted a VNS device in 15 consecutive outpatients with treatment-resistant major depressive episodes, including 10 with major depressive disorder and 5 with bipolar disorder (*DSM-IV* criteria), between November 2005 and August 2006. Existing antidepressant treatment remained fixed as far as clinically possible. The primary outcome was change from baseline in the Beck Depression Inventory (BDI) score. Outcomes were assessed at 6 and 12 months postimplant and compared to those of the VNS pivotal efficacy trial that led to FDA approval of VNS.

Results: The BDI score decreased significantly compared to baseline at 6 months ($P < .05$) and 12 months ($P < .01$), from a mean of 37.8 (SD = 7.8) before VNS activation to a mean of 24.6 (SD = 11.4) at 12 months. By 1 year, 28.6% (n = 4) of the sample responded to VNS and 7.1% (n = 1) remitted according to the BDI. Secondary outcomes on the Hamilton Depression Rating Scale 24-Item showed similar improvement at 1 year, with a 43% response rate (n = 6) and 14.3% remission rate (n = 2). No obvious predictors of response were detected. Side effects of VNS included hoarseness (73%), dyspnea (47%), nausea (40%), pain (33%), and anxiety (20%); no patient terminated treatment due to intolerable side effects.

Conclusions: We found that a substantial minority of patients with extremely difficult-to-treat depressive disorders benefited from VNS in an ambulatory clinical practice, with outcomes comparable to those observed in previous VNS efficacy studies and with a similar side effect profile.

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Vagus nerve stimulation (VNS) is a medical technology for treatment-resistant depression (TRD) that uses an implanted device to stimulate neural networks in the brain. VNS has been in clinical use in the United States since 1997 for the treatment of partial-onset seizures. In 2005, VNS was approved by the US Food and Drug Administration (FDA) as an adjunctive therapy to medications for treatment of nonpsychotic unipolar or bipolar depressive episodes that have failed to respond to at least 4 adequate antidepressant trials.[1]

The VNS device is typically implanted by means of an ambulatory surgical procedure and consists of a pulse generator, a lead, and an electrode. The generator is implanted subcutaneously in the infraclavicular region, and the electrode is wrapped around the left vagus nerve in the neck. Electrical impulses from the pulse generator stimulate afferent fibers of the vagus nerve, which then carry impulses to the nucleus tractus solitarius in the brain stem. The nucleus tractus solitarius establishes connections to other brain regions including limbic structures, the locus ceruleus, and the raphe nuclei.[2,3]

Such connections may explain the effects of VNS in regulation of mood and emotion. The first clinical observation of VNS effects on mood occurred in patients treated with VNS for epilepsy.[4] These patients showed mood improvements that were independent of the effects of VNS on seizure activity. Subsequent open-label pilot work in patients with TRD (n = 60) reported an encouraging response rate of 30.5% after 10 weeks of VNS.[5] However, when VNS stimulation was tested under randomized, controlled conditions (n = 235), the response rate after 10 weeks of VNS (15.2%) was not statistically significantly different from that of the control sham stimulation condition (10%, $P = .25$).[6] At 12 months, with VNS administered under open-label conditions following the 10-week double-blind phase (n = 205), there was further improvement, with a response rate ultimately of 27.2% and a remission rate of 15.8% on the Hamilton Depression Rating Scale 24-Item (HDRS-24).[7] These were significantly better than that in a matched, but nonrandomized, control group of non-VNS patients (n = 124) with TRD who received treatment as usual.[8]

VNS is now FDA approved on the basis of the longer-term efficacy data, but to date no outcomes have been reported regarding its effectiveness in clinical practice. The question of whether VNS is helpful to nonresearch, treatment-seeking patients in the psychiatrist's office is still open. We assessed the effectiveness and tolerability of VNS in a consecutive series of adult patients with TRD (unipolar or bipolar) who received the VNS implant at our university hospital in the first 18 months after the FDA approval. We hypothesized that VNS would improve depression outcomes in TRD patients at 1 year compared to baseline and that it would be well tolerated. A secondary exploratory hypothesis was that the rate of hospitalization for depression and frequency of suicide attempts would be reduced in the year postimplantation as compared to the 12 months preceding.

