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Effects of 12 Months of Vagus Nerve Stimulation in Treatment-Resistant Depression: A Naturalistic Study

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Background: *The need for effective, long-term treatment for recurrent or chronic, treatment-resistant depression is well established.*
Methods: *This naturalistic follow-up describes outpatients with nonpsychotic major depressive* (n = *185) or bipolar (I or II) disorder, depressed phase* (n = *20) who initially received 10 weeks of active* (n = *110) or sham vagus nerve stimulation (VNS)* (n = *95). The initial active group received another 9 months, while the initial sham group received 12 months of VNS. Participants received antidepressant treatments and VNS, both of which could be adjusted.*
Results: *The primary analysis (repeated measures linear regression) revealed a significant reduction in 24-item Hamilton Rating Scale for Depression ($HRSD_{24}$) scores (average improvement, .45 points [SE = .05] per month* ($p < .001$). *At exit, $HRSD_{24}$ response rate was 27.2% (55/202); remission rate ($HRSD_{24} \leq 9$) was 15.8% (32/202). Montgomery Äsberg Depression Rating Scale (28.2% [57/202]) and Clinical Global Impression-Improvement (34.0% [68/200]) showed similar response rates. Voice alteration, dyspnea, and neck pain were the most frequently reported adverse events.*
Conclusions: *These 1-year open trial data found VNS to be well tolerated, suggesting a potential long-term, growing benefit in treatment-resistant depression, albeit in the context of changes in depression treatments. Comparative long-term data are needed to determine whether these benefits can be attributed to VNS.*

Key Words: Vagus nerve stimulation (VNS), major depressive disorder, bipolar disorder, treatment-resistant depression (TRD), clinical trial, efficacy, side effects

Treatment-resistant depression (TRD) is common. The need for better long-term effective treatments is suggested by multiple attempts to establish sequences of treatments (algorithms) that recommend the next best steps when first or subsequent treatments prove inadequate (e.g., Adli et al 2002; Bauer et al 2002; Fava et al 2003; Katon et al 1995; Linden et al 1994; Rush et al 2003, 2004a), and by controlled trials attempting to define prospectively the next best treatment steps (Fava et al 2003; Rush et al 2004a). Indeed, treatment resistance is the primary indication for some treatments, such as electroconvulsive therapy (ECT) (American Psychiatric Association 2000). The rationale for considering vagus nerve stimulation therapy (VNS) as a potentially effective long-term treatment for TRD—especially for patients with a chronic or recurrent course of illness—was presented previously (George et al 2000, Rush et al, this issue; Rush et al 2002; Sackeim et al 2001a).

This study examined the symptomatic outcomes associated with providing VNS as an adjunct to ongoing antidepressant treatments over a 12-month period. Because VNS is delivered by an implanted device with a battery life of 6 to 9 years and because TRD is a long-term illness, the longer-term effects of VNS among patients in treatment-resistant major depressive episodes (MDEs) are of particular interest. Previous naturalistic studies of VNS in patients with epilepsy have suggested that seizure reduction, improvements in quality of life, and tolerability of side effects increase over time (DeGiorgio et al 2000; George et al 1994; Morris and Mueller 1999; Salinsky et al 1996; Vonck et al 1999).

This naturalistic, 1-year study was designed to (1) determine whether statistically significant and clinically meaningful symptom reductions occur with VNS, and (2) examine the longer-term tolerability and safety of VNS. Participants included in the analysis of this 12-month study had been randomized to receive either active or sham VNS during a 12-week acute phase trial (Rush et al, this issue).

The following specific questions are addressed in this report:

1) Did depressive symptoms improve over the 12-month observation period?
2) Were these improvements in symptoms clinically significant and sustained?
3) Did nonVNS treatments for depression differ between participants with clinically significant benefit and those without such benefits?

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Methods and Materials

Study Overview

For entry into this naturalistic phase, participants had to have completed the acute phase randomized comparison of sham versus active VNS (10 weeks of either sham or active VNS delivered after 2 weeks of recovery from device implantation) (Rush et al, this issue). The IRB approvals and informed consents obtained at the beginning of the 12-week acute study (Rush et al, this issue) included consent for participation in this naturalistic follow-up portion of the study (see acknowledgments). Individuals who initially received sham VNS had to requalify to be included in these 12-month analyses. Requalification required having two Hamilton Rating Scale-Depression ($HRSD_{24}$) (Hamilton 1960, 1967) assessments after 8 and 10 weeks of sham VNS (to establish a baseline before activation of the VNS device), with an average score of ≥18 over these two assessments. Participants who initially received sham VNS, but whose average scores were <18, were not eligible for this analysis, but they could elect to receive active VNS for humanitarian reasons.

Those who initially received active VNS in the randomized acute trial and who continued in this study received an additional 9 months of VNS. To be included in this evaluable (efficacy) sample, all participants had to have at least one $HRSD_{24}$ assessment after completing the acute phase study. The degree of treatment resistance was gauged by the number of unsuccessful treatments according to the Antidepressant Treatment History Form (ATHF) qualified trials in the current MDE (Oquendo et al 1999; Prudic et al 1990, 1996; Sackeim et al 1990, 2000, 2001a).

