Prognostic and Prescriptive Predictors of Treatment Response to Adjunctive VNS Therapy in Major Depressive Disorder:

A RECOVER Trial Report

Scott T. Aaronson, MD; Charles R. Conway, MD; Charles Gordon, MS; Ying-Chieh (Lisa) Lee, MS; Mark S. George, MD; John Zajecka, MD; Patricio Riva-Posse, MD; David L. Dunner, MD; Matthew Macaluso, MD; Peter B. Rosenquist, MD; Brian J. Mickey, MD; Yvette I. Sheline, MD; Vasilis C. Hristidis, MD; Hunter Brown, MSW; Christopher L. Kriedt, BSN; Quyen Tran, BS, MBA; Mark T. Bunker, PharmD; Harold A. Sackeim, PhD; and A. John Rush, MD

Abstract

Objective: Vagus nerve stimulation (VNS) therapy is a long-term intervention for treatment-resistant major depression (TRD) adjunctive to treatment as usual (TAU). To enhance clinical decision-making, we identified subgroups that respond especially well or poorly with active VNS vs no stimulation sham VNS (prognostic predictors) and subgroups that specifically benefit from active VNS vs sham VNS (prescriptive predictors).

Methods: In the RECOVER trial, patients with marked TRD (N = 493) were randomized to either active VNS (N = 249) or sham VNS (N = 244); both groups continued TAU. Baseline demographic, clinical, and treatment history characteristics were evaluated as potential prognostic and/or prescriptive outcome predictors. Outcome assessment was based on a tripartite

measure that combined depressive symptoms (Quick Inventory of Depressive Symptomatology—Clinician), psychosocial function (Work Productivity and Activity Impairment Questionnaire item 6), and quality of life (Mini-Quality of Life Enjoyment and Satisfaction Questionnaire). Generalized linear mixed models were employed to identify both prognostic and prescriptive predictors of tripartite outcomes.

Results: Several baseline features predicted outcomes across the entire sample and within the sham VNS group (prognostic prediction). History of treatment with electroconvulsive therapy (ECT; lifetime and current episode) or transcranial magnetic stimulation (TMS; current episode) was associated with poorer prognosis. However, these same features were associated with greater benefit from active VNS vs sham VNS. The presence

of comorbid anxiety disorders was predictive of a better prognosis overall, but smaller benefit from active VNS vs sham VNS.

Conclusions: Marked TRD patients with a history of ECT or TMS had especially poorer outcomes when receiving sham VNS plus TAU for 1 year than those without this history. These same subgroups showed significant differential benefit with active VNS than with sham VNS (positive prescriptive effect). The absence of a comorbid anxiety disorder was linked to superior benefit from active VNS vs sham VNS. These predictors may inform clinical decision-making when considering VNS.

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Author affiliations are listed at the end of this article.

M ajor depressive disorder (MDD) is a common, often chronic or recurrent, condition that typically responds well to initial treatments with psychotherapy or medications. However, 15%–30% of patients with MDD do not have sufficient symptomatic benefit or cannot sustain it after multiple treatment trials.[1–3]

Patients with treatment-resistant depression (TRD)—defined as having had 2 or more failed adequate

antidepressant treatments[3,4]—have greater morbidity, mortality, and considerably higher mental and physical health services costs than those who symptomatically respond to initial treatments.[4–10]

Vagus nerve stimulation (VNS Therapy), an adjunctive treatment for patients with TRD, has been shown to result in meaningful symptomatic improvement in 30%–40% of patients over 1 year.[11,12] The recently completed randomized phase of the

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Clinical Points

- Baseline participant outcomes from the randomized vagus nerve stimulation (VNS) RECOVER trial combining symptom, quality of life, and function were analyzed to determine prognostic and prescriptive outcome predictors.
- History of electroconvulsive therapy (ECT) use in lifetime and current episode or transcranial magnetic stimulation (TMS) use in current episode was prognostic of poorer outcomes across the total sample and superior benefit from active vs sham VNS.
- Adjunctive VNS may be especially effective in marked TRD patients who have not benefitted from ECT or TMS.

