Two-Year Outcome of Vagus Nerve Stimulation (VNS) for Treatment of Major Depressive Episodes

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Background: Vagus nerve stimulation (VNS) had antidepressant effects in an initial open, acute phase pilot study of 59 participants in a treatment-resistant major depressive episode (MDE). We examined the effects of adjunctive VNS over 24 months in this cohort.

Method: Adult outpatients (N = 59) with chronic or recurrent major depressive disorder or bipolar (I or II) disorder and experiencing a treatment-resistant, nonpsychotic MDE (DSM-IV criteria) received 2 years of VNS. Changes in psychotropic medications and VNS stimulus parameters were allowed only after the first 3 months. Response was defined as ≥ 50% reduction from the baseline 28-item Hamilton Rating Scale for Depression (HAM-D-28) total score, and remission was defined as a HAM-D-28 score ≤ 10.

Results: Based on last observation carried forward analyses, HAM-D-28 response rates were 31% (18/59) after 3 months, 44% (26/59) after 1 year, and 42% (25/59) after 2 years of adjunctive VNS. Remission rates were 15% (9/59) at 3 months, 27% (16/59) at 1 year, and 22% (13/59) at 2 years. By 2 years, 2 deaths (unrelated to VNS) had occurred, 4 participants had withdrawn from the study, and 81% (48/59) were still receiving VNS. Longer-term VNS was generally well tolerated.

Conclusion: These results suggest that patients with chronic or recurrent, treatment-resistant depression may show long-term benefit when treated with VNS.

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Maintaining antidepressant effects after acute response to treatment is often challenging, even among patients without marked treatment resistance. Continuation phase pharmacotherapy is associated with relapse rates that range from 20% to 37% among patients with largely non–treatment-resistant depression.[1,2] Relapse rates among patients with treatment-resistant depression are believed to be substantially higher. For example, one study in a research setting observed a relapse and/or recurrence rate greater than 50% in the year following successful electroconvulsive therapy (ECT),[3] and another study of ECT in community practices reported a relapse rate of 64.3% during the first 6 months after remission.[4] In both studies, patients were receiving medication following ECT.

Vagus nerve stimulation (VNS) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with treatment-refractory partial-onset seizures. In naturalistic follow-up studies, VNS has been shown to produce a substantial reduction in seizure frequency with the improvement sustained for up to 3 years.[5] The possible antidepressant effect of VNS was found in an open, acute phase pilot study.[6,7] After the initial 10 weeks of treatment

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with VNS in addition to ongoing, but stable, psychotropic medication regimens, the response rate among 59 participants with a treatment-resistant major depressive episode (MDE) was 31% (N = 18), and the remission rate was 15% (N = 9).[6,7] Given the chronicity of illness and degree of treatment resistance of these participants, these initial results were encouraging. Among the first 30 participants, the beneficial effects were largely sustained at 12 months' follow-up.[8] As with many other antidepressant treatments, the degree of treatment resistance before beginning VNS predicted both acute and longer-term outcome.[7,8]

The current naturalistic follow-up study assessed response and remission over the course of 24 months with VNS used as an adjunctive therapy to other depression treatments for participants with a treatment-resistant, nonpsychotic MDE as part of a major depressive or bipolar I or II disorder. The relationship between treatment resistance in the current MDE and response and/or remission rates after 24 months of VNS was also evaluated. Additional safety, quality of life, and functionality measures were obtained.

METHOD

Recruitment and Consent

The study was conducted at 4 U.S. sites—Baylor College of Medicine, Columbia University/New York State Psychiatric Institute, Medical University of South Carolina, and University of Texas Southwestern Medical Center—in compliance with the Investigational Device Exemption under FDA guidance. Local institutional review boards approved the initial and continuation protocols, and all participants provided a written informed consent. To address the ethical concerns of providing an experimental and untested intervention that required surgery, the inclusion criteria limited enrollment to depressed participants with definite histories of substantial treatment resistance.

