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Original Research

Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: Acute and chronic effects

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ABSTRACT

Background: Major depressive disorder is a prevalent, disabling, and often chronic or recurrent psychiatric condition. About 35% of patients fail to respond to conventional treatment approaches and are considered to have treatment-resistant depression (TRD).
Objective: We compared the safety and effectiveness of different stimulation levels of adjunctive vagus nerve stimulation (VNS) therapy for the treatment of TRD.
Methods: In a multicenter, double blind study, 331 patients with TRD were randomized to one of three dose groups: LOW (0.25 mA current, 130 μs pulse width), MEDIUM (0.5–1.0 mA, 250 μs), or HIGH (1.25–1.5 mA, 250 μs). A highly treatment-resistant population (>97% had failed to respond to ≥6 previous treatments) was enrolled. Response and adverse effects were assessed for 22 weeks (end of acute phase), after which output current could be increased, if clinically warranted. Assessments then continued until Week 50 (end of long-term phase).
Results: VNS therapy was well tolerated. During the acute phase, all groups showed statistically significant improvement on the primary efficacy endpoint (change in Inventory of Depressive Symptomatology-Clinician Administered Version [IDS-C]), but not for any between-treatment group comparisons. In the long-term phase, mean change in IDS-C scores showed continued improvement. Post-hoc analyses demonstrated a statistically significant correlation between total charge delivered per day and decreasing depressive symptoms; and analysis of acute phase responders demonstrated significantly greater durability of response at MEDIUM and HIGH doses than at the LOW dose.
Conclusions: TRD patients who received adjunctive VNS showed significant improvement at study endpoint compared with baseline, and the effect was durable over 1 year. Higher electrical dose parameters were associated with response durability.

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Introduction

Depression is estimated to affect 350 million people worldwide [1]. In the United States, the lifetime prevalence of major depressive disorder (MDD) is approximately 29.9% and the 12-month prevalence is approximately 8.6% [2]. While several modalities have shown effectiveness in the treatment of a major depressive episode, a recent, large prospective trial demonstrated that 35% of patients with MDD do not respond to multiple therapeutic interventions and are considered to have treatment-resistant depression (TRD) [3].

In 2005, the United States Food and Drug Administration (FDA) approved vagus nerve stimulation therapy (VNS) as an adjunctive treatment for patients with TRD [4–10]. Despite FDA approval, some controversy remains as to the overall efficacy of VNS in TRD [11–14].

VNS Therapy® comprises an implanted electrical pulse generator with a bipolar lead and an external programming system that controls intermittent stimulation to the left cervical vagus nerve. And VNS "dosage" refers to a collection of different stimulation parameter settings, determined by a physician and conveyed via telemetry to the implanted pulse generator [15]. These parameters together determine the characteristics of electrical stimulus applied to the nerve. The parameters consist of current (milliamps, mA), pulse width (microseconds, μs), frequency (hertz, Hz), and duty cycle (amount of stimulation time "ON" [seconds] and amount of time "OFF" [minutes]). Presently, recommendations for adjusting VNS dosage in TRD patients have been based primarily on empirical observations from VNS use in medication-resistant epilepsy, and therefore, the optimum stimulation parameter settings for TRD patients are not known. The objective of this FDA-requested, post-marketing study was to compare the safety and effectiveness of VNS administered at different dosage ranges for the adjunctive treatment of TRD.

To establish a dose–response curve in TRD patients, we evaluated 3 VNS doses with variable output current and pulse width while employing the same duty cycle (30 s ON and 5 min OFF) and the same pulse frequency (20 Hz). A "low" dose was chosen to deliver active stimulation at the lowest available device settings for amplitude of output current (0.25 mA) and a narrow pulse width of 130 μs. A "high" dose (1.25–1.5 mA and a standard 250 μs pulse width) was chosen to be more consistent with the higher levels of stimulation often observed in epilepsy treatment [16,17] and TRD trials [8]. The "medium" dose (0.5–1.0 mA, 250 μs) was chosen to track closer to the "high" dose than to the "low" dose, without overlapping the former, potentially providing a better opportunity to demonstrate efficacy versus the "low" dose.

It was hypothesized that medium-and higher-range VNS "doses", defined by the amplitude of the output current (configured with a standard 250 μs pulse width), would be associated with superior clinical outcomes, compared with relatively "low dose" stimulation (defined by the lowest amplitude of output current and a narrower pulse width).

Methods

Study participants

Enrollment criteria for the study included: (1) 18 years of age or older with a diagnosis of chronic (>2 years) or recurrent (≥2 prior episodes) MDD or bipolar disorder (BP), and a current diagnosis of major depressive episode (MDE) as defined by the Diagnostic and Statistical Manual of Mental Disorders [18], and determined using the Mini-International Neuropsychiatric Interview [19]; (2) a history of failure to respond to ≥4 adequate dose/duration of antidepressant treatment trials from at least 2 different antidepressant treatment categories, as documented through medical history and record review; (3) a minimum pre-study and baseline score of 24 on the Montgomery-Åsberg Depression Rating Scale (MADRS; [20]), with no greater than a 25% decrease in the MADRS score between the pre-study and baseline visits required for randomization; (4) currently receiving at least one antidepressant treatment in the form of medication or electro convulsive therapy (ECT); and (5) a stable regimen of all current antidepressant treatments for a minimum of 4 weeks before the baseline visit (ClinicalTrials.gov Identifier: NCT00305565). Note that criteria 1 and 2 are consistent with the approved product labeling [21].

Additionally, patients with BP had to be receiving a mood stabilizer at baseline, and all patients had to be able to complete the necessary evaluations, provide written informed consent, and

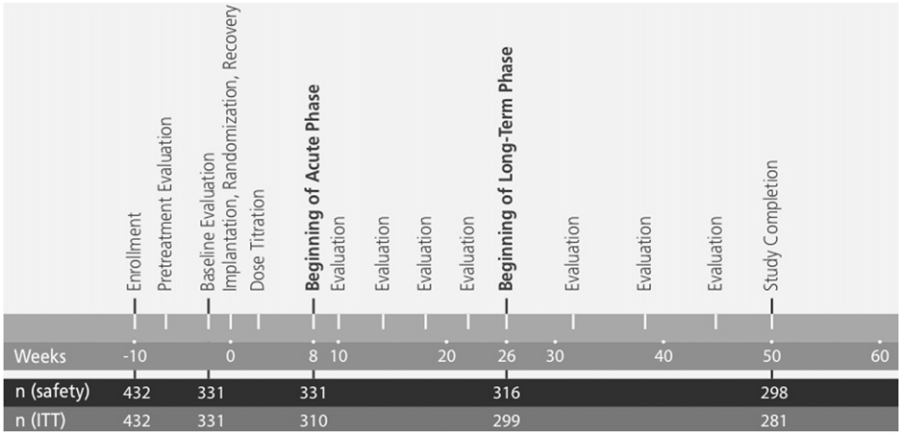

Figure 1. Study overview and disposition of patients.

provide the Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization.