RECOVER trial[13,14] found that adjunctive VNS, delivered over 1 year, exceeded the effects of adjunctive sham VNS in selective measures of depressive symptoms, psychosocial function, and quality of life (QoL), 3 recognized primary outcome domains for depression treatment.[13–16] Nonetheless, the selection and management of optimal candidates for VNS are challenging. Treatment entails outpatient surgery with associated adverse effects, while the therapeutic effects of VNS may not occur for months following device activation.[13,14,16] Clinicians and patients need the ability to predict which patients are likely to benefit from VNS and, once selected, what outcomes to expect. These questions may be addressed by identifying prescriptive and prognostic predictors.[17–20] These predictors provide distinct information that can inform clinical decision-making and care delivery. Prognostic predictors are baseline patient features linked to clinical outcomes, regardless of treatment, and specific to each treatment, in this case, active or sham VNS. Prescriptive predictors are baseline patient features associated with differential outcomes dependent on which intervention is provided, ie, active vs sham VNS. Prognostic associations should inform outcomes in both treatment groups: adjunctive VNS plus treatment as usual (TAU) or sham VNS plus TAU. Prescriptive associations reveal which patient subgroups benefit from adjunctive active VNS more than adjunctive sham VNS.[21]

This report focuses on RECOVER trial participants with markedly treatment-resistant MDD (n = 493) for whom symptomatic, daily function, and quality of life outcomes have been reported.[13,16] We use the qualifier "markedly" as an adverb and "marked" as an adjective to emphasize the extreme degree of treatment resistance previously documented in this sample based on the number of failed treatment trials in both the current episode and lifetime.

RECOVER is a prospective, multicenter, sham-controlled, blinded trial designed to evaluate the safety and effectiveness of adjunctive VNS Therapy in patients with marked TRD. Patients were randomized to receive either active or sham VNS (no stimulation) group, while continuing TAU over 12 months.

To develop prognostic and prescriptive predictors for active VNS, we chose a priori a composite metric that combines depressive symptoms, psychosocial function, and QoL outcomes to provide a more complete picture of potential benefit to the patient,[22] rather than focusing on depressive symptoms alone. Previously, we found that the active VNS group had clinically meaningful improvements significantly beyond that obtained in the sham VNS group in measures of function and QoL, in addition to the difference in symptom improvement.[13,16] The composite metric was more sensitive and applied to more patients than symptoms alone in detecting a difference between the randomized groups in extent of clinically meaningful benefit.

Here, we present analyses of data from the 12-month, randomized-controlled period. These analyses examine which participants with multiple antidepressant and interventional treatment failures experienced the greatest comparative benefit. These patients, therefore, should most likely be recommended for VNS implantation.

METHODS

In the RECOVER study, patients with MDD were randomized to receive active VNS or sham VNS for 12 months. After completing the 12-month participation visit, the sham VNS group received active VNS treatment, and all patients regardless of their original randomization group entered long-term follow-up. Examination of the outcomes in the second year of the trial is not yet complete.

The exploratory analyses in this report were conducted with a database derived from the RECOVER trial. Details on the study rationale, design, and primary and secondary outcomes are provided elsewhere.[13,14] Participants were enrolled at 84 clinical sites in the United States. Ethics committee approval was obtained at each study site, as applicable, and in accordance with the Declaration of Helsinki guidelines. This report is based on data collected in the MDD study arm between October 2019 and April 2024. All participants provided written informed consent before any study-related medical record review or procedure. RECOVER is being conducted under "coverage with evidence development" from the US Centers for Medicare & Medicaid Services. This study was registered with ClinicalTrials.gov (identifier: NCT03887715).

Trial Entry Criteria

Eligible participants were at least 18 years old with a current diagnosis of MDD according to *DSM-5* criteria

and documentation of either chronic or recurrent course.[23] Chronic MDD was defined as the current episode lasting ≥2 years; recurrent MDD was defined as 4 or more lifetime episodes with each episode separated by at least 2 months without meeting *DSM-5* criteria for MDD. The diagnosis was confirmed by Mini-International Neuropsychiatric Interview (MINI) at the site[24,25] and an independent psychiatric medical record review.

Eligibility criteria included insufficient benefit (eg, lack of response) from at least 4 adequate antidepressant treatments in the current episode using the clinician-rated Antidepressant Treatment History Form–Short Form.[26] Eligible patients were at least moderately depressed at baseline with a score ≥22 on the Montgomery-Asberg Depression Rating Scale (MADRS) that was administered on 2 occasions 14–16 days apart.[27] The absolute difference between the 2 MADRS scores could not exceed 25%.