Participants

Eligible participants presented with a nonpsychotic, nonatypical MDE as part of either bipolar (I or II) disorder or major depressive disorder (MDD), defined by DSM-IV criteria.[9] All participants scored ≥ 20 on the 28-item Hamilton Rating Scale for Depression (HAM-D-28)[10,11] before implantation, and ≥ 18 on the HAM-D-28 following the 2-week post-implantation recovery period, after which time the VNS therapy device (VNS Therapy System Pulse Generator; Cyberonics, Houston, Tex.) was activated.

Participants were included if, during the current MDE, they had not benefited sufficiently from adequate trials of at least 2 different classes of antidepressant medications or other somatic treatments as defined by the Antidepressant Treatment History Form (ATHF) criteria.[12] Further, a minimum of 6 weeks of prior psychotherapy during any MDE was required. Participants with bipolar disorder had to be resistant to, be intolerant of, or have a medical contraindication to lithium. Information to complete the ATHF was obtained from participants and significant others, treating physicians, medical records, and pharmacy logs. The ATHF rates each psychotropic medication trial on a scale from 0 to 5, with a score of 3 or greater indicating a failed adequate trial. Compliance, serum drug concentrations when available, and clinical outcome were taken into account in making these ratings. For all medication trials, a score of ≥ 3 required a minimum of 4 weeks at specific dosage thresholds.

The VNS therapy device was implanted in the chest wall, bipolar leads were tunneled under the skin, and electrodes were attached to the left vagus nerve in the neck. Treating physicians used a programming wand attached to a portable computer to adjust stimulation parameters. After a 2-week single-blind recovery period following implantation, which served as a lead-in "placebo" period, the VNS dose (typically the current level) was adjusted over 2 more weeks, after which the stimulation parameters were fixed for the subsequent 8 weeks. Participants were on stable medication regimens for at least 4 weeks before implantation and for 12 weeks following implantation, except that dose reductions were allowed during the latter period.

During the longer-term follow-up study, which followed the acute phase, medications could be changed in type or dose, and ECT could be provided. Furthermore, VNS parameters (e.g., current, frequency, duty cycle) could also be changed.

The acute phase results have been described previously.[6,7] This article provides results from all available participants after 12 and 24 months of adjunctive VNS therapy (Table 1).

Assessments

Unmasked clinical outcome measures included the HAM-D-28, the 10-item Montgomery-Asberg Depression Rating Scale (MADRS),[13] the 11-item Young Mania Rating Scale (YMRS),[14] the Clinical Global Impressions-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) scales,[15] and the Global Assessment of Functioning (GAF).[9] These measurements were obtained at pretreatment (baseline) and at 3 (acute study exit), 6, 9, 12, 15, 18, 21, and 24 months after implantation. Follow-up assessments were completed within the period of 4 weeks before through 4 weeks after scheduled visits. Functional outcomes were assessed with the Medical Outcomes Study (MOS) Short Form-36 (SF-36)[16] at baseline, 3 months (acute study exit), 12 months, and 24 months post-implantation. Short Form-36 normative values, developed from a random sample survey of 2474

Table 1. Participant Flow Over 2 Years With Respect to Participation in the Study, Active Device Status, and Ratings Captured at Key Milestones in the Study

Occasion	Active in Study	Observed Cases	LOCF	Explanted	Death (unrelated to VNS)	Generator Off (only for active participants in study)
Baseline	60[a]	59[a]	NA	0	0	60
3 months	59	59	59	0	0	0
12 months	58[b]	54	59	1[b]	0	0
24 months	53[c,d]	42	59	3[c,e]	2[d]	6[f]

[a]One participant responded to implant alone and did not enter the trial.
[b]One participant withdrew (lack of efficacy).
[c]Three more participants withdrew from the study (lack of efficacy).
[d]Two participants died between 12 and 24 months (1 of sepsis, 1 of lung cancer).
[e]Two explants occurred at 2 years' follow-up.
[f]Generator was turned off.
Abbreviations: LOCF = last observation carried forward, NA = not applicable, VNS = vagus nerve stimulation.

individuals from the general U.S. population, were used for comparative purposes. Norms for the general population ranged from 61 to 84 on a scale of 0 to 100 for the various SF-36 subscales.[16] Adverse events (AEs) were coded with the *Coding Symbols for Thesaurus of Adverse Reaction Terms* (COSTART) dictionary.[17]