Study exclusion criteria reflected approved product labeling, including a history of any psychotic disorder, a history of rapid cycling BP, and clinically significant suicidal intent at the time of screening [21]. Additionally, patients were excluded for a history of drug or alcohol dependence in the last 12 months; a current diagnosis of BP mixed phase; a history of borderline personality disorder; a history of previous VNS system implant; if considered at high risk for surgery; and if currently enrolled in another investigational treatment study.

Study overview

The study was a double blind, randomized comparison of VNS using 3 target ranges of electrical charge (Fig. 1). Eligible patients were enrolled at 29 academic and clinical sites in the United States and were implanted with a VNS Therapy® system consisting of a pulse generator and lead. Following implantation, but prior to the initiation of stimulation, patients were randomized to 1 of 3 treatment groups based on target settings: "low" dose (LOW; output current of 0.25 mA, pulse width of 130 μs), "medium" dose (MEDIUM; 0.5–1.0 mA, 250 μs), or "high" dose (HIGH; 1.25–1.5 mA, 250 μs). All treatment groups employed the same duty cycles (30 s ON and 5 min OFF) and pulse frequencies (20 Hz). All implanted patients were consecutively randomized based on the date of implantation.

The only study personnel unblinded to treatment group assignment were study programmers at each site and clinical engineers (who were employed by the sponsor to monitor the programmers). All other study site and sponsor personnel, and the patients, were blinded to treatment group assignment. The unblinded study programmer at each site obtained the randomization assignment from a designated third party that randomized in blocks of six patients, stratified by site. After a postoperative recovery period (generally 2 weeks in duration following implant), each patient began VNS dose titration according to protocol-specified guidelines. During the first 4-week blinded treatment period, the study programmer titrated the output current to achieve the target setting for each patient's treatment group. Identical titration procedures were performed for all dose groups. Since fewer incremental dose adjustments were required to achieve targeted stimulus parameters for the LOW group, "sham" dose adjustments were performed in this group to ensure uniform titration experiences between groups. The goal for the MEDIUM and HIGH groups was to reach an output current setting corresponding to the upper end of their assigned ranges for output current by the end of the titration period; however, if the minimum target output current was not achieved during the initial 4-week titration period (Weeks 2–6) for individual patients, the titration phase could be extended by 2 weeks to Week 8. Following Week 8, if a patient continued to experience intolerable side effects related to stimulation, the highest tolerable dose for that patient was continued for the duration of the acute phase.

Per protocol, all antidepressant and mood stabilizer treatments received by the patients were to be administered directly by, or under the direct supervision of, the investigators. Also, to the greatest extent possible and consistent with patient welfare, the investigators were to refrain from adding, discontinuing, or changing the intensity of other (i.e., non-VNS) antidepressant or mood stabilizer treatments, including nonpharmacologic treatments, before Week 22 (end of acute phase).

Week 22 of treatment marked the end of the acute phase and was followed by a 28-week "long-term" phase of the study with a goal to examine durability of response and cumulative response over time. During the long-term phase, the blinded study investigator directed the study programmer to increase VNS dosage if clinically warranted to improve antidepressant efficacy. The investigators could also modify the concomitant antidepressant and mood stabilizer treatments during the long-term phase to improve efficacy as clinically indicated, but preferably only after adjusting VNS parameters. To help preserve the study blind, the total maximum output current increase allowed for any patient after Week 22 was 0.75 mA. In addition, the pulse width in the LOW group could be increased to 250 μs after Week 22.

Criteria for evaluation

Efficacy

Antidepressant efficacy of the VNS system was evaluated using the following rating scales. The primary measure was the Inventory of Depressive Symptomatology Clinician Administered Version (IDS-C) [22]. The Quick Inventory of Depressive Symptoms Clinician Administered (QIDS-C) [23] data was extrapolated from the IDS-C. Other mood scales included MADRS [20], Inventory of Depressive Symptomatology Self-Report (IDS-SR) [22], and Clinical Global Impressions-Improvement (CGI-I) [24]. Patients were evaluated at baseline (up to 7 days before implantation), and then at Weeks 10,

14, 18, and 22 (during the acute phase) and at Weeks 26, 32, 38, 44, and 50 (during the long-term phase) (Fig. 1).

Safety

Safety evaluations were made using the Adverse Events Record. Adverse events (AEs) and serious adverse events (SAEs) were evaluated at baseline, at each visit during the implantation/titration period, and at each scheduled follow-up visit during the acute phase and the long-term phase.

Statistical considerations

Sample size calculation

Sample size calculations were based on IDS-SR scores using standard deviation and correlation estimates from a previous study [9] and a difference of 4 points between the HIGH and LOW treatment group averages. The calculations were based on IDS-SR instead of the primary endpoint IDS-C because IDS-SR information was available for this population [9], and because the study instruments are similar in content. Statistical power and sample size estimates for the study were derived based on simulated comparisons of the HIGH vs. LOW and MEDIUM vs. LOW groups using a mixed model repeated measures (MMRM) analysis and the Hochberg method for testing treatment group contrasts [25]. This simulation showed that $n_{RM} = 100$ patients per group (plus appropriate allowance for dropouts) would provide the desired power of $\geq$80%.

Study populations

The following study populations were defined per protocol prior to unblinding of the study results: the safety population included all patients who were implanted and the intent-to-treat population (ITT) was defined as all implanted patients who had a baseline and at least 1 post-stimulation assessment on the primary outcome measure and who were not excluded by an IDS-C baseline score $<$35 or by a baseline IDS-C score in the lower 5th percentile, whichever number was less. Note that the eligibility criterion of a score of $<$24 on MADRS is equivalent to a score of $<$35 on the IDS-C.

Method of analysis

All statistical analyses were performed using SAS® Version 9.1.3 (SAS Institute, Inc., Cary, North Carolina, USA). All tests of hypotheses were 2-tailed, with alpha set at 0.05.