Outcome Evaluations

The primary outcome measure was change over time in the scores of the $HRSD_{24}$ (Hamilton 1960, 1967). The reliability of the clinical evaluators' $HRSD_{24}$ ratings has been reported (Rush et al, this issue). Secondary outcome measures included the 10-item Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979), the Clinical Global Impression Scale (Severity – CGI-S and Improvement – CGI-I) subscales (Guy W 1976), and the 30-item Inventory of Depressive Symptomatology – Self-Report ($IDS\text{-}SR_{30}$) (Rush et al 1996, 2000; 2005; Trivedi et al 2004). The 11-item Young Mania Rating Scale (Young et al 1978) was used to assess manic/hypomanic symptoms.

For participants initially randomized to active VNS, the baseline $HRSD_{24}$, MADRS, $IDS\text{-}SR_{30}$, YMRS, and CGI-S scores were the averages of the two assessments before implantation.

For those who initially received sham VNS, a new baseline was established by averaging these ratings obtained after 8 and 10 weeks of sham VNS. For this group, ratings for the $HRSD_{24}$, MADRS, $IDS\text{-}SR_{30}$, and YMRS were obtained just before VNS activation, and after 1, 2, 3, 4, 6, 8, and 10 weeks of VNS. The CGI-I was collected just before initiating active VNS for the sham group, and after 10 weeks of VNS. After 10 weeks of active VNS had been delivered to each participant, assessments with the $HRSD_{24}$, MADRS, $IDS\text{-}SR_{30}$, YMRS, and CGI-I were obtained monthly for the ensuing 9 months.

During the 12-month study, clinical raters obtaining the CGI, $HRSD_{24}$, and MADRS were masked to VNS parameter settings and to concomitant medications. These clinical raters were not involved in the clinical care of the participants. An unblinded staff member, who collected information on AEs, turned off the VNS device before all clinical ratings were obtained.

Adverse events were collected by the COSTART system (Coding Symbols for Thesaurus of Adverse Reaction Terms) (Food and Drug Administration 1995). Treatment-emergent adverse events (AEs) were defined as those events occurring on or after the date of implantation, not reported as baseline signs/symptoms, and worsening in severity or frequency. Furthermore, the emergence of mania was monitored with the YMRS. The presence of mania was determined by a YMRS score of ≥15, and DSM-IV criteria. For this study, mania had to be deemed related to stimulation to be considered an AE.

VNS and Concomitant Treatments

Active VNS therapy was delivered according to the protocol previously specified (Rush et al, this issue) during the initial 10 weeks (both for participants initially receiving active VNS therapy and those initially receiving sham VNS). Device programming and integrity were checked at each acute phase visit and monthly during the follow-up period.

After 10 weeks of active VNS (for both the initial sham and active VNS groups), VNS stimulation parameters could be adjusted during the ensuing 9 months. Although changes to any setting within the device programming range were allowed, most participants stayed on the original acute-phase VNS settings, except for output current (which typically increased). For the safety sample (n = 233), median settings after 3 months of VNS were .75 mA (range, .00 to 2.00 mA); 20 Hz (range, 5 to 30 Hz); 500 μsec (range, 130 to 750 μsec); 30 sec ON (range, 7 to 30 sec); and 5 min OFF (range, .20 to 180 min). By 12 months the median settings were output current, 1.0 mA, (range, .0 to 2.25 mA); frequency, 20 Hz, (range, 2 to 30 Hz); pulse width, 500 μsec, (range, 130 to 750 μsec); ON time, 30 sec (range, 7 to 60 sec); and OFF time, 5 min OFF (range, .3 to 180 min).

The protocol allowed changes in the types or doses of any psychotropic or other medications after 10 weeks of active VNS for both groups. Concomitant medications and other treatments were recorded at each study visit. In addition, other somatic treatments, e.g., ECT and rTMS, were allowed, as was the addition or deletion of psychotherapy. In many cases, VNS was monitored and adjusted by the study investigator, while medications and other treatments were decided by the participant's regular (noninvestigator) health care provider. In other cases, the VNS investigator also managed all of the participant's treatments.

Statistical Methods

Quintiles Inc. (Research Triangle Park, Durham, North Carolina), a clinical research organization (CRO), primarily conducted clinical monitoring visits. Data were entered, verified, and analyzed using procedures that ensured the accuracy of the data and results. The a priori specified primary outcome is a repeated measures analysis of the $HRSD_{24}$ total score, which estimated the average monthly change in $HRSD_{24}$ over 12 months of stimulation. Months of stimulation were segmented into four quarters of 3 months each, so that a separate slope for change in $HRSD_{24}$ per month was calculated for each quarter, and an overall estimate was calculated by averaging the change across the four segments. The model adjusted for baseline $HRSD_{24}$, acute study treatment group (those originally randomized to active or sham), and pooled site. Sites were pooled before unblinding into four groups for statistical adjustment, such that sites enrolling a similar number of participants were combined in the same pooled site. To handle unequally spaced visits, the correlation of the repeated measurements was modeled with a spatial power covariance structure including a measurement error component. The repeated measures analysis was also completed for the $IDS\text{-}SR_{30}$.