Data Management and Analyses

Data collected by the device manufacturer (Cyberonics; Houston, Tex.) and Quintiles, Inc. (Durham, N.C.), a contract research organization, were provided to the authors in complete form. Response was defined a priori as a ≥ 50% reduction in the mean HAM-D-28 scores relative to the mean of 2 baseline (pre-implantation) visits (or, for secondary analyses, a ≥ 50% reduction from the mean of 2 baseline MADRS scores, or a CGI-I score of 1 or 2). Remission was defined a priori as a HAM-D-28 score of ≤ 10. Durability of response was examined by calculating the percentage of patients who met modified response criteria at the 12- and 24-month time points, and who had met a priori response criteria at earlier time points (3-month or 12-month). In these post hoc analyses, individuals who were responders at the earlier time point and who had at least 40% improvement in HAM-D-28 scores relative to baseline at the subsequent follow-up were classified as showing sustained response. The threshold of 40% at the follow-up time point (established a priori) was adopted so that decreases in the degree of improvement around the 50% cutoff would not negate classification of sustained response.

Fifty-nine participants had reportable data at 3 months, as did 54 of 58 active participants at 12 months. All 59 participants were included in the last observation carried forward (LOCF) analyses. At the 24-month follow-up, 53 participants remained implanted with the VNS device. Ratings were available at the 24-month follow-up for 42 of the 53 implanted patients (see Table 1). Six of these 53 participants had had the device turned off. Of the original 59 participants, 6 were no longer implanted at the 24-month follow-up: 2 had died, and 4 had the device explanted owing to lack of efficacy.

Data Analyses

The following techniques were used: descriptive statistics (including the mean, SD, and median), Shapiro-Wilks test for normality, Kruskal-Wallis test, repeated-measure analysis of variance (ANOVA) with repeated contrasts, and graphic displays. McNemar exact test was used to test the within-group change in remission rates across these time points. Nonparametric Spearman rho correlations were performed to evaluate prognostic factors predictive of HAM-D-28 response at acute study exit and at the 12- and 24-month assessments. All statistical tests were 2-tailed. Significance was set at $p \leq .05$.

RESULTS

Sample Characteristics

Of 60 initially enrolled participants, 59 received VNS and participated in this study. One participant experienced a marked reduction in symptoms after implantation, did not have the VNS device activated at that time, and was not included in the acute efficacy or follow-up samples. Table 2 summarizes the sample characteristics.

Participants had received a mean of 15.7 (± 7.9) unsuccessful clinical treatments during the current MDE.[7] Of these central nervous system (CNS)– active compounds, a mean of 8.6 (± 4.0) were classic antidepressant treatments of which 4.8 (± 2.7) met ATHF criteria for trial adequacy.[7] Table 3 reports the average number of treatments and severity of illness as demonstrated by median length of current depressive episode and length of depressive illness by separating the cohort into 2 or 3, 4 or 5, and 6 or more unsuccessful trials as defined by the ATHF. Although the mean HAM-D-28 scores at baseline were similar across all 3 subgroups, participants with more unsuccessful prior treatment trials had longer current episodes (Kruskal-Wallis test, $p = .004$). Specifically, the difference

Table 2. Demographics and Clinical Characteristics of the Sample (N = 59)

Characteristic	Value
Age at implant, y	
Mean ± SD	46.8 ± 8.7
Median	47.9
Minimum	20.7
Maximum	63.1
Gender, female, N (%)	38 (65)
White, N (%)	58 (98)
Hispanic, N (%)	1 (2)
MDD, recurrent, N (%)	27 (46)
MDD, single episode, N (%)	16 (27)
Bipolar I disorder, N (%)	6 (10)
Bipolar II disorder, N (%)	10 (17)
Baseline HAM-D-28 score	
Mean ± SD	36.8 ± 5.8
Median	37.0
Minimum	23.5
Maximum	51.5
Length of current MDE, y	
Mean ± SD	10.0 ± 10.9
Median	6.8
Minimum	0.3
Maximum	49.5
Total length of mood disorder, y	
Mean ± SD	18.23 ± 7.3
Median	16.0
Minimum	6.0
Maximum	44.0

Abbreviations: HAM-D-28 = 28-item Hamilton Rating Scale for Depression, MDD = major depressive disorder, MDE = major depressive episode.

in the length of the current MDE was statistically significant between groups with an ATHF of 2 or 3 versus ≥ 6 (Dunn multiple comparison test; difference in rank sum = –16.69; $p < .01$).