METHOD

Study Participants

This study included 15 men and women who received VNS implants for the treatment of depression and were followed up at the VNS outpatient clinic at the University of Pennsylvania Health System. All had a *DSM-IV* diagnosis of major depressive disorder (MDD) or bipolar disorder and were currently in a major depressive episode. Patients who had received VNS implants at another institution or who had a primary diagnosis of a psychiatric condition other than MDD or bipolar disorder, or psychotic features in the current episode, were excluded. Otherwise, there were no other exclusion criteria because the study intended to assess the effectiveness of VNS in standard conditions of clinical practice.

Subjects were referred to the VNS clinic from regular outpatient psychiatric practice at the University of Pennsylvania, were referred from psychiatrists in the community, or were self-referred. This study was not funded, and no industry input or support was received in any way. The Institutional Review Board of the University of Pennsylvania approved the study. All study participants signed a written informed consent form in advance of participation.

VNS Treatment

All subjects had an initial evaluation with an attending psychiatrist with expertise in treatment-resistant mood disorders. The psychiatrist determined the severity of depression and history of resistance to treatment of the current depressive episode. Subjects whose depression was judged clinically severe, with a documented history of nonresponse to a minimum of 4 adequate antidepressant trials in the lifetime, were considered appropriate for VNS therapy. Adequacy of prior antidepressant trials was based on the criteria operationalized by Sackeim[9] in the Antidepressant Treatment History Form. A course of electroconvulsive therapy (ECT) was considered adequate if there was a minimum of 6 sessions, either unilateral or bilateral. We did not use a formal depression rating scale to specify a minimum level of depression severity as an inclusion criterion because we intended to recruit patients in the standard conditions pertaining to clinical practice. In this scenario, the use of formal depression scales is uncommon, and depression severity is usually determined by clinician judgment.

This study did not cover the cost of the VNS device or implantation, and patients were not required to participate in this trial to receive VNS therapy. All patients' devices and implants were covered by their medical insurance carrier or Medicare because these patients had sought VNS treatment independently of the trial and their need for treatment was in accordance to the FDA indication for VNS. Once patients had received the VNS implant, they elected to enroll in this trial. Surgery to implant the VNS device was performed by the neurosurgery team at the Hospital of the University of Pennsylvania. Subjects returned to the clinic within 2 weeks for activation of the VNS device. This activation visit was considered baseline for the outcome measures.

All subjects remained on treatment with existing antidepressants, which were held fixed as far as clinically possible, with VNS added adjunctively. Subjects were instructed to schedule visits as clinically indicated; however, outcome measures were administered at baseline and 6 months and 1 year after the VNS implant. Data regarding other variables including demographics, course of illness, and prior treatment history were obtained from the medical records at the outpatient clinic and from treatment records from prior providers.

Outcome Measures

Primary. The primary outcome was change from baseline in Beck Depression Inventory (BDI)[10] score at 6 and 12 months. Baseline (month 0) was defined as the office visit after surgery for activation of the VNS device (usually 2 weeks postimplant). This was judged to be more stringent than selecting the presurgery psychiatric visit as the baseline as it would exclude any improvement occurring as a positive psychological response to surgery itself. We chose the BDI as the primary outcome measure because it is a validated and reliable instrument to assess the level of depressive symptoms.[10] Additionally, in our previous experience using the instrument, we have found it efficient in monitoring depressive symptoms in a busy outpatient clinic. Furthermore, as the BDI is a self-report measure, we felt it would be less subject to the effects of the treating clinician's expectation bias. Clinical response was defined a priori as at least 50% decrease in the BDI endpoint score compared with baseline. Remission was defined as a score ≤ 9 on the BDI at 12 months.

Secondary. Secondary mood outcomes were categorical outcomes (response and remission rates) on the BDI and changes in the Hamilton Depression Rating Scale 17-Item (HDRS-17),[11] HDRS-24, and Clinical Global Impressions-Improvement scale (CGI-I)[12] scores. For the HDRS-17 and HDRS-24, clinical response was defined as at least 50% decrease in baseline score, and remission was defined as a score ≤ 7 for the HDRS-17 and ≤ 9 for the HDRS-24. Response for the CGI-I was defined as a score of 1 (very much improved) or 2 (much improved). Other secondary outcomes included the Beck Anxiety Inventory (BAI),[13] Beck Hopelessness Scale (BHS),[14] and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[15] The numbers of hospitalizations and suicidal attempts in the 12-month period pre- and post-VNS were collected as additional potential indicators of important clinical benefit.

Statistical Software

Statistical analysis was performed using SAS, Version 9.1.3 (SAS Institute, Inc; Cary, North Carolina).