Individuals at immediate risk of suicide requiring hospitalization based on clinical judgment and history, and those with a suicide attempt within the past 6 months prior to baseline, were excluded from the study. Additional study exclusion criteria included careful review of the last 2 years of psychiatric medical history and clinical evaluation of borderline or other personality disorders sufficiently severe to interfere with trial participation, any history of psychotic symptoms, or a primary diagnosis of obsessive-compulsive disorder, eating disorder, posttraumatic stress disorder, dementia, or other major neurocognitive disorder (based on a review of the medical history and clinical assessment by the site investigators). Participants with a *DSM-5* defined substance use disorder without sustained remission for at least the past 12 months were also ineligible. Participants with bipolar depression were included in RECOVER and randomized in a separate cohort.

A Study Eligibility Committee, led by a psychiatrist (author CRC) specializing in TRD and a registered nurse (author CLK) with extensive psychiatric experience, reviewed medical records documenting psychiatric and treatment history to ensure study eligibility criteria were met in individuals already screened by the enrolling sites.

Blinding

Per the clinical study protocol, unblinding was defined as receiving identification of the subject's randomization assignment. The investigators, interviewers, central raters, other study staff, and participants remained blinded by turning OFF the VNS devices in all patients at the start of the clinic visits. Speculation about the randomization assignment by blinded individuals was not considered unblinding (eg, perceived device stimulation or lack of, side effects perceived as possibly related to VNS Therapy, or

improvement or lack of changes in depression status).

As we previously presented,[28] participants were blinded to treatment assignment, with modest differences in guess accuracy: 67.5% in the active VNS + TAU group guessed their treatment assignment correctly, compared to 53.3% in the sham VNS + TAU group—closer to chance. These findings suggest partial blinding success.

Study Assessments

The assessment scales employed in the RECOVER trial have been described elsewhere.[13,14] This report focuses on the Quick Inventory of Depressive Symptomatology—Clinician (QIDS-C) completed by trained, off-site, blinded raters masked to the protocol and treatment groups,[29–32] the patient-rated Mini-Quality of Life Enjoyment and Satisfaction Questionnaire (Mini-Q-LES-Q),[33,34] and the Work Productivity and Activity Impairment Questionnaire (WPAI).[35–37] Thresholds for minimal clinically important difference (MCID) in each outcome domain were established based on prior publications.[38–40]

The QIDS-C assessed 9 depressive symptom domains (each rated 0–3) that define a major depressive episode based on the *DSM-5* over the previous week. Partial response was defined as a ≥30% reduction in the baseline total score based on independent studies that established this threshold as clinically meaningful.[41–43]

The 7-item Mini-Q-LES-Q assessed QoL over the previous week,[34] using a subset of the 14 Q-LES-Q items found most sensitive to change during treatment of MDD (ie, work, household activities, social relationships, family relationships, leisure time activities, ability to function in daily life, and overall sense of well-being). Each item is rated from 1 (very poor) to 5 (very good). To calculate an MCID,[38] we converted to percent maximum scores by subtracting 7 from the raw total score (range, 7–35) and dividing by 28. The MCID for the Mini-Q-LES-Q was estimated a priori to be ≥11.89% increase from baseline based on previous evidence from the 14-item Q-LES-Q.[38]

Item 6 of the WPAI assessed daily functioning. The WPAI measures absenteeism, presenteeism, and productivity for working participants (items 2–5). However, most participants (74.6%) were not employed. Regardless of work status, item 6 assesses the effect of depression (from 0 for "no effect" to 10 for "massive effect") on regular daily activities (work around the house, shopping, childcare, exercising, studying, etc.) over the prior week.[35–37] A MCID on item 6 was a reduction of ≥2 points.[39,40]

In addition to baseline assessments before randomization, depressive symptoms were assessed monthly from months 3 through 12, while QoL and function were assessed quarterly during the 12 months following randomization.