Of the 48 participants who were receiving active VNS at the 24-month follow-up, the median stimulation parameters were an "on" time of 30 seconds (range, 7–60 seconds); an "off' time of 5 minutes (range, 0.2–180 minutes); and a 10% median duty cycle (range, 0.27%–77.78%). For these 48 participants, the median current was 0.75 mA (range, 0.25–3.00 mA). Six patients had been set to zero mA between 15 and 24 months (including 1 patient who was explanted at 24 months).

Overall Status at Follow-Up: Primary Outcome

Table 4 presents results at baseline, 3 months (N = 59), 12 months (observed N = 54), and 24 months (observed N = 42). On the basis of symptom ratings at follow-up assessments, the acute antidepressant effects accounted for the bulk of the improvement, although additional improvement occurred by 12 months and was largely sustained after 24 months of VNS. Specifically, significant within-sample improvements from baseline were observed across the 3-month (acute study exit), 12-month, and 24-month assessments using either HAM-D-28 total scores or percent change in HAM-D-28 total scores in either the observed cases (OC) or the LOCF sample. For the HAM-D-28 total score, the mean (± SD) OC values were 36.8 (± 5.8) at baseline, 24.9 (± 11.2) at 3 months (N = 59), 20.6 (± 11.7) at 12 months (N = 54), and 20.2 (± 11.2) (N = 42) at 24 months (ANOVA, $F = 49.608$, $df = 3$, $p < .0001$). The mean (± SD) LOCF values were 21.1 (± 12.6) at 12 months (N = 59) and 21.6 (± 12.5) at 24 months (N = 59) (ANOVA, $F = 38.307$, $df = 3$, $p < .0001$; see Table 4). A statistical significance was found in OC and LOCF HAM-D-28 total scores between 3 and 12 months ($p = .002$, OC; $p = .017$, LOCF), but not between 12 and 24 months ($p = .068$, OC; $p = .744$, LOCF).

A nonsignificant increase in response rate was found, from 30.5% (N = 18/59) at 3 months to 44.1% at 12 months (N = 26/59, LOCF) (McNemar exact test, $p = .096$). The response rate showed a nonsignificant decrease to 42.4% (N = 25/59, LOCF) at 24 months (McNemar exact test, $p = .648$) (Figure 1).

The remission rate showed a nonsignificant increase from 15.3% (N = 9/59) at 3 months to 27.1% (N = 16/59, LOCF) at 12 months (McNemar exact test, $p = .07$). The remission rate showed a nonsignificant decrease to 22.0% (N = 13/59, LOCF) from 12 to 24 months (McNemar exact test, $p = .549$).

Persistence of Response Given 3-Month and 1-Year Status

Of 18 responders at 3 months, 13 (72%) of 18 participants remained responders at 12 months, and 9 (50%) of 18 participants sustained a clinically meaningful response (≥ 40% reduction in HAM-D-28 score) at 24 months (Table 5). Of 41 nonresponders at 3 months, 13 (32%) of 41 were responders at 12 months, and 16 (39%) of 41 were responders at 24 months. When considering the ≥ 50% reduction in HAM-D-28 cutoff, the likelihood of long-term (24-month) response to VNS was essentially the same for participants who had responded at 3 months (39%, 7/18) as compared with 3-month acute-phase nonresponders (39%, 16/41).

Of 13 responders at 12 months who had not been responders at 3 months, 10 (77%) of 13 sustained a clinically meaningful response (≥ 40% improvement in HAM-D-28 score) at 24 months. Examining LOCF HAM-D-28 total scores, 9 (35%) of 26 participants who were responders at 12 months lost their response at 24 months, whereas 8 (24%) of 33 participants who were nonresponders at 12 months were responders at 24 months.