The protocol-specified primary efficacy endpoint was the mean IDS-C change from baseline over Weeks 10, 14, 18, and 22 of the acute phase. The mean scores were compared over the acute phase based on fitted MMRM analysis of covariance (ANCOVA), adjusting for baseline value and random site effects (29 study sites). Data from study sites with 5 patients or fewer were pooled into one site for this analysis. The primary analysis consisted of contrasts comparing HIGH versus LOW and MEDIUM versus LOW, with scores averaged over the four acute phase visits using the Hochberg approach to adjust for multiplicity [25]. The analysis was performed on the ITT population using MMRM analysis in SAS (SAS PROC GLIMMIX).

Secondary efficacy endpoints included the mean changes from baseline in the continuous score scales (QIDS-C, MADRS, and IDS-SR) over Weeks 10, 14, 18, and 22 of the acute phase. A contrast comparing the LOW treatment to the mean of the MEDIUM and HIGH treatment groups, averaged over the acute treatment phase, was calculated for each of the 3 endpoints. Also, a pre-specified analysis of IDS-C scores was performed that included the per-protocol patients (i.e., only those patients in each treatment group who actually attained their assigned dose during the acute phase).

Response and remission were also analyzed. For the continuous score scales, response was defined as $\geq$50% improvement from baseline and remission was defined as a score of $\leq$14 on the IDS-C and IDS-SR, $\leq$5 on the QIDS-C, or $\leq$9 on the MADRS. For the categorical CGI-I scale, a value of 1 (for "very much improved") or 2 (for "much improved") was considered a response.

Post-hoc exploratory analyses

Two post-hoc exploratory analyses were conducted. The first analysis was performed to compare outcomes with the total amount of charge delivered to the patient and calculated as follows:

$$Q_{\text{Total}} = \left(\frac{T_{\text{period}} \left(\frac{I}{1000} \right) \left(\frac{P_W}{10^6} \right) f(t_{ON} + 4)}{t_{ON} + (t_{OFF} * 60)} \right),$$

with Q_{Total} as total charge (in Coulombs) delivered over a set time period; T_{period} (in seconds) and for this analysis, T_{period} was considered to be 86,400 s, such that Q_{Total} represented the charge delivered per day. The total charge is a function of output current I (mA), pulse width P_W (μs), pulse frequency f (Hz), ON time t_{ON} (s), and OFF time t_{OFF} (min). Four seconds were added to the ON time to account for ramping periods during the initiation and termination of simulation bursts.

To assess the impact of the total charge delivered per day on treatment efficacy, the 271 patients who had at least 2 VNS parameter changes during the trial (baseline through Week 50) were identified. For these patients, irrespective of original treatment group assignment, regression analysis was performed to assess the relationship between reduction from baseline IDS-C score at a given visit (t) and the net dose (expressed as total charge delivery per day) according to parameters set (or maintained) at the prior visit ($t - 1$). Values for total dose were $\log_{10}$ transformed to meet assumptions for normal distribution in statistical tests. Additionally, the slope that quantified the linear regression between these variables was estimated.

A second post hoc exploratory analysis was performed to assess the durability of response across different VNS dose groups. This analysis, comparing the likelihood of continued response at Week 50 for patients who responded at Week 22, was similar to analyses performed on data from previous VNS trials [4,7,26].

Results

Sample characteristics

A total of 331 patients were enrolled in the study at 29 sites and implanted with the VNS system (the safety population). The first patient was enrolled on February 24, 2006 and the last patient visit was performed on February 24, 2010. Of the enrolled patients, 330 patients completed the dose titration. The 22-week acute phase was completed by 316 patients (316/331; 96%) and the 50-week long-term phase was completed by 298 patients (94% of the 316 acute phase completers) (Fig. 1).

The protocol-defined ITT population included 310 patients (LOW group, $n = 102$; MEDIUM group, $n = 101$; and HIGH group, $n = 107$). Table 1 presents the demographic features and psychiatric history of the ITT population. The treatment groups were similar with respect to age, gender, and race. Demographic features were similar for the safety population and for patients who were eliminated from the study during screening (data not shown).

The treatment groups were also similar in terms of psychiatric history. Regardless of treatment group assignment, this was a highly treatment-resistant population and nearly all patients

Table 1
Baseline demographics and clinical features (intent-to-treat population).

Parameter	Treatment group by VNS stimulation level			
	LOW $n = 102$	MEDIUM $n = 101$	HIGH $n = 107$	Total $n = 310$
Age in years, mean (SD)	49.1 (10.5)	47.2 (11.0)	47.4 (10.8)	47.9 (10.8)
Females, %	66.7	68.3	68.2	67.7
Caucasians, %	95.1	95.0	97.2	95.8
Age at onset (yrs), mean (SD)	19.3 (11.0)	21.2 (11.5)	20.4 (10.4)	20.3 (11.0)
Duration of illness (yrs), mean (SD)	29.8 (12.1)	26.3 (10.9)	27.0 (12.1)	27.0 (11.8)
Patients with recurrent MDD, %	74.5	70.3	66.7	68.7
Patients with single-episode MDD, %	5.9	9.9	14.0	10.0
Patients with bipolar I disorder, %	8.8%	10.9%	14.0%	11.3%
Patients with bipolar II disorder, %	10.8%	8.9%	10.3%	10.0%
Length of current episode (yrs), mean (SD)	8.9 (10.2)	8.8 (8.9)	9.3 (12.2)	9.0 (10.5)
Previous electro convulsive therapy, %	59.8%	52.5%	57.9%	56.8%
Prior hospital admissions for mood disorders, mean (SD)	4.0 (5.1)	3.9 (6.1)	2.8 (3.3)	3.6 (4.9)
Lifetime suicide attempts prior to enrollment, %	54.9%	43.6%	38.7%	45.6%
Baseline IDS-C score, mean (SD)	46.4 (8.0)	45.8 (7.5)	45.7 (8.0)	46.0 (7.9)
Baseline MADRS score, mean (SD)	34.2 (5.2)	33.9 (4.4)	34.1 (4.4)	34.1 (4.7)
Number of unsuccessful mood disorder treatments over lifetime				
2–3	2.0%	0	0	0.6%
4–5	1.0%	3.0%	2.8%	2.3%
≥6	97.1%	97.0%	97.2%	97.1%
Unsuccessful treatments during the current depressive episode				
2–3	5.9%	5.9%	3.8%	5.2%
4–5	9.9%	12.9%	17.1%	13.4%
≥6	84.2%	81.2%	79.0%	81.4%

(>97%) had experienced at least 6 unsuccessful mood disorder treatments during their lifetime. On average, patients had experienced 3–4 prior hospital admissions for mood disorders, and nearly half of all patients had attempted suicide at least once prior to enrollment. Approximately 80% of patients across all treatment groups had experienced 6 or more unsuccessful adequate dose/duration antidepressant treatments trials during the current depressive episode. In addition, over 50% of patients across all treatment groups had received ECT.