Statistical Analysis Plan

The significance of the differences between baseline and follow-up means was assessed using a paired *t* test and the Wilcoxon signed rank test for normally distributed and nonnormally distributed outcomes, respectively. A mixed-effects model using SAS PROC MIXED was used to impute missing

data at either baseline or the follow-up period. In this model, the longitudinal outcome measured at months 0, 6, and 12 was regressed on time from baseline. Time was treated as a fixed effect, and in addition there were 2 random effects, a random intercept and slope, which represent patient-level deviation from fixed-effect intercept and slope, respectively. Best Linear Unbiased Prediction (BLUP) estimators were used to estimate parameters.

To evaluate for confounding variables, mixed-effects models were used to evaluate the effect of baseline outcome on postbaseline outcome at 6 or 12 months. Models in which there was a significant effect of baseline outcome on the postbaseline outcome were adjusted for an additional demographic or clinical course variable. Covariates that were found to render the association of the baseline outcome on the postbaseline outcome insignificant were considered confounders.

A random intercepts multivariate model was used to test whether VNS settings, including current, duty cycle, and pulse width (130 vs >250 microseconds), were associated with primary or secondary outcomes measured at 6 and 12 months. The effect of each of the VNS setting variables on outcome was assessed in a separate model. These models also adjusted for the number of months after baseline. For VNS setting variables found to be significantly related to outcome, we examined if any demographic or clinical course variables confounded the effect of VNS setting on outcome. Two-tailed *P* values were used for all statistical tests. Statistical significance was set at 5%.

RESULTS

Sample Characteristics

A total of 15 consecutive patients received implants between November 2005 and August 2006. Thirteen patients completed 1 year of follow-up in the outpatient clinic. One subject, whose depression improved, moved out of the area after 6 months' follow-up, and another dropped out of treatment and was unwilling to attend follow-up assessments. Table 1 shows the clinical characteristics of the sample. The mean age of the sample was 49 years (SD = 10.0), with 9 women and 6 men. All participants were white. Ten suffered from unipolar depression, and 5 had bipolar depression.

Table 1. Comparison of Clinical Characteristics in the Present Study (N = 15) and the Pivotal Study of VNS + TAU Versus TAU (N = 205)

Variable	Present Study	Pivotal Study[a]	*P* Value
Age, mean (SD), y	49 (10.0)	46.3 (8.9)	.36
Sex			
Male, %	40	36	.78
Female, %	60	64	
Unipolar, %	66.7	90	.019
Bipolar, %	33.3	10	
Length of current MDE, mean (SD), mo	63.8 (78.8)	49.9 (52.1)	.51
Chronic (>2 y) current MDE, %	86.7	68	.16
ECT exposure, %			
Lifetime	86.7	53	.014
During current MDE	66.7	35	.023
Age at onset of first symptoms of illness, mean (SD), y	17.2 (10.9)	21.8 (11.9)	.14
Duration of illness, mean (SD), y	31.7 (11.1)	25.5 (11.9)	.056
No. of lifetime episodes of depression, %			
≤2	13.3	24	<.001
3–5	13.3	34	
6–10	6.7	27	
>10	66.7	9	
Unknown	0	5	
No. of lifetime suicide attempts, mean (SD)	2.13 (2.95)	0.61 (1.08)	.070
No. of suicide attempts, %			
Lifetime			
0	46.7	68	
1	20.0	17	
2	0	7	
3	6.7	4	
4	6.7	2	
5	0	2	
7	13.3	0	
8	6.7	0	
10	0	<1	
Within 12 mo prior to VNS			
0	86.7	>99	.013
1	6.7	<1	
2	6.7	0	
Treatment-induced hypomania or mania, %	6.6	8	.99
No. of lifetime prior hospitalizations for mood disorders, mean (SD)	7.3 (7.3)	2.7 (5.4)	.031

[a]Data from George et al.[8]
Abbreviations: ECT = electroconvulsive therapy, MDE = major depressive episode, TAU = treatment as usual, VNS = vagus nerve stimulation.

Illness Severity and Treatment-Resistant Depression Status

Our patients had a high degree of illness severity as evidenced by the mean length of the current major depressive episode (63.8 months) and by the high percentage of ECT failure. Prior to VNS implantation, 10 (66.7%) had received ECT without benefit in the current episode; 3 other patients had received ECT during a previous episode.

