A 1-Year Pilot Study of Vagus Nerve Stimulation in Treatment-Resistant Rapid-Cycling Bipolar Disorder

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Objective: Vagus nerve stimulation (VNS) appears to be an effective treatment option for patients with treatment-resistant unipolar and bipolar depression. The aim of the present study was to investigate the efficacy of VNS in a group of patients with treatment-resistant rapid-cycling bipolar disorder (RCBD) who were excluded from previous trials.

Method: Nine outpatients with a DSM-IV-TR diagnosis of treatment-resistant RCBD were treated for 40 weeks with open-label VNS. The first patient was enrolled in June 2001, and the last patient completed the study in July 2005. Patients recorded their depression and mania mood symptoms on a daily basis throughout the study using the National Institute of Mental Health prospective life charting methodology and daily mood ratings. Patients were assessed every 2 weeks during the 2-month baseline period before device activation, every 2 weeks for the remaining 40 weeks of the study, and at the end of the study with the 24-item Hamilton Rating Scale for Depression (HAM-D-24), the 10-item Montgomery-Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Clinical Global Impressions (CGI) scale, the Global Assessment of Functioning (GAF) scale, and the 30-item Inventory of Depressive Symptomatology Self-Report (IDS-SR-30). Any adverse events or device complications were also recorded at each visit. The prospective life charts were analyzed by calculating the area under the curve. Statistical analysis was performed with a mixed-model repeated-measures regression analysis for repeated measures of the various rating scales. Significant p values were $\leq .05$.

Results: Over the 12-month study period, VNS was associated with a 38.1% mean improvement in overall illness as compared to baseline ($p = .012$), as well as significant reductions in symptoms as measured by the HAM-D-24 ($p = .043$), MADRS ($p = .003$), CGI ($p = .013$), and GAF ($p < .001$) rating scales. Common adverse events were voice alteration during stimulation and hoarseness.

Conclusion: These data suggest that VNS may be an efficacious and well-tolerated treatment option for patients with treatment-resistant RCBD. Currently, no comparison is available in the literature. Larger randomized trials are needed to verify these findings.

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Rapid-cycling bipolar disorder (RCBD), defined as 4 or more fully syndromic mood disturbances in the preceding 12 months,[1] is associated with a relatively poor treatment response.[2] Anticonvulsants have been some of the most effective treatments to date for RCBD, although relapse rates remain high.[3] Vagus nerve stimulation (VNS) therapy (Cyberonics, Inc., Houston, Tex.) is an anticonvulsant treatment that is delivered by a small pacemaker-like device. Vagus nerve stimulation was approved by the U.S. Food and Drug Administration (FDA) in 1997 as treatment for refractory partial-onset epileptic seizures and, more recently, in 2005, for adjunctive long-term treatment of chronic or recurrent depression for patients who are experiencing a major depressive episode (unipolar or bipolar) and have not had an adequate response to 4 or more antidepressant treatments.

In the pivotal study[4] that led to FDA approval for VNS for major depressive episodes, 23 patients with bipolar depression were included among the 222 evaluable patients (last observation carried forward) in the acute phase of the trial, but those with RCBD were excluded because of the known differences in course of illness for these patients.[4] Given the unmet need for effective RCBD therapies, an innovative treatment may have a substantial public health impact. The objective of the

present study was to assess the efficacy and safety of VNS as adjunctive treatment for treatment-resistant RCBD.

METHOD

Patient Population

This study included men and women, aged 18 to 70 years. All participants met criteria for RCBD according to the DSM-IV-TR.[1] Patients were required to have a history of depressive, manic, or hypomanic symptoms at least 50% of the time in the prior year despite ongoing treatment, as documented by the National Institute of Mental Health retrospective life charting methodology (NIMH LCM-r).[5] Additionally, participants had to meet criteria for treatment resistance, which was defined as intolerance or nonresponse to treatment with both lithium and valproate and at least 2 of the following, either as monotherapy or in combination: carbamazepine, lamotrigine, gabapentin, topiramate, olanzapine, risperidone, quetiapine, or clozapine.