Antidepressant treatment modalities being used prior to study enrollment were similarly distributed across treatment groups and demonstrated the complexity of treatment for this population (data not shown).

VNS parameters and concomitant antidepressant treatments

Mean doses for all treatment groups were consistent with the protocol-specified target dose ranges at both Weeks 10 and 22 (the acute phase). Dosing related protocol deviations were reported in all groups; and from Weeks 10–22, such deviations were noted in 0.9%–2.7%, 2.8%–5.6%, and 8%–8.8% in the LOW, MEDIUM, and HIGH groups, respectively. Unfortunately, some of these deviations occurred due to errors by the study programmers.

Overall, all treatments were generally well-tolerated, although a dose effect was noted in relation to tolerability at both Weeks 10 and 18; the percentage of patients in the safety population who reached their assigned dose were as follows: HIGH (74.3% at Week 10 and 72.6% at Week 18), MEDIUM (85% at Week 10 and 87.9% at Week 18), and LOW (88.3% at Week 10 and 85.6% at Week 18). The primary reasons for not attaining the assigned doses were general discomfort, increased cough, voice alteration, hoarseness, and other (i.e., non-specified reasons).

Despite the difficult nature of the enrolled patients' depression, the proportion of patients who had mood disorder treatments added or removed during the acute phase was modest and evenly distributed among the VNS treatment groups; it ranged from 12% to 16% patients who added treatments and 13% to 15% of patients who removed treatment (data not shown).

Acute phase results

Results of the per-protocol primary efficacy analysis of ITT population are presented in Table 2 (i.e., change in mean IDS-C score from baseline over Weeks 10, 14, 18, and 22). Unfortunately, the MMRM ANCOVA analysis of the primary hypothesis of a dose-response difference was not realized, as the results did not show statistically significant differences for any of the between-treatment group comparisons over time (LOW vs. MEDIUM, $P = 0.8131$; LOW vs. HIGH, $P = 0.8027$; MEDIUM vs. HIGH, $P = 0.9921$). However, mean IDS-C scores showed statistically significant improvement during the weeks after the initiation of stimulation for all treatment groups combined ($P = 0.0023$; data not shown).

Similar results were seen for the secondary analyses. There was a statistically significant improvement observed for all treatment groups combined: $P = 0.0005$ for QIDS-C, $P < 0.0001$ for MADRS,

Table 2
Mean change in IDS-C score relative to baseline, acute phase (intent-to-treat population).

IDS-C score at baseline or relative to baseline	Treatment group by VNS stimulation level			
	LOW mean (SD)	MEDIUM mean (SD)	HIGH mean (SD)	Total mean (SD)
Baseline	46.4 (8.0) $n = 102$	45.8 (7.5) $n = 101$	45.7 (8.0) $n = 107$	46.0 (7.9) $n = 310$
Week 10	−9.0 (10.4) $n = 101$	−9.8 (10.3) $n = 100$	−8.3 (11.0) $n = 106$	−9.0 (10.6) $n = 307$
Week 14	−10.2 (11.4) $n = 101$	−10.7 (12.3) $n = 96$	−9.9 (11.6) $n = 105$	−10.3 (11.7) $n = 302$
Week 18	−10.7 (10.2) $n = 97$	−10.3 (12.7) $n = 97$	−12.3 (11.2) $n = 101$	−11.1 (11.4) $n = 295$
Week 22	−10.2 (11.4) $n = 97$	−11.5 (12.9) $n = 97$	−11.5 (13.4) $n = 105$	−11.1 (12.6) $n = 299$

Note: numbers of patients with available data at each assessement point are indicated.

$P < 0.0001$ for CGI-I, and $P = 0.0003$ for IDS-SR. For all rating scales, there were no statistically significant differences noted between treatment groups. When IDS-C scores were analyzed only for those patients in each treatment group who attained their assigned dose during the acute phase (Fig. 2), the combined MEDIUM and HIGH dose groups averaged about 2 points more improvement at Week 22 than did the LOW dose group ($P = 0.089$).

The percentage of patients experiencing a response or a remission at the end of the Week 22 acute phase (i.e., at least a 50% improvement in depression symptoms) is presented by treatment group for each of the rating scales in Fig. 3A and B, respectively. At Week 22, approximately 20% of patients experienced a response, as reflected by IDS-C scores. While the response rate was numerically higher in the HIGH group compared with the MEDIUM and LOW groups for each measure, there were no significant differences in response rates among the treatment groups (Fig. 3A).

Approximately 9%–11% of patients in both the MEDIUM and HIGH groups experienced remission by Week 22 for each of the rating scales, compared with 5%–6% of patients in the LOW group (Fig. 3B). No statistically significant results were noted for any of the between-group comparisons.

Results from the long-term phase

Analysis of the results from the long-term phase (Week 22–50), including mean and percent change of rating scale scores, and percentage of responders and remitters, served as secondary endpoints.

Fig. 4 shows mean IDS-C scores of patients in the LOW, MEDIUM, and HIGH groups from baseline through Week 50. Depression symptoms, as reflected by changes in IDS-C scores relative to baseline, showed continued improvement over the long-term phase.

The cumulative benefit of VNS is also observed in Fig. 5, which depicts the percent of responders in the 3 dose groups at Weeks 26, 32, 38, 44, and 50 emerging from the sample of patients who had failed to respond at the end of the acute phase (Week 22). By Week 50, up to 25% of these patients demonstrated a ≥50% reduction in the IDS-C score.