Effectiveness

Primary outcome. The mean BDI score at 1 year (24.6, SD = 11.37) was 35% lower than the mean baseline BDI score (37.8, SD = 7.78) (Figure 1). Paired *t* tests carried out between baseline and posttreatment visits found a significant difference between baseline and postbaseline BDI values at 6 months ($t_{13} = 2.69$, $P < .05$) and 12 months ($t_{13} = 3.92$, $P < .01$). In the mixed-effects model, there were no variables that confounded the effect of baseline BDI score on postbaseline BDI score.

Secondary outcomes. Regarding categorical outcomes on the BDI, the response rate was 21.4% (3 of 14) at 6 months and 28.6% (4 of 14) at 1 year. There were 2 remitters at 6 months (14.3%) and 1 at 12 months (7.1%). Figure 2 shows BDI, HDRS-17, HDRS-24, and CGI-I scores at baseline, 6 months, and 12 months. HDRS-17 scores decreased significantly from baseline to posttreatment with VNS at both 6 months ($t_{13} = 5.57$, $P < .0001$) and 1 year ($t_{13} = 4.64$, $P < .001$). Mean HDRS-17 scores fell by 9.9 points over the year, representing a 45% reduction in depression severity in the sample. Mean HDRS-17 score at 1 year was 12.3 (7.0) versus a mean HDRS-17 score at baseline of 21.9 (4.2). Since there was no significant effect of baseline HDRS-17 score on the 12 month

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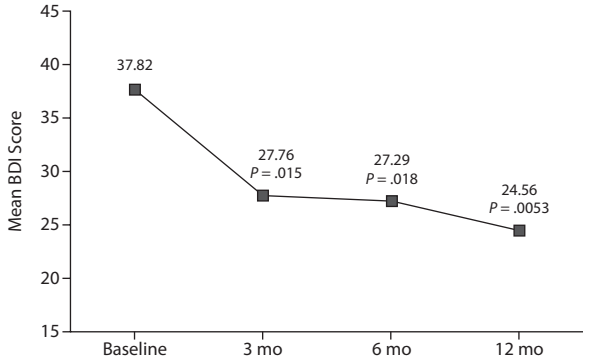
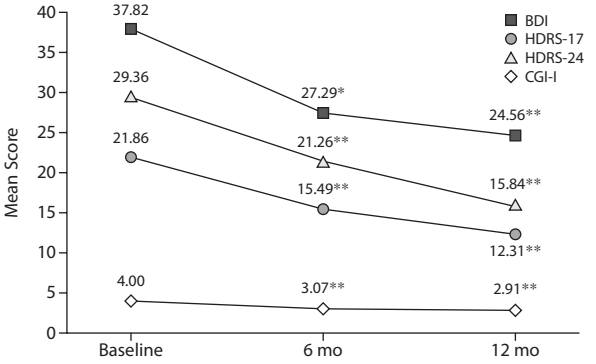
Figure 1. BDI Scores From Baseline to Endpoint in Patients With Treatment-Resistant Depression Receiving VNS (n = 14)



Abbreviations: BDI = Beck Depression Inventory, VNS = vagus nerve stimulation.

Figure 2. Comparison of All Disease-State Scale Outcomes (HDRS-17, HDRS-24, CGI-I, and BDI) in Patients With Treatment-Resistant Depression Receiving VNS (n = 14)



*$P < .05$.
**$P < .01$.
Abbreviations: BDI = Beck Depression Inventory, CGI-I = Clinical Global Impressions-Improvement scale, HDRS-17 = Hamilton Depression Rating Scale 17-Item, HDRS-24 = Hamilton Depression Rating Scale 24-Item, VNS = vagus nerve stimulation.

HDRS-17 score in the mixed-effects model, there was no need to examine for potential confounders.

Likewise, the HDRS-24 score was significantly lower at 6 months ($t_{13} = 4.84$, $P < .001$) and 12 months ($t_{13} = 5.26$, $P < .001$). At 1 year, mean HDRS-24 scores fell by 13.6 points, indicating a 46% level of improvement. Mean 1 year HDRS-24 score was 15.8 (8.9) versus a mean baseline HDRS-24 score of 29.4 (4.6). Since there was no significant effect of baseline HDRS-24 score on 12 month HDRS-24 score in the mixed-effects model, there was no need to examine potential confounders.