Secondary Outcomes

Mean scores of both OC and LOCF groups for the MADRS, YMRS, and CGI-I are provided in Table 4. MADRS percent change from baseline for both OC and LOCF samples significantly improved over time (ANOVA, $F = 45.5$ [$F = 42.82$], $df = 3$, $p < .0001$). The CGI-I scores at 3 months, 12 months, and 24 months

Table 3. Summary of the Treatment History and Level of Treatment Resistance in the Cohort at Study Entry (N = 59)

	Level of Treatment Resistance[a]														
	ATHF Score 2 or 3 (N = 22)					ATHF Score 4 or 5 (N = 16)					ATHF Score ≥ 6 (N = 21)				
Participant Characteristic	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
No. of unsuccessful ATHF-defined treatments (current MDE)[b]	2.3	0.5	…	…	…	4.3	0.5	…	…	…	8.0	1.8	…	…	…
No. of unsuccessful mood disorder treatments (current MDE)	11.0	4.5	12.0	3.0	20.0	16.4	6.7	16.0	7.0	28.0	20.5	8.6	19.0	10.0	44.0
No. of unsuccessful mood disorder treatments (lifetime)	15.9	5.4	15.0	6.0	28.0	20.0	7.0	17.5	10.0	29.0	21.4	8.5	19.0	10.0	44.0
Lifetime depression, y	14.7	10.7	11.4	2.2	37.0	23.6	12.0	23.1	7.1	49.5	17.7	10.4	17.3	2.6	45.2
Duration of current MDE, y	5.4	7.8	2.7	0.2	37.0	12.9	13.1	10.5	0.8	49.5	12.8	10.6	9.5	2.1	45.2
Baseline HAM-D-28 score	36.0	6.2	37.7	23.5	45.5	37.0	4.3	37.5	27.5	43.0	37.5	6.5	37.0	26.0	51.5

[a]Resistance refers to the current MDE.
[b]Mood disorder treatments included antidepressant medications (tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, bupropion, venlafaxine, nefazodone, and trazodone [>200 mg per day]). Other mood disorder treatments included mood stabilizers, psychostimulants, antipsychotics, anxiolytics, phototherapy, and other types of alternative treatments (e.g., St. John's wort, flaxseed oil, and fish oil).
Abbreviations: ATHF = Antidepressant Treatment History Form, HAM-D-28 = 28-item Hamilton Rating Scale for Depression, Max = maximum, MDE = major depressive episode, Min = minimum.
Symbol: … = not applicable.

were also significantly improved (ANOVA, $F = 4.3$, $df = 2$, $p = .017$ [$F = 3.85$, $df = 2$, $p = .024$]), whereas the YMRS scores at 3 months, 12 months, and 24 months showed no significant change over time (ANOVA, $F = 1.47$, $df = 3$, $p = .23$ [$F = 1.86$, $df = 3$, $p = .14$]).

Functional Measures

The GAF scores at baseline, 3 months, 12 months, and 24 months are shown in Table 4. A significant improvement over time was found (ANOVA, $df = 3$) for both OC ($F = 27.33$, $p < .0001$) and for the LOCF analysis ($F = 44.86$, $p < .0001$).

Participants completed the MOS SF-36 at baseline (before VNS) and at 3 months (N = 57), 12 months (N = 49), and 24 months (N = 30). At 3 months after implant, participants were asked to compare specific functional assessment in MOS SF-36 with 1 year earlier, and 26% of them (N = 15) reported an improvement in health, 56% (N = 32) reported the same level of health, and 18% (N = 10) reported that their health had deteriorated. At 12 months, participants compared subjective improvement with their condition before implantation, and 47% (N = 23) reported it as improved, 33% (N = 16) as the same, and 20% (N = 10) as worse. Finally, at 24 months, compared with the pre-implant baseline, 56% (N = 17) felt improved, 37% (N = 11) the same, and 7% (N = 2) worse. Additional functional improvements at the assessment intervals are shown in Table 6.