Study Design

The study was an open-label, nonrandomized, single-arm, longitudinal, pilot study conducted at 2 sites. It was approved by the institutional review boards at both participating sites, and all patients provided verbal and written informed consent after a full explanation of the procedures. The first patient was enrolled in June 2001, and the last patient completed the study in July 2005.

Baseline period. The study protocol prescribed that prior to implantation with the VNS device, patients would complete an 8-week baseline period. Patients were not discontinued from their psychotropic medications but, rather, had to have maintained a stable psychotropic medication regimen for at least 4 weeks prior to their baseline visit. This medication regimen was continued throughout all phases of the study. During the baseline period, clinical evaluations were performed every 2 weeks, and patients were given a prospective life chart and instructed to rate the severity of depressive or manic symptoms each day. This chart was subsequently reviewed by a clinician, and adjustments could be made by the patient and clinician at these visits if deemed necessary to ensure uniformity both within and across subjects. Study personnel at both sites were trained in the use of these procedures. To qualify for implantation with VNS, participants had to have ongoing manic, hypomanic, or depressive symptoms for over 50% of the time during the baseline assessment period, as assessed using the prospective daily self-rated life charts.

Implantation. The device implantation and treatment delivery used in this study were identical to those in the studies of treatment-resistant epilepsy[6–8] and depression.[4]

Recovery period. Following device implantation, there was a 14-day period during which VNS remained off to allow for surgical recovery.

Stimulation adjustment period. The initial stimulation parameters called for in the protocol were 20 Hz, 500-microsecond pulse width, and an on/off cycle of 5 minutes on and 30 seconds off. At the end of the recovery phase, the device was initially programmed to an output current of 0.25 mA and was increased gradually in 0.25-mA increments to a comfortably tolerated setting not to exceed 0.75 mA. Once a tolerable output current level was obtained during the first stimulation adjustment visit, patients left the clinic with these settings. Additional increases in 0.25-mA increments could be made at any time during a 2-week stimulation adjustment period following recovery, with a target output current of 0.75 mA—or a lower level if this level was not comfortable for the participant. Clinical evaluations were allowed as often as needed for the purpose of adjusting the stimulation parameters.

Treatment period. After the 2-week stimulation adjustment period, participants were seen every 2 weeks during the treatment period, which consisted of the remaining 40 weeks of the study. Stimulation parameter settings for each patient were held constant for 10 weeks after the stimulation adjustment period unless side effects necessitated a change in the settings. If there was no improvement after 10 weeks of treatment, several changes could be made to the stimulation parameters. These changes included increasing the output current to 2.0 mA maximum, providing that this degree of stimulation was comfortable for the patient, or different *on* and *off* times (duty cycles) could be tried in order to enhance effectiveness and tolerability. Additionally, other parameters, such as the frequency, could be changed. The total length of stimulation, including the 2-week stimulation adjustment period, was 42 weeks. A protocol deviation occurred in 1 patient for whom the duty cycle off time was 180 minutes.

Concomitant Treatment

Due to the severity of illness, the protocol allowed for the use of psychotropic medications. Clinicians at both sites made every effort to keep medication dosage and type stable for at least 4 weeks prior to the baseline visit as well as during the baseline visits and the 44 weeks postimplantation during which the study took place (data are available on request). If a rescue medication was needed in the investigator's clinical judgment, up to 3 mg/day of lorazepam, 20 mg/day of olanzapine, or 20 mg/day of citalopram could be added. However, clinical judgment and patient history and response could dictate the choice of rescue medication use. Over the course of up to 1 year of follow-up, 3 subjects had a medication added (bupropion, N = 1; quetiapine, N = 2; clozapine, N = 1; risperidone, N = 1). Six subjects either had no other psychotropic medication added or had decreases in concomitant psychotropic medication. Simultaneous use of investigational drugs, investigational devices, or electroconvulsive therapy was not permitted during the study.