According to the HDRS-17, 6 subjects (43%) were responders and 3 subjects (21.4%) met criteria for remission after 1 year of VNS treatment. Similarly, according to the HDRS-24, 6 subjects (43%) responded and 2 subjects (14.3%) met criteria for remission after 1 year of VNS treatment.

With respect to CGI-I scores, 6 patients (42.9%) were much or very much improved (rating of ≤ 2) at the end of 1 year. Other secondary outcomes including the BAI, BHS, and Q-LES-Q did not change at 6 months or 1 year postimplant.

Hospitalizations and Suicide Attempts

Comparison between the mean number of hospitalizations in the 12 months prior to VNS therapy and the year after showed a decrease from a mean of 1.33/patient/year before to 0.86/patient/year after VNS therapy, a 35% reduction; however, this change was not statistically significant ($P = .22$). Similarly, the mean number of suicide attempts decreased overall from baseline in the year after surgery. The mean number of suicide attempts was 0.20/patient/year at baseline versus 0.13/patient/year in the year after VNS, a 35% reduction, but, again, this reduction did not reach statistical significance ($P = .58$).

The Wilcoxon signed rank test was used to further assess differences between the 12 months before and after VNS therapy. The median (25%–75% interquartile range) in the 12 months prior to VNS was 1.00 and remained the same after 1 year, with a median of 1.00. No statistically significant differences were found between hospitalizations before and after VNS (Wilcoxon signed rank = −7.5, $P = .39$).

In terms of suicidal attempts 12 months before and after VNS, the median (25%–75% interquartile range) in the 12 months prior to VNS was 0.0 and did not change after 1 year of VNS therapy, with a median of 0.0. No statistically significant differences were found in number of suicidal attempts before and after VNS (Wilcoxon signed rank = −1, $P = .99$).

Predictors of Response

Analysis of possible predictors of clinical response, per the 1 year BDI score, was conducted using logistic regression examining demographic and clinical variables including age, sex, diagnosis (unipolar versus bipolar depression), ECT exposure in the current major depressive episode (MDE), lifetime history of ECT, duration of the current MDE (months), duration of illness (years), duration of diagnosis (years), lifetime number of MDEs, and baseline BDI score significantly predicted response at 12 months. None of these variables were significantly associated with BDI improvement at the .05 level, but exposure to ECT in the current MDE had a marginally significant association with BDI response (OR = 10.50; 95% CI, 0.67–165.05). In other words, although the difference was not statistically significant, those who received ECT during the current MDE were more likely to be VNS responders according to the BDI.

Adverse Events

There were no serious adverse events related to surgery. Adverse events were similar to those reported in other VNS studies and included hoarseness (73%), dyspnea (47%), nausea (40%), pain (33%), and anxiety (20%) (Table 2). Other side effects such as cough, chest tightness, sore throat, dysphagia, and earache, among others, were also reported (6.7% each). These side effects were judged generally to be mild in

Table 2. Side Effects of Vagus Nerve Stimulation (n = 15 patients)

Side Effect	n	%
Hoarseness	11	73.3
Dyspnea	7	46.7
Nausea	6	40.0
Pain	5	33.3
Discomfort	4	26.7
Anxiety	3	20.0
Other[a]	1 (each)	6.7

[a]Cough, chest tightness, stridor, laryngism, reflux, sore throat, sweating, earache, dysphagia, snoring, tingling.

Table 3. Vagus Nerve Stimulation (VNS) Dosing in the Present Study and the Pivotal Study of VNS + TAU Versus TAU

Parameter	Present Study, Median at 6 mo	Present Study, Median at 1 y	Pivotal Study: VNS + TAU, Median[a]
Output current, mA	1.5	1.3	1
Signal frequency, Hz	30	25	20
Pulse width, microseconds	250	220	500
On time, seconds	30	21.6	30
Off time, minutes	3	1.1	5
Duty cycle (% On time)	27	34.8	10

[a]Data from Rush et al.[7]
Abbreviation: TAU = treatment as usual.

severity and were present during stimulation only. All but 1 patient tolerated the stimulation well; this patient eventually requested deactivation due to hoarseness.

There was 1 serious psychiatric adverse event of a breakthrough manic episode in a patient with bipolar disorder type I. The episode required hospitalization and medication adjustment. However, it was ultimately deemed not to be related to the stimulation and did not require changes in or discontinuation of VNS therapy.