Predictors of Long-Term Response

After 3 months of VNS, the number of unsuccessful adequate antidepressant treatment trials during the current depressive episode (Table 3) correlated with nonresponse to VNS (nonparametric Spearman rho correlation, $r = –0.329$, $p = .01$). Participants with fewer unsuccessful adequate antidepressant treatment trials had higher response rates.[8] This relationship between prior treatment resistance and VNS response (measured by HAM-D-28 change) held true at the 12-month LOCF assessment ($r = –0.297$, $p = .022$) but not at the 24-month LOCF assessment ($r = –0.05$, $p = .7$). Thus, the degree of treatment resistance at study entry and based on the number of failed treatment trials defined by ATHF correlated with nonresponse at 3 and 12 months, but not at 24 months. Thus, improvement at 24 months was unrelated to baseline ATHF treatment resistance. The percent changes from baseline were 43.8%, 49.1%, and 42.9% at 3, 12, and 24 months, respectively, in participants with an ATHF of 2 or 3. In participants with an ATHF of 4 or 5, the percent changes from baseline were 35.2%, 55.2%, and 45%, respectively. Finally, in participants with an ATHF of 6 or greater, results revealed 13.4%, 27.25%, and 33.3% change from baseline (Figure 2).

Concomitant Treatments

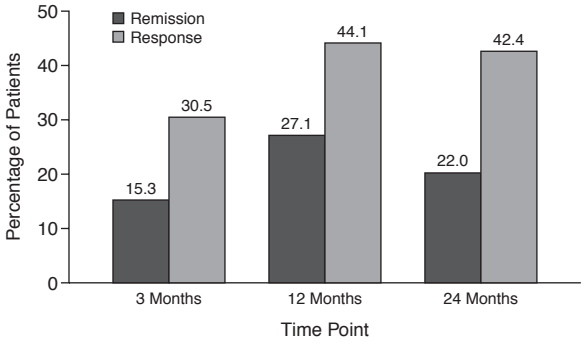
Three participants received a course of ECT during the 24-month period while receiving VNS therapy. Not accounting for any changes in doses, the mean concomitant psychotropic, including sedative hypnotic, or anxiolytic, as well as antidepressant and mood-stabilizing medications, was 4.3 (± 1.9) at both baseline and 3 months, 4.5 (± 2.4) at 12 months, and 4.9 (± 2.5) at 24 months (OC). The mean number of concomitant antidepressant medications was 1.5 (± 0.9) at baseline and at exit from the acute phase, 1.6 (± 0.9) at 12 months, and 1.6 (± 0.9) at 24 months. No statistically significant difference was found across these 3 intervals for number of concomitant psychotropic medications (ANOVA,

Table 4. Outcome Measures at Baseline, 3 Months, 12 Months, and 24 Months[a]

Outcome Measure	Time Point: Baseline N	Baseline Score	3 Months N	3 Months Score	12 Months N	12 Months Score	24 Months N	24 Months Score
HAM-D-28								
OC	59	36.8 ± 5.8	59	24.9 ± 11.2[b]	54	20.6 ± 11.7[b]	42	20.2 ± 11.2[b]
LOCF	59	36.8 ± 5.8	59	24.9 ± 11.2[b]	59	21.1 ± 12.6[b]	59	21.6 ± 12.5[b]
MADRS								
OC	59	33.4 ± 5.7	59	22.9 ± 11.7[b]	34	12.6 ± 9.6[b]	42	19.9 ± 11.4[b]
LOCF	59	33.4 ± 5.7	59	22.9 ± 11.7[b]	59	16.8 ± 12.1[b]	59	19.8 ± 11.1[b]
YMRS								
OC	59	2.1 ± 1.6	59	2.1 ± 3.3	55	1.5 ± 3.4	43	1.4 ± 2.3
LOCF	59	2.1 ± 1.6	59	2.1 ± 3.3	59	1.4 ± 3.3	59	1.2 ± 2.0
GAF								
OC	59	40.6 ± 6.0	59	57.4 ± 16.2[b]	51	62.8 ± 19.7[b]	42	62.6 ± 14.9[b]
LOCF	59	40.6 ± 6.0	59	57.4 ± 16.2[b]	59	61.6 ± 19.1[b]	59	62.0 ± 17.3[b]
CGI								
OC	59	4.1 ± 0.7	59	2.9 ± 1.1[b]	55	2.5 ± 1.3[b]	42	2.4 ± 1.2[b]
LOCF	59	4.1 ± 0.7	59	2.9 ± 1.1[b]	59	2.5 ± 1.3[b]	59	2.4 ± 1.2[b]

[a]All scores reported as mean ± SD.
[b]Statistically significant from baseline.
Abbreviations: CGI = Clinical Global Impressions scale, GAF = Global Assessment of Functioning, HAM-D-28 = 28-Item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, OC = observed cases, YMRS = Young Mania Rating Scale.