Statistical Analyses

The data were pooled across study sites. The average of the last 2 MADRS assessments before device implantation was used as the baseline MADRS value. For the other assessments, the baseline was defined as the latest nonmissing assessment prior to device implantation. The tripartite outcome metric used 4 measurement occasions from assessments at months 3, 6, 9, and 12 following implantation for the prognostic assessment and outcomes only at month 12 for both prognostic and prescriptive analyses. The tripartite outcome measure determined at each measurement occasion whether there was a clinically meaningful improvement from baseline in each of 3 outcome domains: depressive symptoms (QIDS-C), psychosocial function (WPAI item 6), and QoL (Mini-Q-LES-Q). An improvement of ≥30% in the QIDS-C PR, ≥11.89% in the Mini-Q-LES-Q, and ≥2 in WPAI Item 6 were considered a priori as denoting minimal clinically meaningful benefits. Thus, for each scale and at each of the 4 measurement occasions, we determined whether a minimal clinical meaningful benefit was achieved. At each measurement occasion, patients were assigned a score of 0 or 1, depending on whether they demonstrated clinically meaningful benefit in any domain. Missing data at any measurement point were considered as indicating no benefit at that time.

Generalized linear mixed models (GLMM) were employed to identify both prognostic and prescriptive predictors of tripartite outcomes, utilizing the binary indicator (0 or 1) of clinically meaningful benefit in any domain at each measurement occasion. Two sets of analyses examined potential prognostic predictors. One goal of this trial was to identify patient features predictive of outcome in this marked TRD population regardless of treatment with VNS. A series of GLMMs were performed on the total sample of active VNS and sham VNS patients (N = 493). These models were applied to the binary tripartite outcome, first analyzed separately at month 12 and subsequently using repeated measures at months 3, 6, 9, and 12. Each model incorporated a random intercept and a logit link function, adjusting for covariates including visit month, age group (<65 and ≥65), and baseline MADRS score group (<34 and ≥34). These GLMMs sequentially incorporated individual patient demographic, clinical, and treatment history characteristics as covariates to identify prognostic predictors. Additionally, similar analyses were conducted separately within each treatment group (active VNS and sham VNS).

To identify prescriptive predictors, the GLMM analyses used to determine prognostic factors in the total sample at month 12 were repeated, now incorporating treatment group and the treatment group-by-time interaction as model terms. These models sequentially tested outcome differences between the active VNS and sham VNS groups at each level of the potential prescriptive predictors. These analyses produced odds ratios (ORs) and 95% confidence intervals (CIs), quantifying degree of outcome differentiation between active VNS and sham VNS across subgroups defined by potential predictive patient characteristics (eg, history of electroconvulsive therapy [ECT]). Subgroups with a lower bound of the 95% CI >1 were considered to exhibit statistically significant separation favoring active VNS over sham. Additionally, subgroups with an OR point estimate >1.87 demonstrated a numerically greater observed treatment effect compared to the overall sample. In other words, these analyses identified patient subgroups that consistently demonstrated greater benefit with active VNS compared to sham VNS, as indicated by a lower bound of the 95% CI >1. Moreover, the magnitude of this effect was equal to or greater than that observed across the full sample. Notably, subgroup identification did not require a statistically significant difference between the identified subgroup and its counterpart without the patient feature (eg, with vs without history of ECT exposure).

The number needed to treat (NNT) was calculated for the prescriptive analyses. The observed proportions of patients achieving a positive outcome on the tripartite metric were recorded separately for the active VNS and sham VNS groups. The NNT was derived as the reciprocal of the absolute difference in event rates between the two groups.

The 33 variables examined as potential predictors are listed in Supplementary Table 1. If the baseline value of the variable was significantly associated with the composite end point, it was identified as a prognostic variable. If the baseline value of a variable was significantly associated with a differential probability of response to the composite end point, favoring active vs sham VNS, it was identified as a prescriptive variable. Each of the 33 variables could fall into one of following categories: neither prognostic nor prescriptive, both prognostic and prescriptive, only prognostic, or only prescriptive.

Variables such as ethnicity were excluded from the analysis if one level comprised more than 90% of the sample, leaving fewer than 50 patients in another level. A large number of prespecified baseline variables were analyzed to identify factors associated with treatment response, consistent with the trial's stated objectives. As no correction for multiple comparisons was applied, findings should be interpreted with appropriate caution given the number of statistical tests conducted. Two-tailed P values <0.05 were considered statistically significant. Analyses were conducted using SAS 9.4 (Cary, NC).

RESULTS

The report presents findings from all 493 patients with MDD who were randomized, including 249 patients in the active VNS group and 244 patients in the sham VNS group.