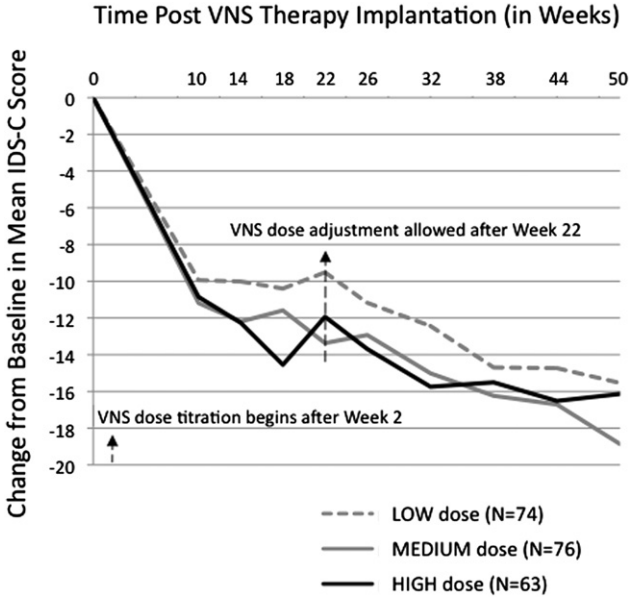

Figure 2. Per protocol analysis of change from baseline in mean IDS-C scores by treatment groups. Note that the figure presents only the patients who attained their assigned dose during the acute phase (up to Week 22).

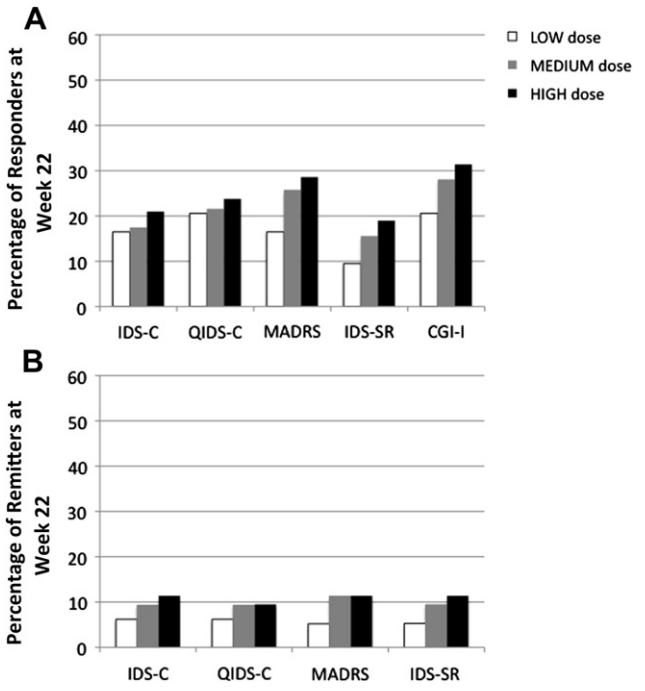

Figure 3. Vagus nerve stimulation response (A) and remission (B) rates at Week 22 (end of the acute phase) by treatment group for each of the rating scales. CGI-I = Clinical Global Impressions-Improvement; IDS-C = Inventory of Depressive Symptomatology Clinician Administered Version; IDS-SR = IDS-Self-Report; MADRS = Montgomery Åsberg Depression Rating Scale; QIDS-C = Quick Inventory of Depressive Symptoms Clinician Administered.

Across all assessment scales, the response and remission rates for each dose group were numerically higher at Week 50 compared with the rates at Week 22. At Week 50, response rates for the various scales ranged from 27% to 42% in the LOW group, 36% to 53% in the MEDIUM group, and 27% to 48% in the HIGH group (Fig. 6A). Remission rates were comparable between the treatment groups for each scale and ranged from 15% to 23% (Fig. 6B). There were no significant differences in response rates among the treatment groups.

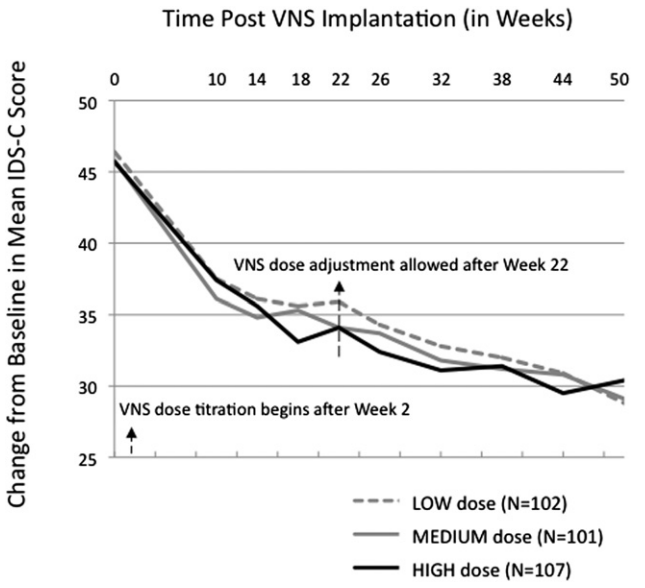

Figure 4. Mean IDS-C scores in the LOW, MEDIUM, and HIGH dose groups from baseline through Week 50 (end of long-term phase).

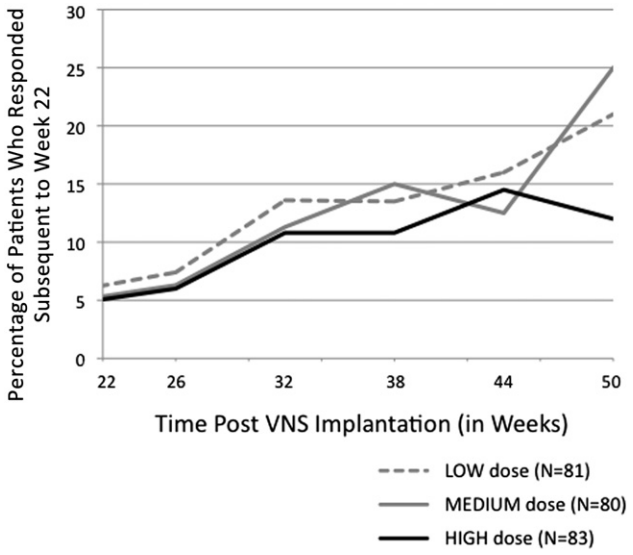

Figure 5. Cumulative benefit of vagus nerve stimulation in patients who did not exhibit a response at Week 22 (end of the acute phase). The figure depicts the percentage of responders by treatment group at Weeks 26, 32, 38, 44, and 50 emerging from the sample of patients who had failed to respond at Week 22.

Post-hoc exploratory analyses

Regression analyses of change in IDS-C score vs. total charge delivered per day

The quantity of charge delivered (total charge per day in millicoulombs [mC]) was examined in relation to clinical status (IDS-C score at each visit in the acute and long-term phases), and the results revealed a significant negative relationship ($r = -0.21$; $P < 0.001$). This suggests that a higher dosage of electrical stimulation was associated with decreased depression symptomatology.