Figure 1. Rates of Remission and Response (LOCF) to Vagus Nerve Stimulation Therapy Over 2 Years (N = 59)[a]



[a]Although change was substantial from baseline to 3 months (the acute trial), the difference between response rates at 3, 12, or 24 months was not statistically significant (p > .05).
Abbreviation: LOCF = last observation carried forward.

Table 5. Clinical Outcomes Over Time in 18 Participants With 3-Month Acute Response to Vagus Nerve Stimulation Therapy[a]

HAM-D-28 Status at 3 Months	12-Month Outcome[b]	24-Month Outcome[c]
80%–100% (N = 4)	3 continued improved, 1 < 40%	3 continued improved, 1 < 40%
60%–79% (N = 8)	6 continued improved, 2 < 40%	4 continued improved, 4 < 40%
50%–59% (N = 6)	4 continued improved, 2 < 40%	2 remained > 40%, 4 were below this threshold
Total:	13/18 continued well, 5 < 40%	9/18 remained well, 9 < 40%
Percentage:	72.2% remained well	50% remained well

[a]Response defined as ≥ 40% improvement in HAM-D-28 score from baseline.
[b]Continued improved mean HAM-D-28 was ≥ 40% at 12 months.
[c]Continued improved mean HAM-D-28 was ≥ 40% at 24 months.

F = 0.93, df = 2, p = .39) or antidepressant medications (ANOVA, F = 0.2, df = 2, p = .82).

Adverse Events and Participant Withdrawal

The most common AEs at 3 months versus 24 months were voice alteration (60% versus 27%), dyspnea (15% versus 8%), and neck pain (22% versus 13%). These effects were typically mild and restricted to the time of stimulation. By 24 months, 6 of 59 (10%) participants had stopped VNS and had withdrawn from the study. No participant discontinued VNS solely because of AEs. Of these 6 participants, 2 died: 1 of sepsis after colorectal surgery and 1 of lung cancer. Four participants had the generator explanted owing to lack of efficacy (2 of these 4 participants had their last visit at 24 months). An additional 6 participants (including 1 participant who was explanted at 24 months) had chosen to leave the VNS generator in place, but had it turned off several months before their 24-month visit. Thus, of the original 59 participants who were implanted, 48 of 59 (81%) still had the device implanted and active at 24 months.

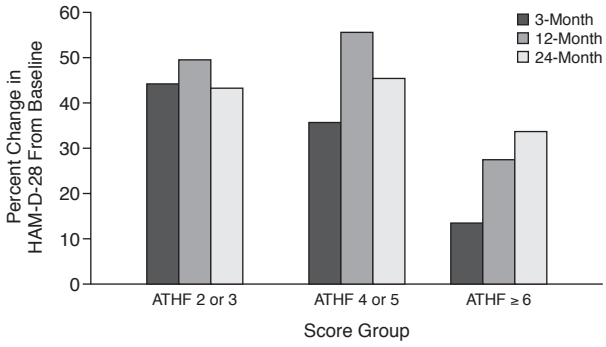
Between the initiation of stimulation (turning on the device) and the 24-month follow-up, 40 serious AEs (SAEs) involving 25 participants occurred, of which 30 SAEs involving 21 participants occurred during the naturalistic follow-up. These 40 AEs included 3 for suicide attempts, 10 for worsened depression, 1 for dysphoria, 2 for a manic episode, 1 for agitation, and 1 for CNS toxicity.