To assess clinical relevance, response was defined a priori as a reduction of 50% or more in the score compared with baseline for the $HRSD_{24,}$ IDS-SR_{30}, or MADRS, or a CGI-I of 1 or 2 (much or very much improved). Remission was defined a priori as a score ≤9 on the $HRSD_{24,}$ ≤14 for the IDS-$SR_{30,}$ or ≤10 on the MADRS. In the calculation of response and remission rates, participants who exited because of VNS therapy-related adverse events (AEs) or lack of efficacy, met suicide exclusion criteria, attempted suicide that resulted in significant (>3 days) hospitalization, or developed mania or four or more periods of mood rapid cycling were declared treatment failures. Change in response status from 3 months to 12 months and exit using last observation carried forward (LOCF) were evaluated for statistical significance via McNemar's test.

Because this manuscript concentrates on the period between the end of the acute phase to 12-month exit, an LOCF analysis of the period between 3 and 12 months was used. Participants who lacked scores for an evaluation (e.g., MADRS) at 3 months could not be included in this analysis, thus accounting for the number of participants being slightly less than 205.

To further assess the clinical relevance of symptom improvement, we described the durability of benefit by defining a "sustained response" a priori as achieving at least a ≥50% reduction in baseline symptoms ($HRSD_{24}$) at least once during the last quarter (months 9, 10, 11, or 12), and achieving at least a ≥40% reduction from baseline on at least two other of the $HRSD_{24}$ assessments in the quarter. The reason for the ≥40% rule was to remove the effects of error of measurement or minor symptomatic change on response rates, while also requiring at least a clinically significant symptom reduction on the other.

Relationship of NonVNS Treatments to Outcome

To evaluate the potential relevance of concomitant treatment on longer-term outcomes, $HRSD_{24}$ responders and nonresponders at exit (LOCF) were compared for changes in nonVNS mood disorder treatments (categorized as removed/decreased dose, no change, or added/increased dose) with a Mantel-Haenszel Chi-square test for ordinal data using standardized midranks.

Statistical significance was set at $p \leq .050$. Inferential conclusions regarding VNS effectiveness in this study were limited to the single a priori primary outcome (repeated measures of $HRSD_{24}$). We interpreted *p*-values from all secondary outcomes as descriptive in nature; no adjustments were made for multiple comparisons.

Results

Sample Development

The evaluable (n = 205) sample was developed from the implanted/randomized sample (n = 235). Of these 235 participants, two participants were not included in this analysis of the 12-month outcomes (one because of suicide during the acute phase; one because of device explantation secondary to infection during the acute phase). The remaining 233 participants formed the 12-month safety sample.

Of these 233 participants, 28 were not evaluable for efficacy. Three participants had $HRSD_{24}$ scores <18 after implantation, four participants in the initial active VNS group had no $HRSD_{24}$ scores after acute phase exit, and 21 initial sham participants did not average ≥18 on the $HRSD_{24}$ at 8 and 10 weeks of sham treatment. The exclusion of the initial sham participants who scored <18 at the end of acute phase sham VNS provided a conservative estimate of longer-term effects. The remaining 205 participants formed the evaluable (efficacy) sample for the 12-month analyses in this report.

The completer sample was developed from the 205 evaluable participants. Of 205 evaluable participants, 17 discontinued participation before 1 year (four because of adverse events; seven because of lack of efficacy, six because of other participant decisions), six did not have stimulation ≥80% of the time, and five had neither an 11- nor 12-month $HRSD_{24}$ score. The remaining 177 participants constituted the completer sample.

In addition to LOCF analyses performed for the 177 participants who completed the 12-month study, analyses also were performed using an observed sample. For the observed sample, only participants with data available for each measurement at each time point were included, thus the n may vary.

Sample Characteristics

Table 1 describes the evaluable (n = 205) sample. Most participants had MDD with a substantial degree of treatment