Stimulation Parameters

Mean stimulation parameters were as follows: output current = 1.3 mA (range, 0.75–2 mA), signal frequency = 25 Hz, and pulse width = 220 microseconds (Table 3). The average time on of stimulation was 21.6 seconds, with an average of 1.1 minutes of off time, representing a mean duty cycle of 34.8%.

Mixed-effects models were used to examine the association of each VNS parameter (output current, pulse width, and duty cycle) with the primary and secondary clinical outcomes. These models did not show an effect of VNS parameters on any of the clinical outcomes except for a positive association between increased output current and decreased BAI score (β coefficient = −13.69, $P = .036$) and increased Q-LES-Q score (β coefficient = 26.13, $P = .006$).

Comparison of Our Clinical Results to Those of the Pivotal VNS Trial

We compared the baseline characteristics of our clinical sample to those of the VNS plus treatment-as-usual pivotal trial sample of George et al.[8] *t* Tests for continuous variables and Fisher exact test for discrete or binary variables showed a statistically significant difference in the following characteristics between the 2 samples: unipolar versus bipolar diagnosis ($P = .019$), exposure to ECT in the current MDE ($P = .023$), lifetime exposure to ECT ($P = .014$), lifetime number of MDEs ($P < .001$), number of suicidal attempts in the last 12 months ($P = .013$), and lifetime number of prior hospitalizations for mood disorders ($P = .031$) (Table 1). In all instances, the clinical sample at our center was the one more severely ill in terms of their baseline characteristics.

Table 4. Comparison of Study Outcomes Between the Present Study and the Pivotal Study of VNS + TAU Versus TAU

Variable	Present Study	Pivotal Study: VNS + TAU[a]	*P* Value
HDRS-24 score, mean (SD)			
Baseline	29.36 (4.58)	28.0 (5.7)	.37
12 mo	15.84 (8.8)	19.6 (9.7)	.15
HDRS response rate, %	42.86	29.8	.16
HDRS-24 remission (score ≤ 9), %	14.3	17.1	.79
CGI-I score of 1 or 2, %	42.86	36.5	.21

[a]Data from George et al.[8]
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, HDRS-24 = Hamilton Depression Rating Scale 24-Item, TAU = treatment as usual, VNS = vagus nerve stimulation.

However, the comparison of study outcomes using both *t* tests and Fisher exact test for the HDRS-24 change at 12 months and the HDRS-24 response rate and remission rate and the CGI-I change at 1 year found no statistically significant differences between the 2 groups; thus, level of improvement in these different populations was similar after 12 months of VNS despite differences in baseline severity (Table 4).

DISCUSSION

The principal finding of this study is that VNS effectiveness in a clinical practice devoted to the care of individuals with TRD was at least comparable to the efficacy outcomes reported from prior controlled clinical trials. The response rate on the primary outcome measure, the self-rated BDI, was 21.4% at 6 months, which increased to 28.6% at 1 year. Interestingly, the 1-year response rates per the clinician-rated mood scales, including the 17- and 24-item versions of the HDRS, were higher than that of the BDI, with a response rate of 43% on both scales. This may be due to the fact that depressed patients' subjective awareness of improvement tends to be somewhat less than that perceived by others, possibly related to the pessimism intrinsic to severe depression.

When the response rates and remission rates in this study are compared to those in other published 1-year open-label VNS clinical trials, by means of the same HDRS clinician-administered scales, the outcomes are also quite similar. Marangell et al[16] reported a response rate of 46% on the HDRS-28 and a 29% remission rate at 1 year (n = 30). Separately, in the pivotal trial, George et al[8] reported that 12 months of VNS (n = 205) added to treatment as usual (which

could be varied depending on clinical need) produced a response rate of 29.8% and a remission rate of 17.1%, according to the HDRS-24.

Our effectiveness study, with the same scale (HDRS-24), found a response rate of 43% and a remission rate of 14.3% at 1 year. Thus, effectiveness outcomes of our study fell between those of the 2 prior efficacy studies and overall appear comparable. When continuous rather than categorical outcomes are assessed, also with the HDRS-24, the same pattern of results is observed, with similar endpoint scores on the HDRS-24 at 1 year (15.84 in our study vs 19.6 in the pivotal trial), with no statistically significant differences in outcomes in this study, as compared to the pivotal trial that led to FDA approval.