A multivariate stepwise regression analysis was conducted using backward elimination with a significance level of 0.15 to assess the impact of the following important covariates: baseline parameters (age, gender, race, duration of depression, recurrent/single episode MDD, diagnosis of bipolar disorder, co-morbid anxiety disorder, suicide risk, suicide attempts by history, number of major depressive episodes, prior ECT treatment history, and total number of adequate drug trials), visit number (e.g., time on treatment), and concurrent medication treatment regimen (e.g., atypical antipsychotic, anticonvulsants, and antidepressants). Dose distribution of each treatment group by visit week is presented in Fig. 7, and as evident there was significant overlap in total charge per day between the groups.

Due to the skewed distribution in total charge per day, a log transformation was applied to the dose and each log unit dose increase (in mC/day) was associated with a slope of -4.9 ($P < 0.001$) for IDS-C and -2.2 ($P = 0.02$) for MADRS. Hence, for the IDS-C and MADRS, there is an estimated 5-point and 2-point reduction, respectively, for every $\log_{10}$ unit increase in total charge per day. In addition to log dose, visit number ($P < 0.001$), concurrent use of anti-convulsants ($P = 0.003$), serotonin-specific reuptake inhibitors ($P = 0.034$), and atypical antipsychotics ($P = 0.052$) resulted in improved reductions in the IDS-C. Patients having a greater number of prior major depressive episodes ($P = 0.002$) also experienced a greater reduction in IDS-C. Conversely, patients with a history of a greater number of treatments for depression (e.g., adequate drug trials [$P = 0.039$] or ECT history [$P = 0.112$]) tended to experience a lower reduction in IDS-C.

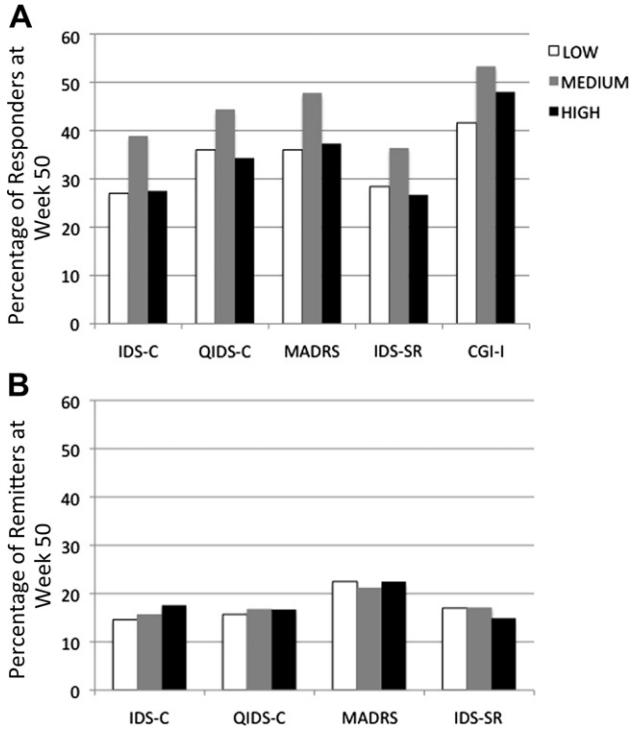

Figure 6. Vagus nerve stimulation response (A) and remission (B) rates at Week 50 (end of the long-term phase) by treatment group for each of the rating scales. CGI-I = Clinical Global Impressions-Improvement; IDS-C = Inventory of Depressive Symptomatology Clinician Administered Version; IDS-SR = IDS-Self-Report; MADRS = Montgomery Åsberg Depression Rating Scale; QIDS-C = Quick Inventory of Depressive Symptoms Clinician Administered.

Durability of response between dosing groups

To quantitatively evaluate the durability of the improvements with VNS treatment, response rates generated by IDS-C and MADRS scores were analyzed. The proportion of responders at the end of the acute phase who were also responders at the end of the long-term phase was determined (Table 3). For both scales, the MEDIUM and HIGH groups exhibited high rates of sustained

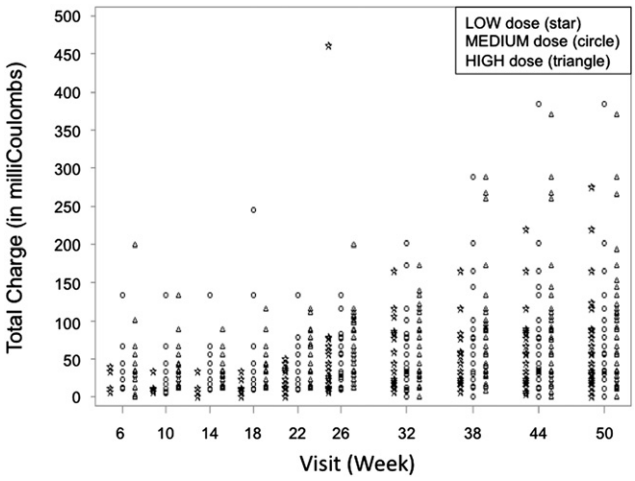

Figure 7. Distribution of total charge (mC) as a function of output current (mA), pulse width (μs), pulse frequency (Hz), ON time (s), and OFF time (min) for the LOW, MEDIUM, and HIGH dose groups is presented by visit (ie, number of weeks following implantation of the VNS Therapy system). The VNS parameter settings used in the calculation were the values after dose adjustments were made at each visit (if necessary).

Table 3
Proportion of responders at Week 22 with a sustained IDS-C or MADRS response at Week 50.

Parameter	Treatment group by VNS stimulation level			
	LOW $n = 111$	MEDIUM $n = 107$	HIGH $n = 113$	Total $n = 331$
IDS-C				
Number of patients with at least 50% improvement at Week 22	16	17	22	55
Number of patients with at least 50% improvement at Week 50	7	15	18	40
Proportion of responders at Week 22 with sustained response at Week 50	43.8%	88.2%	81.8%	72.7%
MADRS				
Number of patients with at least 50% improvement at Week 22	16	25	30	71
Number of patients with at least 50% improvement at Week 50	11	23	23	57
Proportion of responders at Week 22 with sustained response at Week 50	68.8%	92.0%	76.7%	80.3%

response (88.2% and 92% for the MEDIUM group, and 81.8% and 76.7% for the HIGH group on the IDS-C and MADRS, respectively). The sustained response rate in the LOW group was substantially less than the MEDIUM or HIGH groups on both the IDS-C (43.8%) and MADRS (68.8%) scales. Pairwise comparisons between MEDIUM and HIGH groups and the LOW group detected statistically significant differences on the IDS-C (LOW vs. MEDIUM, $P = 0.0186$; LOW vs. HIGH, $P = 0.0166$), but not the MADRS.