Table 1. Baseline Demographics and Clinical Features

Parameter	Evaluable (n = 205)
Mean Age in Years [mean (SD)]	46.3 (8.9) (median 47.0)
% Female	63.9
% Caucasian	96.6
% MDD	90.2
% Bipolar I or II	9.8
% With Recurrent MDD (*n*)	78.5 (161/205)
% With single-episode MDD (*n*)	11.7 (24/205)
% Attempted Suicide (Lifetime)	31.7 (65/205)
Length of Current MDE (Months) [mean (SD)]	49.9 (52.1) (median 34.0)
% In Current MDE ≥2 Years	68.3 (140/205)
Age at Onset of First Mood Episode (years) [mean (SD)]	21.8 (11.9)
Length of Illness (Years) [mean (SD)]	25.5 (11.9) (median 25.5)
Number of Failed ATHF Trials, Current MDE [mean (SD)]	3.5 (1.3)
% ECT In Lifetime	52.7
% ECT In Current MDE	35.1
Lifetime Hospitalizations for Mood Disorder [mean (SD)]	2.7 (5.4) (median 1.0)
Baseline $HRSD_{24}$ [mean (SD)][a]	28.0 ± 5.7
Baseline MADRS [mean (SD)][a]	30.8 ± 6.9
Baseline IDS-SR_{30} [mean (SD)][a]	42.9 ± 10.0
Lifetime MDEs (%)	
0–2	24.4
3–5	33.7
6–10	27.3
>10	9.3
Unknown	5.4
% With Unsuccessful ATHF Trials[b]	
2–3	56.6 (116/205)
4–5	35.1 (72/205)
≥6	8.3 (17/205)

MDD, major depressive disorder; MDE, major depressive episode; ATHF, Antidepressant Treatment History Form; ECT, electroconvulsive therapy; $HRSD_{24}$, 24-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; IDS-SR_{30}, 30-item Inventory of Depressive Symptomatology-Self Report.

[a]For participants who received VNS at randomization, severity measures were obtained at baseline before implantation. For those who initially received sham treatment, baseline severity measures were the average of those obtained after 8 and 10 weeks of sham treatment.

[b]In current MDE.

resistance. Table 2 shows the proportion of participants treated in both the current MDE and in their lifetimes with different groups of psychotropic agents. Most participants had received two or more SSRIs (for the current episode, 53.7% (110/205); for lifetime, 91.7% (188/205)). This participant group had long-standing illness (more than 25 years), with a substantial proportion having been hospitalized, having received ECT, and having an extensive exposure to a wide variety of medications.

Did Symptoms Improve Over the 12-Month Observation Period?

For the primary analysis, 205 patients provided data at 3 months, 197 at 6 months, 186 at 9 months, and 181 at 12 months. Figure 1 shows the observed $HRSD_{24}$ average at each time point as well as estimates from the repeated measures regression model for the evaluable sample. On average, the $HRSD_{24}$ score improved .45 (SE = .05) points per month (repeated measures $t = 8.25$, $df = 654$, $p < .001$). Based on the evaluable sample ($n = 205$), all quarters showed an improvement over time, with the largest average monthly increase seen in the first quarter (1.22 points, SE = .17, repeated measures $t = 7.29$, $df = 793$, $p < .001$).

Improvement in the third quarter was also statistically significant (.45 points, SE = .18, repeated measures $t = 2.54$, $df = 972$, $p = .011$) Similar results were obtained with the $IDS\text{-}SR_{30}$ (average improvement per month = .52 points (SE = .08, repeated measures $t = 6.79$, $df = 631$, $p < .001$). Table 3 lists the mean scores of the $HRSD_{24,}$ $IDS\text{-}SR_{30,}$ and MADRS at baseline and 12 months. All three measures reveal statistically significant reductions over 12 months.

A comparison of the participants who had been randomized to the control group with those who received stimulation during the acute phase of this study (intent to treat sample) showed that for the sham group, $HRSD_{24}$ scores were lower at baseline (mean $HRSD_{24}$ of 24.6 vs. 28.7; *t*-test $t = 4.55$, $df = 227$, $p < .001$) and the sham group did not improve as much over time (active vs. sham estimate of $HRSD_{24}$ averaged across all time points = −1.96, SE = .63; repeated measures $t = 3.14$, $df = 253$, $p = .002$).

Were the Improvements in Depressive Symptoms Clinically Meaningful?

We conducted several appraisals of the clinical importance of this symptomatic improvement. Figure 2 shows the response and remission rates for the $HRSD_{24}$, MADRS, and $IDS\text{-}SR_{30}$ at 3, 6, 9, and 12 months and LOCF beyond 3 months. Recall that an LOCF analysis of the period between 3 and 12 months was used. For $HRSD_{24}$, 27.2% (55/202) participants achieved a response at exit (LOCF), and 15.8% (32/202) achieved a remission. For the observed participants, the $HRSD_{24}$ response rate after 12 months was 29.8% (54/181), while the $HRSD_{24}$ remission rate was 17.1% (31/181).

Similar response and remission rates were obtained with the MADRS (response of 28.2% for LOCF [57/202] and of 31.5% for observed evaluable [57/181]; remission of 20.3% for LOCF [41/202] and of 22.7% for observed evaluable [41/181]) and the $IDS\text{-}SR_{30}$ (response of 19.9% for LOCF [40/201] and of 21.7% for observed [39/180]; remission of 13.4% for LOCF [27/201] and of 15.0% for observed [27/180]).