Table 1. Demographic and Clinical Characteristics With Overall Illness Percent Improvement

Patient No.	Sex	Age, y	Diagnosis Type[a]	Age at Illness Onset, y	Age at Diagnosis, y	No. of Prior Suicide Attempts	Concurrent Mood Disorder Treatments at Baseline	Overall Illness[b] Percent Improvement From Baseline, Mean ± SD
1	F	42	I	20	20	2	Valproic acid, AAP, MAOI, bupropion, SSRI	55.1 ± 77.2
2	F	52	I	6	45	0	Valproic acid, AAP, BZD, bupropion, STIM	22.2 ± 42.2
3	M	43	I	23	31	0	Lamotrigine, AAP, SNRI, TCA	64.9 ± 33.8
4	M	48	II	7	34	1	Lamotrigine, AAP, BZD, SNRI, SSRI	4.5 ± 82.1
5	F	52	I	5	20	6	Gabapentin, AAP, SNRI, SSRI	82.7 ± 35.8
6	F	23	II	14	14	2	Valproic acid, AAP, BZD, bupropion, SSRI	63.7 ± 42.8
7	F	57	I	30	32	1	Carbamazepine, AAP, BZD, SSRI, TCA	32.3 ± 52.2
8	F	51	I	19	21	2	None reported	12.7 ± 39.6
9	F	54	I	19	35	0	Lamotrigine, AAP, lithium, bupropion, SSRI	3.6 ± 38.6

[a]Diagnosis type refers to bipolar I disorder for type I and bipolar II disorder for type II.
[b]Assessed by the National Institute of Mental Health prospective life charting methodology.
Abbreviations: AAP = atypical antipsychotic, BZD = benzodiazepine, F = female, M = male, MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, STIM = stimulant, TCA = tricyclic antidepressant.

Evaluations and Efficacy Measures

During the 2-month baseline period, initial evaluations included neurologic, medical, and medication histories; physical and neurologic examinations; and cardiac monitoring, using a Holter device, for patients who were more than 50 years old. Patients were diagnosed using the Structured Clinical Interview for DSM-IV-TR (SCID-I/P) criteria.[9] The self-rated prospective life charting method[10] was used by each patient to record his or her depression and mania mood symptoms on a daily basis throughout the study. Mood symptom severity was rated on the following scale ranging from –4 to +4: –4 = severe depression, –3 = high-moderate depression, –2 = low-moderate depression, –1 = mild depression, 0 = none, +1 = mild mania, +2 = low-moderate mania, +3 = high-moderate mania, +4 = severe mania.

Mood ratings were recorded each day on a bar graph such that the relative time symptomatic in a given month could be calculated as the area under the curve. Patients were instructed to rate both depressive and manic symptoms each day and could score on both dimensions. The area under the curve measurements could be compared to assess changes in the duration and severity of symptoms throughout the study. These mood charts were reviewed with a clinician during each study visit and could be adjusted if deemed necessary in the clinician's judgment. For example, if a subject charted moderate depression but discussion with a clinician about level of functioning and actual symptoms reflected a milder level of depression, the patient and clinician could choose to modify the chart.

The presence of depressive symptoms was further assessed by using the 28-item Hamilton Rating Scale for Depression (HAM-D-28)[11–13] and the 10-item Montgomery-Asberg Depression Rating Scale (MADRS).[14] Even though the HAM-D-28 was administered, the first 24 items defined the HAM-D-24 score, which was reported for each patient. The HAM-D-24 uses the first 17 items of the HAM-D-17[11] and adds the items of diurnal variation, depersonalization and derealization, paranoid symptoms, obsessional and compulsive symptoms, helplessness, hopelessness, and worthlessness.