Safety

Overall, VNS was well tolerated, as shown by the very high rate of completion (94.3%) during the long-term phase.

Table 4 summarizes AEs considered related to the implantation surgery observed at ≥1% incidence in all patients; the most common of these AEs were incision pain (18.7%), incision site reaction (9.4%), and voice alteration (7.6%) (Table 4).

Table 5 summarizes AEs that occurred post-implant at ≥10% incidence in all patients. AEs reported with the greatest frequency were voice alteration, dyspnea, pain, paresthesia, incision pain, and increased cough. These AEs were also reported in prior studies of VNS in TRD [4,8,9,27]. Most of the AEs were distributed evenly among the treatment groups, however, a dose-effect relationship was noted for pain: 25.2%, 28.0%, and 41.6% in the LOW, MEDIUM, and HIGH groups, respectively.

SAEs were reported in 66 patients (66/331; 19.9%). Most of the events were reported in 1–3 patients in all 3 dose groups combined (i.e., reported in less than 1% of total patients per SAE), with the following exceptions. Suicide attempts were reported more frequently in the LOW dose group (6.3%) than they were in either the MEDIUM (0.9%) or HIGH (3.5%) dose groups (LOW vs. combined MEDIUM and HIGH dose groups, $P = 0.065$). Depression was reported slightly more frequently in the LOW dose group (7.2%) compared with the MEDIUM (5.6%) or HIGH (3.5%) dose groups. Six patients died during the study, including 1 patient who died from a pulmonary embolism following bariatric surgery, 1 patient died in a motor vehicle accident, 2 patients died from cardiovascular system related causes (both had pre-existing cardiovascular disease), and 2 patients committed suicide (one patient was from the LOW dose group with a history of 2 lifetime suicide attempts; and the other patient was from the HIGH dose group and had no history of prior suicide attempts, but the investigator considered the event to be not related to VNS implantation or stimulation).

Table 4
Prevalence of implantation-related adverse events at ≥1% incidence in total patients (safety population).

Adverse event, *n* (%)	Treatment group by VNS stimulation level			
	LOW $n = 111$	MEDIUM $n = 107$	HIGH $n = 113$	Total $n = 331$
Incision pain	20 (18.0%)	23 (21.5%)	19 (16.8%)	62 (18.7%)
Incision site reaction	15 (13.5%)	6 (5.6%)	10 (8.8%)	31 (9.4%)
Voice alteration	7 (6.3%)	13 (12.1%)	5 (4.4%)	25 (7.6%)
Pain	5 (4.5%)	5 (4.7%)	10 (8.8%)	20 (6.0%)
Device site reaction	5 (4.5%)	3 (2.8%)	3 (2.7%)	11 (3.3%)
Paresthesia	2 (1.8%)	2 (1.9%)	4 (3.5%)	8 (2.4%)
Pharyngitis	2 (1.8%)	2 (1.9%)	2 (1.8%)	6 (1.8%)
Neck pain	1 (0.9%)	0	4 (3.5%)	5 (1.5%)
Device site pain	4 (3.6%)	0	0	4 (1.2%)

Discussion

General findings

This study represents the first attempt to systematically study the dose–response relationship of VNS Therapy in the treatment of TRD. In a large group of patients randomized to three different target ranges of electrical charge (LOW, MEDIUM, and HIGH groups), we did not find significant differences between the treatment groups in antidepressant efficacy during the acute phase (Weeks 8–22; primary hypothesis) or the chronic phase (Weeks 26–50). Although the effect sizes were limited, statistically significant decreases in mean depression scores (based on IDS-C) were observed in all three VNS cohorts. Furthermore, sustained stimulation—with allowance for increased current and pulse width following the acute phase—led to further reduction in mean IDS-C scores for all three cohorts. The study also demonstrates that patients in the LOW stimulation group were significantly more likely to have depressive relapse at 50 weeks than those in the combined MEDIUM and HIGH dose cohorts. Hence, the study findings further suggest that VNS has antidepressant efficacy in a subset of severely treatment-resistant depressive patients and that higher dose current may result in more sustained responses.

Table 5
Prevalence of post-implant adverse events at ≥10% incidence in total patients (safety population).

Adverse event, *n* (%)	Treatment group by VNS stimulation level			
	LOW $n = 111$	MEDIUM $n = 107$	HIGH $n = 113$	Total $n = 331$
Voice alteration	71 (64.0)	82 (76.6)	86 (76.1)	239 (72.2)
Dyspnea	33 (29.7%)	36 (33.6%)	38 (33.6%)	107 (32.3%)
Pain	28 (25.2%)	30 (28.0%)	47 (41.6%)	105 (31.7%)
Paresthesia	31 (27.9%)	35 (32.7%)	39 (34.5%)	105 (31.7%)
Incision pain	24 (21.6%)	33 (30.8%)	27 (23.9%)	84 (25.4%)
Increased cough	27 (24.3%)	28 (26.2%)	28 (24.8%)	83 (25.1%)
Headache	19 (17.1%)	21 (19.6%)	21 (18.6%)	61 (18.4%)
Depression	25 (22.5%)	14 (13.1%)	21 (18.6%)	60 (18.1%)
Pharyngitis	19 (17.1%)	19 (17.8%)	19 (16.8%)	57 (17.2%)
Hypertonia	22 (19.8%)	17 (15.9%)	17 (15.0%)	56 (16.9%)
Neck pain	12 (10.8%)	14 (13.1%)	20 (17.7%)	46 (13.9%)
Dysphagia	10 (9.0%)	17 (15.9%)	18 (15.9%)	45 (13.6%)
Nasopharyngitis	16 (14.4%)	17 (15.9%)	12 (10.6%)	45 (13.6%)
Incision site reaction	18 (16.2%)	11 (10.3%)	13 (11.5%)	42 (12.7%)
Nausea	15 (13.5%)	15 (14.0%)	9 (8.0%)	39 (11.8%)
Anxiety	13 (11.7)	12 (11.2)	13 (11.5)	38 (11.5)
Insomnia	12 (10.8%)	12 (11.2%)	12 (10.6%)	36 (10.9%)
Device site reaction	16 (14.4%)	8 (7.5%)	9 (8.0%)	33 (10.0%)

Lack of separation of treatment cohorts

Several factors may have contributed to the failure to detect a significant difference on the primary outcome measure (i.e., improvement in IDS-C depression rating scores) between the randomly assigned stimulation groups. Firstly, not all patients in a given treatment cohort were "sequestered" into distinct VNS parameter settings due to a range of patient tolerability to VNS stimulation; this is most evident in Fig. 7, where significant overlap in total charge per day is seen between the three randomized treatment groups. This issue was also evident in previous VNS clinical trials [4,8,27]. Secondly, several difficult decisions had to be made in the design of this study, e.g., (1) what would be considered "sham" treatment settings that would also preserve the blind and (2) how long should patients remain in the acute treatment phase given the severity of illness.