Figure 2 shows that the response rates ($HRSD_{24}$ and MADRS) and the remission rates ($HRSD_{24,}$ MADRS, and the $IDS\text{-}SR_{30}$) doubled from 3 to 12 months. Changes in response and remission status from 3 months to 12 months and exit (LOCF) were statistically significant for $HRSD_{24}$ and MADRS based on McNemar's test (all *p*-values < .005). The CGI-I ratings confirmed these findings with 19.6% (39/199) participants at 3 months, 24.9% (49/197) at 6 months, 27.7% (51/184) at 9 months, and 36.5% (66/181) at 12 months rated as 1 or 2 (very much or much improved; evaluable sample, 34.0% [68/200] LOCF). This increase in both response and remission rates is not attributable to participant attrition because the LOCF response and remission rates also reflected an increasing proportion of responders and remitters from 3 months to study exit.

To further examine clinical benefit, we calculated the percentage of participants in the completer sample ($n = 177$) with a "sustained response" using the $HRSD_{24}$ data at months 9, 10, 11, and 12. At least one visit had to show a ≥50% reduction in baseline $HRSD_{24}$ total score, and another two of these visits had to achieve at least a ≥40% reduction in baseline total score. Of the completer sample (LOCF), 29.4% (52/177) participants had a response at 12 months and 26.6% (47/177) participants had a "sustained response." Of the 52 participants who were responders at 12 months, 73.1% (38/52) were also "sustained responders." Of the 47 participants with a "sustained response," 66% (31/47) met the criteria for response at all 4 points (9. 10, 11, and 12 months).

Table 2. Proportion of Participants Who Received Various Psychotropic Treatments (Current MDE and Lifetime; $n = 205$)

Treatment	Current MDE (%)	Lifetime (%)
Heterocyclics/TCAs	50.2	83.4
SSRIs	90.2	>99
MAOIs	24.4	42.4
Other Antidepressants[a]	93.7	>99
Lithium	36.6	66.3
Anticonvulsants	51.7	62.4
Stimulants	43.4	55.1
Atypical Antipsychotics	41.5	48.3
Non atypical Antipsychotics	10.7	34.6
Other[b]	45.4	56.6
ECT	35.1	52.7

MDE, major depressive episode; TCA, tricyclic antidepressants; SSRI, selective serotionin reuptake inhibitor; MAOI, monoamine oxidase inhibitor; ECT, electroconvlsive therapy.

[a]Includes, for example, bupropion, nefazodone, mirtazapine.

[b]Includes, for example, St. John's Wort, SAMe, cognitive therapy, benzodiazepines.

Did NonVNS Treatments Differ between Participants with and without Clinical Benefits?

We divided the sample into responders and nonresponders based on the $HRSD_{24}$ at exit (LOCF, $n = 205$). Of the responders, 5.5% (3/55) were on no concomitant medications, while none of the 150 nonresponders were on no medication (Mantel Haenszel χ^2 (1 *df*) = 8.3, $p = .0040$). Medications were removed or decreased only (no additions or dose increases) in 12.7% (7/55) responders and in 9.3% (14/150) nonresponders. Altogether 30.9% (17/55) responders (including the three responders who received no concomitant medications) had no medication changes as compared with 14.0% (21/150) nonresponders. Finally, 56.4% (31/55) responders had either an increase in dose or had a medication added as compared with 76.7% (115/150) nonresponders. The nonresponders had significantly more medication changes/dose increases compared with the responders (Mantel Haenszel χ^2 (1 *df*) = 8.054, $p = .005$).

Adverse Events

Two participants discontinued treatment during the first 3 months of VNS (one because of suicide after 5 weeks of active

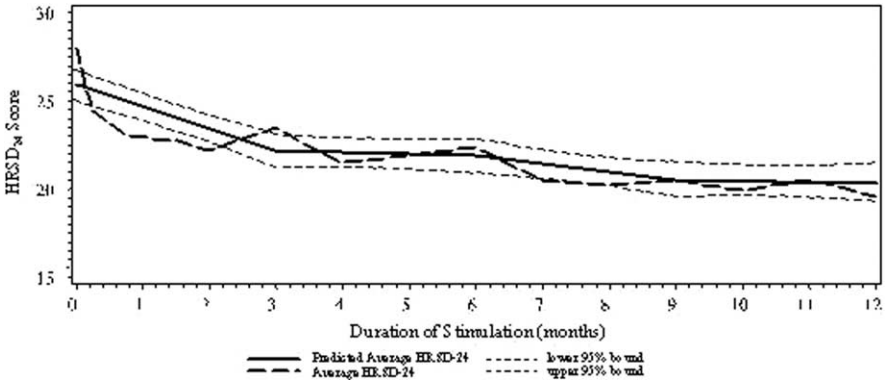

Figure 1. Observed and predicted average $HRSD_{24}$ evaluable sample ($n = 205$). Predicted values are based on repeated measures linear regression of the $HRSD_{24}$ total score at Weeks 1, 3, 6, 8, 10 and Months 4-12 of stimulation with a spatial power covariance structure, and with fixed effects for pre-stimulation baseline $HRSD_{24}$. Acute treatment group, pooled site indicator variables, and months of stimulation segmented into 4 quarters. The predicted average $HRSD_{24}$ values and 95% CI represent a hypothetical patient with average pre-stimulation $HRSD_{24}$ values; with an averaging across treatment groups and pooled sites. $HRSD_{24}$, 24-item Hamilton Rating Scale for Depression.

stimulation and one because of wound infection that required device removal). The participant who committed suicide after receiving about 5 weeks of VNS had, before entering the study, attempted suicide once and had been hospitalized for depression on three occasions. The remaining 233 implanted participants were analyzed for long-term safety. Twenty-four (24) participants discontinued during the 12-month phase: seven for adverse events of which two were deaths (see below), and 17 for lack of efficacy or other reasons.