Self-reported symptoms of depression were assessed using the 30-item Inventory of Depressive Symptomatology Self-Report (IDS-SR-30).[15–17] Symptoms of mania and hypomania were additionally assessed using the Young Mania Rating Scale (YMRS).[18] The Clinical Global Impressions (CGI)[19] ratings were used to evaluate overall symptom change and change in symptom severity. The Global Assessment of Functioning (GAF)[1] score was also used to assess overall level of functioning that takes psychological, social, and occupational factors into consideration.

Each of these assessments was performed every 2 weeks during the 8-week baseline period, prior to device activation, every 2 weeks for the remaining 40 weeks of the study, and then at the end of the study. Any adverse events or device complications were documented at each visit as well.

Statistical Analysis

Age, sex, illness type, age at diagnosis, number of prior attempted suicides, mood disorder treatments at baseline, and overall illness percent improvement from baseline were given for individual patients.

The primary a priori endpoint was symptom severity as assessed by the NIMH prospective life charting methodology (NIMH LCM-p).[10] The LCM-p severity rating scores for depression and mania—integer values of 0 to 4—were averaged over the baseline and treatment (excluding data from recovery and adjustment) periods, respectively, to obtain overall baseline and VNS treatment means for each patient. Overall mean improvement (baseline minus VNS) and percent improvement for depression, mania, and total illness (depression + mania) were

Table 2. NIMH Life Charting Methodology Clinical Outcomes for Vagus Nerve Stimulation (N = 9)

Efficacy Measure[a]	Baseline Score, Mean ± SD	Improvement From Baseline, Mean ± SD (SEM)	p Value (Ho: μ = 0)	Percent Improvement in the Mean From Baseline[b,c]
Total illness	2.08 ± 0.61	0.79 ± 0.73 (0.24)	.012*	38.1
Depression symptoms	1.83 ± 0.82	0.69 ± 0.72 (0.24)	.021*	37.9
Mania symptoms	0.25 ± 0.25	0.10 ± 0.17 (0.06)	.103	40.2

[a]Assessed by NIMH life charting methodology.
[b]Mean improvement from baseline divided by baseline mean × 100.
[c]These values were calculated before the values were rounded for the baseline score and the improvement from baseline.
*Statistically significant, p < .05.
Abbreviations: Ho = null hypothesis, NIMH = National Institute of Mental Health, SEM = standard error of the mean.

Table 3. Secondary Clinical Outcomes for Vagus Nerve Stimulation (N = 9)

Efficacy Measure	Baseline Score, Mean ± SD	Absolute Improvement From Baseline, Mean ± SD[a] (SEM)	p Value (Ho: μ = 0)	Percent Improvement From Baseline, Mean ± SD[a] (SEM)	p Value (Ho: μ = 0)
HAM-D-24	20.9 ± 7.2	7.1 ± 9.5 (2.2)	.015*	27.3 ± 49.7 (11.1)	.043*
YMRS	7.4 ± 8.2	4.2 ± 5.0 (0.4)	< .001*	–18.5 ± 295.1 (50.6)	.726
MADRS	22.6 ± 5.9	9.2 ± 9.7 (1.9)	.002*	38.3 ± 46.2 (8.4)	.003*
CGI	4.2 ± 0.7	1.0 ± 1.3 (0.3)	.009*	20.6 ± 32.3 (6.3)	.013*
IDS-SR	33.1 ± 10.7	7.9 ± 14.8 (3.7)	.071	17.3 ± 46.6 (10.6)	.147
GAF	55.1 ± 6.2	10.7 ± 8.7 (1.4)	< .001*	21.4 ± 16.4 (2.7)	< .001*

[a]$SD = \sqrt{\hat{\sigma}_B^2 + \hat{\sigma}_W^2}$, where σ_B^2 and σ_W^2 are estimates, respectively, of between-patient and within-patient variance components.
*Statistically significant, p < .05.
Abbreviations: CGI = Clinical Global Impressions scale, GAF = Global Assessment of Functioning scale, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, Ho = null hypothesis, IDS-SR = Inventory of Depressive Symptomatology–Self-Report, MADRS = Montgomery-Asberg Depression Rating Scale, SEM = standard error of the mean, YMRS = Young Mania Rating Scale.

calculated for each patient and analyzed for statistical significance using the paired t test. In addition, mixed-model repeated-measures (MMRM) regression analysis with patients as random effects and first-order autoregressive V-C matrix (SAS software, Version 9.1.3; SAS Institute Inc., Cary, N.C.; PROC GLIMMIX) was performed on the daily total illness scores for the purpose of characterizing trends over time.