Overall, results achieved in our clinical practice were comparable to those in prior VNS studies, despite the fact that our patient population was more severely ill than those in previous VNS studies. When compared to the sample in the pivotal trial described by George et al,[8] our clinic population of patients with VNS implants were more severely ill on the basis of several statistically significant features including more exposure to ECT (both in the current episode and in the subject's lifetime), a greater number of lifetime depressive episodes, a greater number of prior hospitalizations due to mood episodes, and a higher number of suicidal attempts in the 12 months prior to VNS.

Thus, it appears to be the case that the results reported in the controlled VNS trials generalize well to clinical practice for our cohort of patients with VNS implants, despite a more severe degree of illness at baseline.

One other VNS efficacy study has also reported results extending to 1 year. This is the recent European multicenter study that followed 74 patients and found a 53% response rate and 33% remission rate after 1 year as measured by the HDRS-24.[17] When remission rates at 1 year are compared between the 3 prior efficacy studies (Marangell et al,[16] George et al,[8] and Schlaepfer et al[17]) and this study, there is a suggestion, at least, that the actual remission rates may be lower in the most severely ill and treatment-resistant patients. Thus, the remission rate at 1 year in this study was 14.3% compared to 33% observed in the European study,[17] 29% in the Marangell et al[16] study, and 17.1% in the George et al[8] trial.

On secondary outcomes, we did not find a significant increase in quality of life as measured by the Q-LES-Q,[15] in contrast to the findings of Marangell et al,[16] who reported improvements using a similar scale in the physical, social, mental, and vitality domains of the Medical Outcomes Study 36-Item Short Form Health Survey with VNS. We are not aware of other prior studies that have measured anxiety or hopelessness with VNS stimulation. Interestingly, our patients' level of hopelessness did not improve despite the measurable improvement in depressive symptoms. It is possible that the chronicity of their depression and previous lack of success with numerous treatments may explain the high level of enduring hopelessness seen in this population.

Decreases in hospitalization and suicidal attempts are clearly important long-term clinical outcomes for any antidepressant treatment. Contrary to our prediction, although VNS was beneficial in improving depressive symptoms, we observed no significant changes in rates of hospitalization or suicidal attempts after 1 year of VNS. This may be due to low power to detect such differences due to the constrained sample size, and the numerical differences we detected were in the right direction. In the year post-VNS, there were no suicides or suicide attempts in our patient cohort. However, 1 bipolar subject did complete suicide 2.5 years after VNS implantation. This was judged to be related to the intractable nature of her depression rather than due to VNS.

The dose of VNS in terms of stimulation parameters applied was higher in this versus prior studies. In particular, the mean output current (1.3 mA) and duty cycle (34%) were higher than in the pivotal study[8] (1.0 mA, 10% duty cycle) and the European study[17] (1.25 mA, 10% duty cycle). Our mean pulse width (220 microseconds) was shorter than used in those studies. According to previous reports, a pulse width of 250 microseconds produces the same global activations in fMRI as the 500-microsecond width. Thus, a 250-microsecond pulse width can be considered relatively optimal.[18] Overall, despite the higher stimulation settings utilized clinically, our results were not better than those reported by George et al[8] and Schlaepfer et al.[17] Although VNS settings in general did not correlate with overall antidepressant response in this study, a higher output current was associated with decreased anxiety and increase in the level of functioning.

Optimal parameters for VNS dosing have not been established for depression and are the subject of an ongoing study. Results from this study will hopefully guide VNS dosing in the future. Finally, although side effects were still mild in severity, we had a higher rate of side effects compared to those of the pivotal[8] and the European studies,[17] probably related to our higher stimulation parameters.

Limitations of our study include its open-label nature and the small sample size. The open-label design might limit the interpretability of our outcomes due to the lack of a sham comparison. Similarly, because of the open-label design, a placebo response cannot be totally ruled out. However, we consider a placebo response here unlikely given our patients' depression severity, the stability of the improvements across different outcome measures, the increase in response over time (6 vs 12 months), and finally the consistency of our response rates when compared to existing literature.[7,8]

Our small sample size reflected both the specialized nature of this intervention and the lack of access to this procedure due to the restrictive insurance policies. Anecdotally, we found that most patients experienced an initial denial of coverage from their insurance carrier, and in all cases it was necessary to provide a detailed rationale and clinical justification for VNS despite its FDA approval. Nonetheless, future larger studies should provide additional information for clinicians managing TRD on the effectiveness of VNS as an intervention for challenging cases.

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