One death due to esophageal cancer occurred before device implantation; one suicide (mentioned previously) occurred during the acute phase of the study, after 5 weeks of active VNS. One additional death occurred during the subsequent 9 months of VNS. A 61-year-old Caucasian female participant with bipolar disorder was found dead of unknown causes. An autopsy was not performed, but the coroner saw no evidence of homicide or suicide.

Table 4 summarizes stimulation-related AEs observed at ≥5% incidence by quarter. At 3 months of VNS, the stimulation-related AEs reported with the greatest frequency were voice alteration, increased cough, neck pain, dyspnea, and dysphasia. After 12 months of VNS, the frequency of reported AEs held constant or decreased. Voice alteration remained the most frequently reported, followed by dyspnea and neck pain.

VNS was generally well tolerated with either a reduction or no increase in adverse events from 3 to 12 months of VNS. Rates of dysphagia, 13% during the first quarter, decreased to 4% by the fourth quarter. Paresthesia (from 11% to 4%), increased cough (from 24% to 6%), and laryngismus (from 10% to 5%) decreased between the first and fourth quarters. The most frequently reported adverse event, voice alteration, remained fairly constant over the study period (reported by more than half the participants during each quarter). Altogether, these data suggest that VNS is well tolerated and most adverse events are reduced over time.

Development of Mania/Hypomania. Three participants developed manic symptoms that met criteria (YMRS ≥15 and confirmed by DSM-IV) (two during the first 3 months and one during the subsequent 9 months of VNS). Both participants who developed manic symptoms during the first 3 months of VNS had mild symptoms that resolved in 1 to 2 weeks. One participant had a bipolar diagnosis, and one had a history of treatment-induced mania. The first participant experienced manic symptoms when stimulation was initiated. By the time of the next visit, the symptoms had subsided and device parameters were increased from .25 to .50 mA. VNS parameters were not changed for the second participant whose parameters remained at .75 mA during the episode. The participant with a manic reaction during the subsequent 9 months of VNS had a diagnosis of unipolar depression at baseline. Stimulation, which was 2.25 mA when the episode began, was stopped on the day that the participant was hospitalized. Stimulation remained off during the episode, which lasted about 2 months, and was restarted at .50 mA about a month after the episode ended, increased to 1.00 mA about 2 weeks later, and increased to 1.50 mA about 2 additional weeks later.

Three additional participants had an elevated YMRS score (≥15) after the first 3 months of VNS, but they did not meet DSM-IV criteria. Two of these participants had bipolar disorder. These hypomanic symptoms were brief (1 to 3 days) and subsided without changes in medication dose or type or VNS settings.

There was no clinically meaningful change in systolic or diastolic blood pressure, heart rate, respiration rate, or weight (baseline to exit). Of the 172 participants on whom body weight was available, 21 (12.2%) participants had gained more than 7% of their baseline body weight by study exit, and 23 (13.4%) participants had lost more than 7% of their baseline body weight by study exit.

Worsening of Depression. During the 12-month study, 30 participants had worsening of depression sufficient to require hospitalization. Of these 30 participants, 24 (80%) had a history of hospitalization for worsening depression before study enroll-

Table 3. Symptom Ratings at Baseline and 12 Months (Mean and SD)

	Baseline	12 Months (Observed)	12 Months (LOCF)	*p*-value[a]
$HRSD_{24}$	28.0 ± 5.7 ($n = 205$)	19.6 ± 9.7 ($n = 180$)	20.6 ± 9.9 ($n = 205$)	<.001
$IDS\text{-}SR_{30}$	42.9 ± 10.0 ($n = 204$)	32.6 ± 15.3 ($n = 180$)	33.6 ± 15.4 ($n = 204$)	<.001
MADRS	30.8 ± 6.9 ($n = 205$)	21.2 ± 11.5 ($n = 181$)	22.2 ± 11.7 ($n = 205$)	<.001

$HRSD_{24}$, 24-item Hamilton Rating Scale for Depression; $IDS\text{-}SR_{30}$, 30-item Inventory For Depressive Symptomatology-Self Report; MADRS, Montgomery - Asberg Depression Rating Scale.

[a] *p*-values are based on paired *t*-tests comparing between baseline, 12 months (observed), and 12 months LOCF (Last Observation Carried Forward). The treatment effect in repeated measures linear regressions for the HRSD and IDS-SR also resulted in $p < .001$.