Secondary outcome measures—HAM-D-24, YMRS, MADRS, CGI, IDS-SR-30, and GAF—were analyzed using MMRM analysis of covariance with patients as random effects in the model, visit (14–52) as a fixed effect, and baseline score as a covariate. The baseline score was calculated as the mean of four 8-week baseline scores. A compound symmetric V-C matrix was postulated allowing estimates of between-patient and within-patient variance components, σ_B^2 and σ_W^2, respectively. Hence, the standard deviation of the overall sample mean was estimated as $SD = \sqrt{\hat{\sigma}_B^2 + \hat{\sigma}_W^2}$. Linear and quadratic trends over visits were tested by using contrasts.

RESULTS

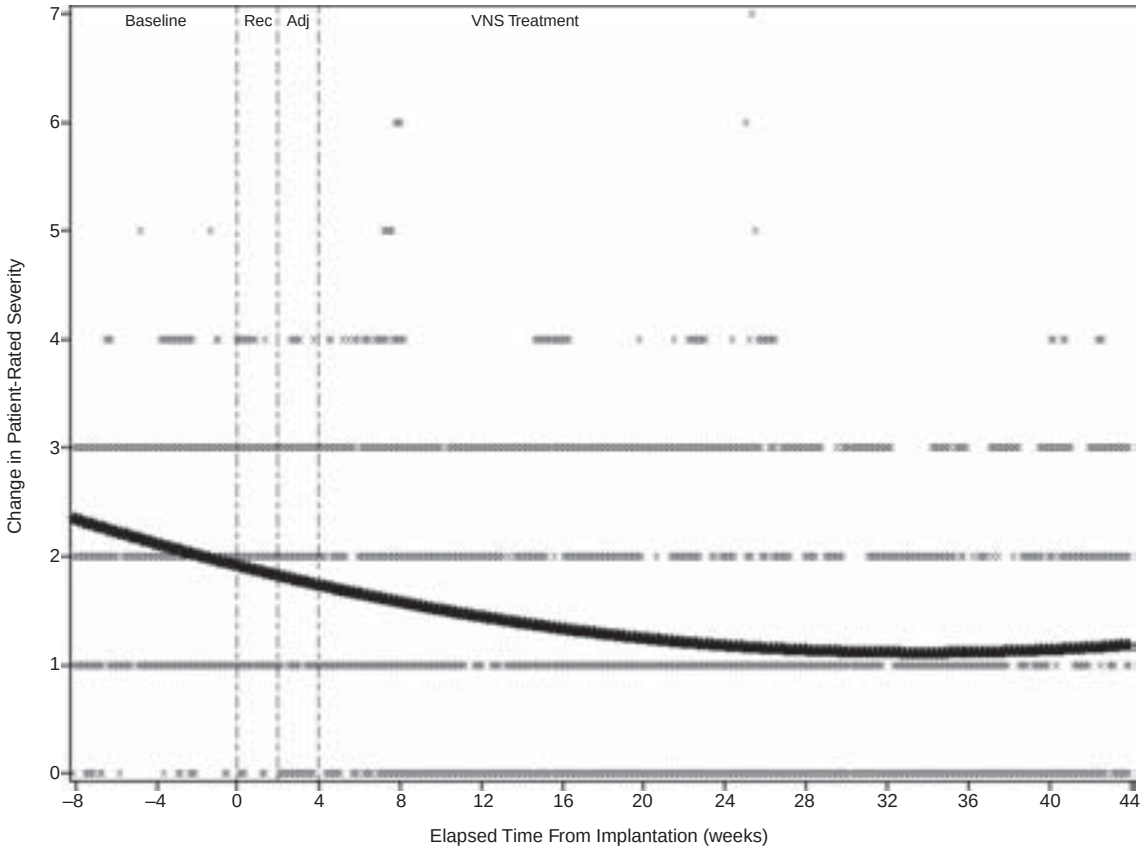
Patients

A total of 12 patients were enrolled, and 10 subjects were implanted with the VNS device. Two patients exited the study during the baseline period because they did not meet eligibility criteria. Additionally, of the 10 subjects implanted, 2 subjects did not complete the 40-week treatment period. Reasons for termination after implantation were noncompliance with study procedures (N = 1) and suicide (N = 1). In the investigators' judgment, the suicide was not related to the treatment but, rather, to the underlying mood disorder. Of the 10 subjects implanted, the patient who was noncompliant with study procedures was not evaluable for efficacy. Therefore, 9 participants are included in the efficacy analysis. Demographic and clinical characteristics are reported for the 9 evaluable patients and are summarized in Table 1. Concomitant mood disorder treatments and percent improvement in total illness severity score relative to the baseline are also included in this table. There were 7 women and 2 men, and the mean ± SD age was 46.9 ± 10.2 years.

Efficacy

The primary efficacy endpoint was change in severity of symptoms following VNS treatment (N = 9) as assessed by the LCM-p through up to 12 months of follow-up (Table 2). Averaged over the 12-month study period, VNS was associated with a 38.1% mean improvement from baseline in total illness scores (mean ± SD: 0.79 ± 0.73, p = .012). Similarly, a 37.9% improvement (0.69 ± 0.72, p = .021) was exhibited in depression symptom scores, and a 40.2% improvement (0.10 ± 0.17, p = .103), in mania symptom scores. The mean improvement from baseline in total illness and depression scores