For the LOW stimulation group, the lowest settings for output current and pulse width were selected to strike a balance between the risk of unblinding with no stimulation versus the risk that even quite modest stimulation could provide some therapeutic support (as was seen in epilepsy studies [16,17]). However, even this cautious strategy did not adequately protect the treatment blind as 73% of the LOW dose group (versus 41% of the MEDIUM and 31% of the HIGH dose groups) accurately guessed their treatment group assignment at the end of the acute phase.

Findings from the largest naturalistic, open-label study of VNS in TRD suggests that chronic VNS treatment leads to a cumulative increase in response over the course of the first year: 15% of patients responded to VNS at 3 months, 18% at 6 months, 23% at 9 months, and 30% at 12 months [8]. Hence, over 50% of patients responded to VNS *after 6 months* (24 weeks) of treatment; a timepoint beyond the acute phase endpoint (at Week 22) in the current study design. In placing the timing of the end of the acute phase at 22 weeks, a balance was sought between the clear understanding that VNS response rates at 12 months are higher than at 5 months and the need to not place severely ill patients in a restricted treatment paradigm for an extended time [8]. Therefore, a longer duration of stimulation (i.e., beyond 6 to 7 months or longer) may have been required to separate out differential antidepressant effects of the VNS doses.

Challenging issues with study design

In general, psychiatric studies of treatment-resistant disease populations are relatively few and provide significant ethical challenges. In particular, if a treatment modality (e.g., VNS or deep brain stimulation [DBS]) requires extended exposure (which is likely $\geq$6 months for VNS), at what point does it become unethical to continue providing "sham" treatment? For example, in this study of a highly treatment-resistant patient population, 2 patients completed suicide during the study, which emphasizes the gravity of the disease process. Discussions between the field of psychiatry and the FDA regarding such complex questions of study design and blinding for devices in the treatment of depression have been raised recently [28].

This post-approval dosing study was required by the FDA as a condition of approval of VNS Therapy for TRD. In conjunction with the FDA, the study was developed to balance the desire to create a dose-response curve for a novel implantable device with the need to ethically study the treatment of patients with particularly severe manifestations of depressive illness using a treatment that may require a long exposure to demonstrate response. To a significant extent, this is a new psychiatric treatment paradigm for which there are few guideposts, and currently, the only similar therapeutic model that may serve as a reference is DBS [29].

Post-hoc analyses findings

To more precisely investigate the effects of dosage upon antidepressant outcomes, a post-hoc multivariate regression analysis was employed using continuous rather than categorical measures that accounted for the total charge delivered (per day) to each patient based upon all relevant electrical VNS parameters. The analysis showed a modest correlation between a higher charge per day and a greater antidepressant effect. Though this correlation is statistically significant, the effect size is rather limited ($r = -0.21$; $P < 0.001$). Further, the relatively low rate of responders makes it statistically difficult to draw conclusions regarding independent variables driving the response outcomes.

Recent work suggests that the multiple parameters contribute meaningfully to dose-response relationships in neurostimulation and should be reported independently [15]. For this study, there was little variability in other parameters (such as, pulse width, frequency, and duty cycle), and regression analysis of response through these parameters would not have been informative. Furthermore, the categorical groups of LOW, MEDIUM, and HIGH dose confounded changes in multiple parameters (current and pulse width), making examination of the independent contribution of individual parameters not possible.

Additional findings

There were several other important positive findings of this study. Individual patients receiving adjunct VNS continued to improve after the initial acute phase, consistent with the results of earlier studies that a specific advantage of VNS in TRD appears to be sustained antidepressant response [26]. Such results provide additional support for durability of VNS response in a population where relapse with even the most aggressive treatment (e.g., ECT), is common [30]. Additionally, this study demonstrated that the MEDIUM and HIGH dose groups had greater proportions of patients with sustained response (based on IDS-C rating scale) at Week 50 (88.2% and 81.8%, respectively) than the LOW dose group (43.8%); hence, titrating to a higher dose (i.e., targeting an output current of 1.0 to 1.25 mA with a pulse width of 250 μs) may lead to more sustained antidepressant benefit. However, individual patient tolerability should be considered during the dosing process as higher output current may be associated with less tolerability and time to adapt to increased dose should be considered. Finally, the study showed very high completion rates supportive of the tolerability of this intervention for patients with TRD.

Conclusions

Within the limits of this study design, the results demonstrated that TRD patients receiving adjunctive VNS in an open-label setting had significant improvement at study endpoint compared with baseline, and the effect was durable over 1 year (unusual for the population being studied). The sustained improvement was in a higher proportion of TRD patients than has been seen in treatment-as-usual studies of comparable TRD populations [5]; albeit a statistically significant improvement was not evident between dosing arms, even in the per-protocol group. Additionally, the post-hoc analysis that considered charge delivery among patients in all treatment groups was utilized to better extract the effect of dosage on clinical outcome; and this analysis revealed a correlation between increased electrical stimulation and decreased depression symptomatology.

There is growing evidence suggestive that response to some neuromodulation strategies (VNS and DBS in particular) may take a year to effect necessary neurophysiological changes [29,31–33].

Rather than sham-controlled studies handicapping allowed treatment for a year in patients with a potentially life-threatening illness, perhaps the paradigm needs to be changed to comparing aggressive treatment-as-usual to VNS or DBS. While there may be a sacrifice in consistency with drug studies in depressed patients, it would be a great loss for patients with treatment-resistant illness to have their options limited because psychiatry has not figured out how best to evaluate efficacy.

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