Prognostic Predictors of Outcome

Table 1 presents the baseline variables that were significantly associated with benefit in the GLMM analyses, as defined by the tripartite metric using months 3–12 or only month 12. These variables are a subset of the 33 potential predictors examined (Supplementary Table 1 and Supplementary Table 2).

Multiple variables related to treatment history demonstrated consistent prognostic predictive power. Despite the sample being marked TRD, patients with more than 10 failed antidepressant treatments or a lifetime history of ECT or transcranial magnetic stimulation (TMS) in the current episode had poorer outcomes. Among psychiatric comorbidities, a current or historical panic disorder and generalized anxiety disorder were predictors of better outcome.

Prescriptive Predictors of Outcome

Across the 66 levels of the 33 tested variables, all 66 subgroups (100%) had an OR >1, indicating that greater benefit in the active VNS group vs the sham VNS group was generally seen in this sample for the tripartite outcome (Supplementary Table 3). Figure 1 and Figure 2 show the relationship between the presence or absence of selected treatment history features (Figure 1) or selected anxiety disorders based on the MINI (Figure 2) and the magnitude of the treatment group difference (active VNS vs sham VNS) at the month 12 visit. The differential treatment effect is represented by the OR within each subgroup.

Use of ECT, whether lifetime or in the current episode, was associated with a greater benefit with active vs sham VNS (Figure 1). This effect was observed both in patients with positive and negative response to ECT, as lack of exposure to ECT was linked to a less positive separation. Similarly, treatment with TMS in the current episode was associated with a greater benefit from active vs sham VNS. Thus, exposure to either ECT or TMS was associated with greater differential benefit of active over sham VNS (OR 2.08, 95% CI, 1.31–3.29, NNT = 5.8). In contrast, the use of esketamine (current episode;

Table 1.