Figure 1. Overall Illness as Measured by the National Institute of Mental Health Life Charting Methodology: Individual Responses and Trend Curve[a] (N = 9)



[a]Statistically significant linear ($p < .0001$) and quadratic ($p = .020$) trend coefficients.
Abbreviations: Adj = adjustment, Rec = recovery, VNS = vagus nerve stimulation.

was statistically significant at $p < .05$. In addition, a statistically significant ($p < .0001$) decrease in total illness scores is exhibited in the graph of Figure 1.

Both absolute and percent changes from baseline were analyzed for the secondary clinical outcomes (Table 3). Treatment with VNS for up to 12 months showed a statistically significant overall mean percent improvement from baseline in the HAM-D-24 ($p = .043$), MADRS ($p = .003$), CGI ($p = .013$), and GAF ($p < .001$) rating scales. The mean percent change from baseline for YMRS was negative (–18.5%), indicating a worsening condition in general, but was not statistically different from zero ($p = .726$); however, the YMRS mean improvement from baseline (4.2) was statistically significant ($p < .001$). The apparent contradiction is the result of a negatively skewed percent improvement distribution occasioned by 2 patients' exhibiting YMRS scores that did worsen with time but which were exaggerated to extreme value status owing to low baseline scores when expressed as percentages. The mean percent improvement from baseline of 17.3% in IDS-SR-30 also reflected improvement but was not statistically significant ($p = .147$).

Adverse Events

No patients withdrew from the study because of adverse events. The adverse events that occurred in more than 2 of the patients were hoarseness, postoperative pain/burning at the device site, voice change with stimulation, and shortness of breath. The majority of these adverse effects improved with adjustment of the device parameters. No serious adverse events related to VNS occurred during the study.