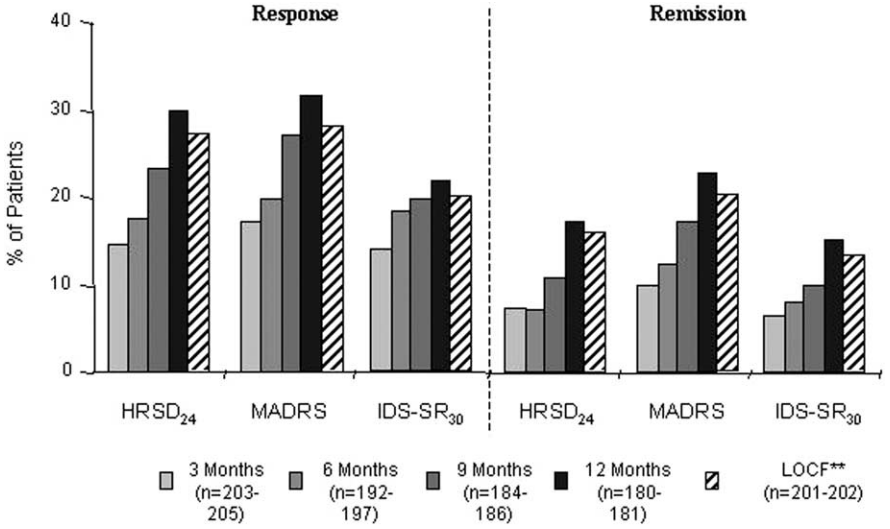

Figure 2. $HRSD_{24}$, MADRS, and IDS-SR_{30} response and remission rates [evaluable participants*]. *The number of participants varies by time interval as based on observed-case analyses. The range for the number of participants with available data at each time interval is provided. **An LOCF analysis of the period between 3 and 12 months was used. Participants who lacked scores for an evaluation at 3 months could not be included in this analysis, thus accounting for the number of participants being slightly less than 205. $HRSD_{24}$, 24-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; IDS-SR_{30}, 30-item Inventory of Depressive Symptomatology-Self-Report.

ment. Further, the percentage of participants with worsening of depression based on the $HRSD_{24}$ ratings of <0% reduction from baseline (i.e., worsening), decreased over time: 27.1% (48/177, completer sample) at 3 months, 25.1% (44/175) at 6 months, 18.1% (31/171) at 9 months, and 17.2% (30/174) at 1 year (observed cases).

Two participants each made one suicide attempt (one coded by COSTART as an overdose) during the first 3 months of receiving VNS, and five participants made six suicide attempts over the ensuing 9 months of VNS (one participant made two attempts). One attempt occurred after 3 months of VNS, one after 4 months, three after 5 months, and one after 11 months. The participant who attempted suicide twice made both attempts after 5 months of VNS (the attempts occurred about 2 weeks apart). Of the seven participants who attempted suicide, four (57.1%) had a prior history of at least one suicide attempt.

Discussion

This 12-month study (n = 205) of VNS used as an adjunct to other antidepressant treatments in patients with treatment-resistant, chronic or recurrent mood disorders revealed statistically significant reductions in depressive symptoms. The primary repeated measures linear regression analysis of the evaluable sample revealed a statistically significant reduction over time in both the $HRSD_{24}$ total scores and the IDS-SR_{30} total scores.

The clinical relevance of the symptom reduction was demonstrated by the response and remission rates of several measures. For example, the $HRSD_{24}$ revealed that 27.2% (55/202) of evaluable participants achieved a response at exit (LOCF) and 15.8% (32/202) achieved a remission. Similar results were obtained with the MADRS: 28.2% (57/202) response and 20.3% (41/202) remission. Furthermore, most (73.1%) of those with a

Table 4. Prevalence of Observed Stimulation-Related AEs at ≥5% Incidence by Quarters[a]

	3 Mos (n = 232)[b]	6 Mos (n = 225)[b]	9 Mos (n = 218)[b]	12 Mos (n = 209)[b]
Adverse Event				
Headache	12 (5%)	9 (4%)	9 (4%)	8 (4%)
Neck pain	38 (16%)	25 (11%)	31 (14%)	27 (13%)
Pain	13 (6%)	14 (6%)	11 (5%)	13 (6%)
Dysphagia	31 (13%)	19 (8%)	15 (7%)	9 (4%)
Nausea	13 (6%)	5 (2%)	5 (2%)	4 (2%)
Insomnia	10 (4%)	5 (2%)	6 (3%)	2 (1%)
Paresthesia	26 (11%)	15 (7%)	7 (3%)	9 (4%)
Cough increased	55 (24%)	20 (9%)	15 (7%)	13 (6%)
Dyspnea	33 (14%)	35 (16%)	33 (15%)	34 (16%)
Laryngismus	23 (10%)	18 (8%)	16 (7%)	10 (5%)
Pharyingitis	14 (6%)	8 (4%)	8 (4%)	11 (5%)
Voice alteration	135 (58%)	135 (60%)	125 (57%)	113 (54%)
Serious Adverse Event				
Mania	2 (1%)	1 (<1%)	0	0
Suicide attempts	2 (1%)	3 (1%)	1 (<1%)[c]	1 (<1%)
Worsening depression	12 (5.2%)	15 (6.7%)	10 (4.6%)	12 (5.7%)
Hospitalizations	13	19	14	14

AE, adverse event.
[a]Tallies are provided by quarter. Participants may have had multiple events across the 12-month study.
[b]Number of participants reporting during the particular interval.
[c]Two attempts.

response by $HRSD_{24}$ during the final quarter of stimulation met our a priori definition of a "sustained $HRSD_{24}$ response."