Clinical and Treatment History Features With Significant Prognostic Outcomes (Variables Demonstrating a Significant Difference in the 3-, 6-, 9-, and 12-Month Analysis or at the 12-Month Visit Only)
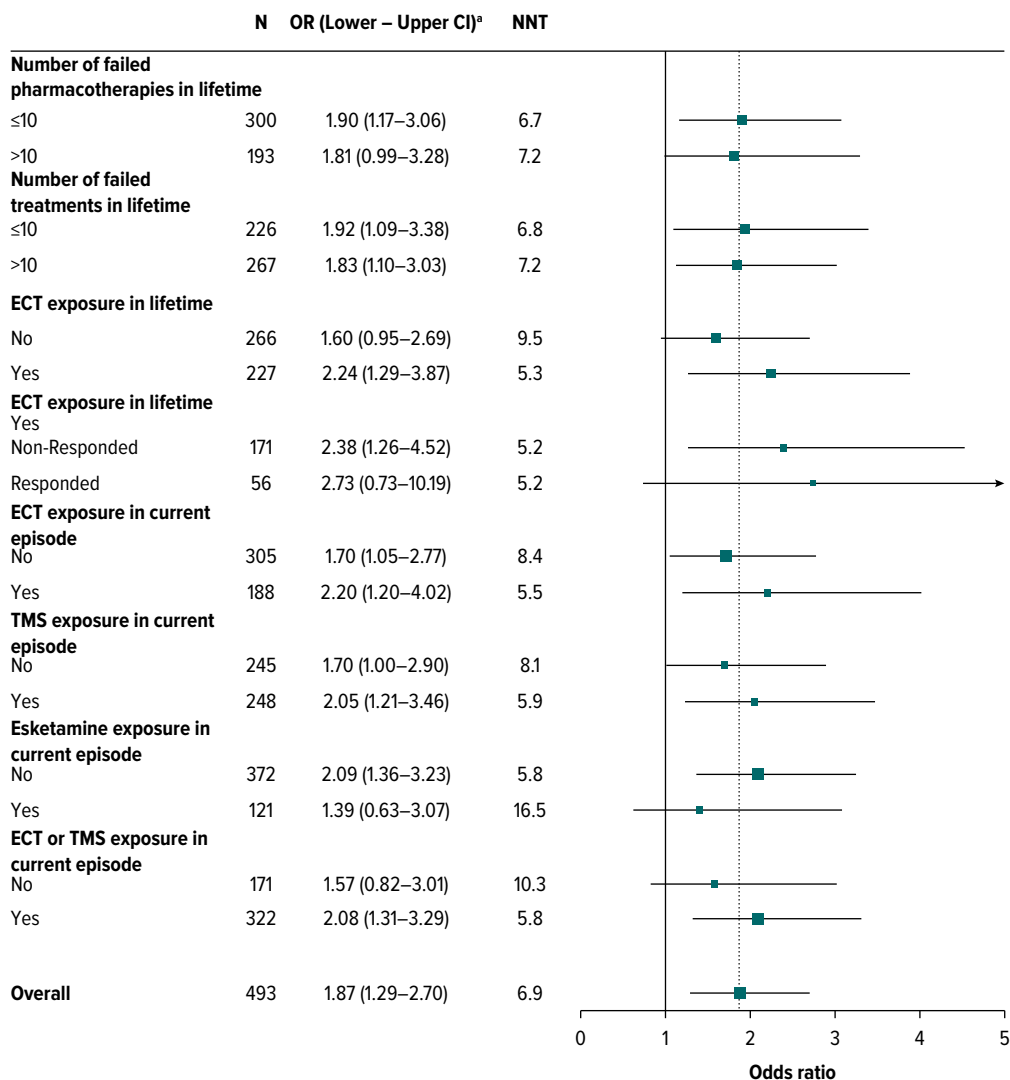
	3–12 mo Odds ratio (95% CI)[a]			12 mo Odds ratio (95% CI)[a]		
	Total (N = 493)	Sham VNS (N = 244)	Active VNS (N = 249)	Total (N = 493)	Sham VNS (N = 244)	Active VNS (N = 249)
Number of failed treatments in lifetime ≤10 vs >10	1.32 (1.01–1.73)	NS	NS	NS	NS	NS
ECT exposure in lifetime No vs yes	1.56 (1.19–2.05)	1.76 (1.21–2.56)	NS	1.46 (1.01–2.12)	NS	NS
ECT exposure in current episode No vs yes	1.65 (1.25–2.18)	1.79 (1.22–2.63)	1.56 (1.03–2.35)	1.59 (1.09–2.33)	1.73 (1.02–2.94)	NS
TMS exposure in current episode No vs yes	1.36 (1.04–1.77)	1.64 (1.13–2.39)	NS	NS	NS	NS
ECT or TMS exposure in current episode No vs yes	1.69 (1.27–2.25)	1.93 (1.30–2.88)	NS	NS	NS	NS
EQ-5D VAS ≥51 vs <51	NS	1.52 (1.04–2.22)	NS	NS	NS	NS
MINI panic disorder in lifetime Yes vs no	1.56 (1.14–2.14)	NS	NS	NS	NS	NS
MINI panic disorder in past month Yes vs no	2.15 (1.42–3.25)	2.29 (1.26–4.15)	1.97 (1.09–3.56)	2.98 (1.56–5.71)	4.41 (1.69–11.50)	NS
MINI generalized anxiety disorder in past 6 mo Yes vs no	NS	NS	NS	1.48 (1.01–2.18)	2.15 (1.25–3.71)	NS
Anxiety disorder[b] Yes vs no	NS	NS	NS	NS	2.06 (1.21–3.51)	NS

[a]ORs indicate the relative probability of response to the tripartite outcome comparing 2 levels of a baseline covariate within the specified population. The first level of the baseline covariate shown, eg, ≤10, has a higher probability of response than the second level shown.
[b]Anxiety disorder is based on generalized anxiety disorder, panic disorder (in lifetime), agoraphobia (in current major depressive episode), or social anxiety disorder (in current major depressive episode).
Abbreviations: ECT = electroconvulsive therapy, EQ-5D-VAS = EuroQoL-5 Dimensions Visual Analog Scale, MINI = Mini International Neuropsychiatric Interview, NS = not significant, OR = odds ratio, TMS = transcranial magnetic stimulation, VNS = vagus nerve stimulation.

Figure 1.