DISCUSSION

This investigation is the first prospective study of patients with RCBD treated with VNS reported in the literature. This 12-month, open-label study of VNS used in 9 patients with treatment-resistant RCBD revealed overall reductions in manic and depressive symptoms. Percent improvements of 38.1%, 37.9%, and 40.2% (by prospec-

tive life charts) in overall illness, depressive symptoms, and mania symptoms, respectively, as well as statistically significant reductions in symptoms as measured with the HAM-D-24 ($p = .043$), MADRS ($p = .003$), CGI ($p = .013$), and GAF ($p < .001$) rating scales, suggest efficacy in this highly treatment-resistant group. Vagus nerve stimulation was well tolerated, with the overall pattern of side effects during the trial being similar to those reported in the studies of epilepsy[6–8] and depression.[4] The most common side effect was voice alteration during stimulation. The incidence and severity of this side effect are typically related to the intensity of the output current and tended to improve following stimulation adjustments. No patients discontinued VNS because of adverse events.

Given that RCBD is characterized by a high degree of variability, monthly or even weekly cross-sectional ratings may miss entire episodes or mood fluctuations that occur between clinical evaluations. Utilization of the NIMH LCM-p[10] was a strength of this study. This methodology was used to quantify a more detailed longitudinal course of the patients' symptoms, which allowed for a more accurate description of the severity, frequency, and duration of the patients' illness and their response to VNS.

The design of the study had several limitations. The trial was an open-label, uncontrolled study, making it possible that some of the improvement was secondary to spontaneous remission or placebo response. Although this limitation can be confirmed only with a randomized, sham-controlled trial, several factors argue against this possibility. A placebo response tends to have a different pattern than that seen with a drug treatment effect. Symptomatic improvement seen with VNS was generally more delayed in onset and was gradual and stable, which resembles the pattern seen with a drug treatment effect rather than that seen in a placebo response.[20] This pattern of improvement also resembles that seen in the VNS depression trials.[4,21,22] Additionally, because this was a treatment-resistant group, the patients had many prior opportunities to exhibit a placebo response. They were also, in part, selected because of the chronicity of their disease (patients had to be symptomatic at least 50% of the time in the prior year despite ongoing treatment), making the possibility of spontaneous remission low.

Patients varied considerably in the type of concomitant pharmacologic treatment they received, and medications and dosages were changed during the trial. Ideally, a controlled trial would definitively rule out the effects of concomitant pharmacologic treatment. The use of combination therapy has become standard care in the treatment of the majority of patients with bipolar disorder.[23–25] The National Center for Health Statistics examined prescriptions for psychotropic medications in more than 38,000 visits to physicians and found that one of the strongest predictors of psychotropic polypharmacy was a diagnosis of bipolar disorder.[26] Hence, varied and complex medication regimens at study entry are to be expected in this population. The fact that 6 of the 9 subjects had no psychotropic medication changes or only decreases in concomitant psychotropics is also noteworthy because ongoing mood symptoms typically lead to the addition of psychotropics.

Trials for treatments of RCBD are limited. Calabrese et al.[27] conducted a double-blind, parallel-group comparison of lithium and divalproex for the long-term treatment of RCBD in 254 patients whose illness was not characterized as treatment-resistant. The rates of relapse into a mood episode were 56% for lithium treatment and 50% for divalproex treatment, and none of the outcome comparisons reached statistical significance.[27] Another trial[28] compared lamotrigine to placebo in 324 RCBD patients, and although 41% of patients in the treatment group were stable without relapse for 6 months, the time to additional pharmacotherapy between the 2 groups did not reach statistical significance.[28] Small open trials of high-dose thyroxine augmentation for treatment-resistant RCBD have yielded positive results. Bauer and Whybrow[29] found that 10 of 11 patients improved significantly following high-dose levothyroxine augmentation. Baumgartner and colleagues[30] reported significant decreases in the mean number of relapses and mean duration of hospitalization in 6 patients treated with high-dose thyroxine augmentation.

The results of this study suggest that VNS may be a viable treatment option for some patients with treatment-resistant RCBD. Randomized, sham-controlled, and more adequately powered trials are needed to further elucidate the efficacy and utilization of VNS in patients with treatment-resistant RCBD.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), levothyroxine (Synthroid, Tirosint, and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax and others).

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