There was a general pattern of increasing response rates observed at 3, 6, 9, and 12 months based on the $HRSD_{24}$, CGI-I, MADRS, and $IDS\text{-}SR_{30}$. For example, CGI-I ratings revealed an increase in response rates from 19.6% at 3 months to 34.0% (LOCF) at 12 months. A statistically significant increase in response rates was seen between 3 and 12 months (LOCF) for $HRSD_{24}$ and MADRS ($p < .005$).

Three participants experienced a manic syndrome over the 12 months of this study. Of these, one had a baseline diagnosis of bipolar disorder and one had a history of treatment-induced mania. An additional three participants developed hypomanic symptoms within 3 months of starting VNS that were not sufficient to meet DSM-IV TR criteria for a manic episode, of which two had a bipolar disorder diagnosis at baseline. Some investigators would view the tendency of a treatment such as VNS to induce manic or hypomanic symptoms as evidence of antidepressant activity (Goodwin and Jamison 1990).

VNS was generally well tolerated. Adverse events were quite similar to those reported in both TRD and epilepsy patients (Morris and Mueller 1999; Sackeim et al 2001b; Vagus Nerve Stimulation Study Group 1995). The prevalence of side effects remained constant or decreased over the 1-year study. Data based on worsening of depression as defined by a worsening of the $HRSD_{24}$ total score do not suggest an increasing risk of worsening of depression over time with continuing VNS.

Three deaths occurred (one due to suicide after 5 weeks of VNS, one due to cancer before implantation, one due to unknown causes after 10 weeks of VNS). While 30 participants required hospitalization for worsened depression, 24 had a history of being hospitalized for such an event before the study. Seven participants attempted suicide, of whom four had made attempts prior to the study.

This group of highly chronic or recurrent, treatment-resistant participants has rarely been the subject of such long-term investigations. The 1-year outcomes of this open trial suggest that 12 months of VNS is associated with clinically meaningful antidepressant effects. This study has several limitations. They include 1) nonmasked ratings, 2) lack of an active treatment control group, and 3) the fact that treatments could be adjusted or changed after the initial 3 months of VNS.

Could the long-term improvements be due to placebo effects? This possibility is unlikely because one would have to believe that placebo effects would increase over time, that they would be largely sustained, and that they would occur in 20% to 35% of such treatment resistant, chronically ill participants. In fact, placebo effects are known to be seen acutely in nonTRD and to wane, rather than increase, over time (Quitkin et al 1987).

The longer-term improvements in this study could have been a result of a naturally occurring improvement in depression, but, given the treatment-resistant nature of the sample, such a cause and effect seems very unlikely. Furthermore, long-term medication trials uniformly reveal a decrease, rather than an increase, in efficacy over time with medication even in nonTRD patients. Continuing on medication in the long term in nonTRD patients who respond acutely is associated with a 10% to 40% relapse/recurrence rate (Greden 2001). In addition, spontaneous improvement that grows over time is very unusual in these types of patients (Rush et al 2004b).

Could medication changes have caused the improvement that increased over the 12-month observation period? An examination of medication changes over the 12-month observation period revealed fewer medication changes or dose increases in VNS responders than in VNS nonresponders. This finding suggests that medication changes are not likely the cause of the responses observed over the 12-month period. Of course, these medication changes cannot be dissociated from the concurrent use of VNS. That is, VNS may have increased the efficacy of medications that otherwise would not have been effective. However, medication changes were less frequent among VNS responders than among VNS nonresponders, and three VNS responders were on no medication at all from baseline to exit. In addition, George et al (this issue) reported that those without medication changes accounted for virtually all of the improvements seen over time.

Without a control or comparison group, however, one cannot be totally certain that these longer-term clinically meaningful benefits are attributable to VNS. On the other hand, let us consider nonchronic, nontreatment-resistant depressed patients, the vast majority of whom have never been hospitalized. About 50% of these patients respond to acute treatment (Depression Guideline Panel 1993). Of these responders, roughly 25% relapse or recur over 9 to 12 months (Greden 2001). Thus, only 38.5% of the original sample will evidence a response at 1 year. In this context, the 25% to 33% response rates achieved after 1 year of VNS are impressive, especially since over 70% of those responses were "sustained" between 9 and 12 months. George et al (this issue) provide outcome data on a comparable group of chronically ill, treatment-resistant depressed patients who were actively treated without receiving VNS for 1 year.

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