Table 6. Percentage of Personal Functional Improvement From Baseline Subjective Assessment (MOS SF-36) in a Cohort of Patients Receiving Vagus Nerve Stimulation Therapy

	Score					
	3 Months (N = 59)		12 Months (N = 49)		24 Months (N = 30)	
Subscale	%	± SD	%	± SD	%	± SD
General health perception	2.6	25.4	5.3	24.4	8.8	21.5
Vitality	14.9	20.9	22.1	27.3	26.7	40.5
Social functioning	15.6	28.1	24.2	33.6	38.3	30.6
Emotional role	10.7	37.7	24.8	47.4	26.7	40.5
Mental health	16.1	21.7	24.5	27.1	33.6	25.5
Physical functioning	0.5	22.2	3.4	24.4	7.8	19.9
Bodily pain	–7.6	29.7	–4.3	28.9	0.1	28.7

Abbreviations: MOS = Medical Outcomes Study, SF-36 = Short Form-36.

Figure 2. Response to Vagus Nerve Stimulation Therapy Over 2 Years as a Function of Treatment Resistance, by ATHF Score



Abbreviations: ATHF = Antidepressant Treatment History Form, HAM-D-28 = 28-item Hamilton Rating Scale for Depression.

All other SAEs were not psychiatrically related. No SAE was thought to be device related. There were no complications resulting from the use of ECT while the VNS device was implanted. The VNS device was turned off during the administration of ECT.

DISCUSSION

This report provides valuable insight into the long-term care of a particularly treatment-resistant patient population. The naturalistic 24-month follow-up study of ongoing adjunctive VNS for severely depressed participants revealed that most of the antidepressant response to VNS was observed during the acute phase, although additional improvement was also seen at 12 months. The benefits seen at 12 months were largely sustained for the group at 24 months, analogous to findings with VNS in epilepsy.[5] In general, 2 of 3 initial responders were likely to show continued clinical benefit after 12 months of VNS, and 1 of 2 initial responders continued to evidence response after 24 months. This finding contrasts with some of the long-term follow-up studies in which relapse rates in depressed populations with similar levels of treatment resistance have exceeded 60%.[4] Interestingly, 39% of the initial nonresponders showed substantial benefit by 24 months. The degree of functional improvement found at 3 months continued to increase at both 12 and 24 months.

As expected,[5,7,8] side effects also diminished despite the treatment-resistant nature of this sample and the participants' potential susceptibility to AEs. Through 24 months, VNS continued to be well tolerated, with low dropout rates. Of the original cohort, 90% still had the VNS system implanted, and 81% (48/59) of the original group still had the device activated. It is noteworthy that of the 6 participants explanted by the 24-month follow-up, none were explanted solely because of AEs.

Of importance is that two thirds of the acute responders to VNS sustained their responses at 1 year, and half did so at 2 years. Although response rates were not significantly different at 12 and 24 months, individual responses varied considerably over time, with the response rates of 9 participants decreasing to less than the 40% benchmark from 12 to 24 months. Conversely, 8 other participants improved in status from nonresponse at 12 months to response at 24 months.

Further work is needed to identify predictors of treatment response at both the short (3- and 12-month) and longer (24-month) time points. Mirroring the finding of the acute trial, greater treatment resistance at the start of the trial was associated with nonresponse at 12 months. This relationship was no longer significant at the 24-month evaluation. In fact, the response status of approximately equal numbers of participants changed between the first and second year. This change in response status raises the question of whether, after some period of no response to VNS, a long-term lack of benefit could be predicted. While these open data suggest that even after a full year of an initially minimal response, adjunctive VNS may still be useful, controlled studies are needed to fully address this hypothesis.

This study has limitations inherent in its naturalistic follow-up design. As this was a pilot study, no control group was included in the design, which makes it difficult to compare these outcomes with those from other continuation and maintenance studies of other antidepressant strategies. In addition, Axis II and substance abuse comorbid diagnoses were not collected. After completion of the acute phase, the study lacked control over stimulation parameters, concomitant psychopharmacology, and ECT treatments. Although these participants were treatment resistant, with a median duration greater than 6 years for the current MDE, the possibility of spontaneous partial or total remission attributable to the natural course of the disease must also be consid-

ered.[18] The small sample size and concomitant treatments prohibit drawing any conclusions regarding the type of interventions most useful to "rescue" relapsed participants.

In summary, adjunctive VNS demonstrated a sustained clinical response over 2 years in a treatment-resistant cohort. Individual responses varied, and VNS was generally well tolerated, with a low attrition rate.

Drug names: bupropion (Wellbutrin and others), lithium (Eskalith, Lithobid, and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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