Evaluation of Treatment History as Prescriptive Predictors With a Probability of Response Based on the Treatment Effect of Active VNS Vs Sham VNS for the Tripartite Measure at Month 12

	N	OR (Lower – Upper CI)[a]	NNT
Number of failed pharmacotherapies in lifetime			
≤10	300	1.90 (1.17–3.06)	6.7
>10	193	1.81 (0.99–3.28)	7.2
Number of failed treatments in lifetime			
≤10	226	1.92 (1.09–3.38)	6.8
>10	267	1.83 (1.10–3.03)	7.2
ECT exposure in lifetime			
No	266	1.60 (0.95–2.69)	9.5
Yes	227	2.24 (1.29–3.87)	5.3
ECT exposure in lifetime Yes			
Non-Responded	171	2.38 (1.26–4.52)	5.2
Responded	56	2.73 (0.73–10.19)	5.2
ECT exposure in current episode			
No	305	1.70 (1.05–2.77)	8.4
Yes	188	2.20 (1.20–4.02)	5.5
TMS exposure in current episode			
No	245	1.70 (1.00–2.90)	8.1
Yes	248	2.05 (1.21–3.46)	5.9
Esketamine exposure in current episode			
No	372	2.09 (1.36–3.23)	5.8
Yes	121	1.39 (0.63–3.07)	16.5
ECT or TMS exposure in current episode			
No	171	1.57 (0.82–3.01)	10.3
Yes	322	2.08 (1.31–3.29)	5.8
Overall	493	1.87 (1.29–2.70)	6.9

Odds ratio (x-axis: 0, 1, 2, 3, 4, 5)

[a]ORs indicate the relative probability of response to the tripartite outcome comparing active VNS+TAU vs sham VNS+TAU at different values of the baseline covariates. OR >1 favor active VNS+TAU. Dark vertical line is placed at odds ratio of 1. Any subgroup with a lower bound (95% CI) >1 showed statistical separation favoring VNS over sham (ie, whether there was a statistical separation of the superiority of active VNS vs sham VNS for specific variables). Type 1 error was not controlled, and no adjustments were made for multiple comparisons. Light vertical line is placed at odds ratio of 1.87. Any subgroup with an OR point estimate >1.87 had an arithmetically higher observed treatment effect compared to entire modified intent-to-treat (mITT) sample.

Abbreviations: ECT = electroconvulsive therapy, N = number of study participants in sample, NNT = number needed to treat, OR = odds ratio, TAU = treatment as usual, TMS = transcranial magnetic stimulation, VNS = vagus nerve stimulation.

approximately 25% of the sample) was associated with less of a differential benefit with active vs sham VNS.

Why Are Some Variables Both Prognostic and Prescriptive?

Figure 3 presents the proportion of patients at month 12 with a positive outcome on any dimension of the composite tripartite measure, separately for the active VNS and sham VNS groups, and as a function of exposure to ECT, TMS, or either of these interventional procedures. Both treatment groups showed the same relationship, with exposure to interventional treatments associated with poorer outcomes. However, this effect was especially pronounced in the sham VNS group, so that the treatment group differences were greatest for those with poorer prognosis, ie, the patients with exposure to these

Figure 2.

Evaluation of Anxiety Symptoms or Disorders as Prescriptive Predictors With a Probability of Response Based on the Treatment Effect of Active VNS Vs Sham VNS for the Tripartite Measure at Month 12

	N	OR (Lower – Upper CI)[a]	NNT
MINI post-traumatic stress disorder in past month			
No	414	1.87 (1.25–2.81)	6.8
Yes	79	2.12 (0.74–6.06)	6.1
MINI panic disorder in lifetime			
No	371	1.89 (1.24–2.89)	6.6
Yes	122	1.72 (0.77–3.82)	8.5
MINI panic disorder in past month			
No	428	1.98 (1.33–2.94)	6.1
Yes	65	1.02 (0.28–3.69)	NA
MINI agoraphobia at baseline			
No	410	1.96 (1.30–2.96)	6.4
Yes	83	1.64 (0.63–4.28)	10.5
MINI social anxiety disorder in past month			
No	392	2.05 (1.35–3.11)	6.1
Yes	101	1.40 (0.59–3.34)	14.2
MINI generalized anxiety disorder in past 6 months			
No	304	2.46 (1.53–3.95)	4.6
Yes	189	1.16 (0.62–2.15)	31.7
Anxiety disorder[b]			
No	237	2.61 (1.52–4.48)	4.4
Yes	266	1.36 (0.80–2.29)	14.6
Overall	493	1.87 (1.29–2.70)	6.9
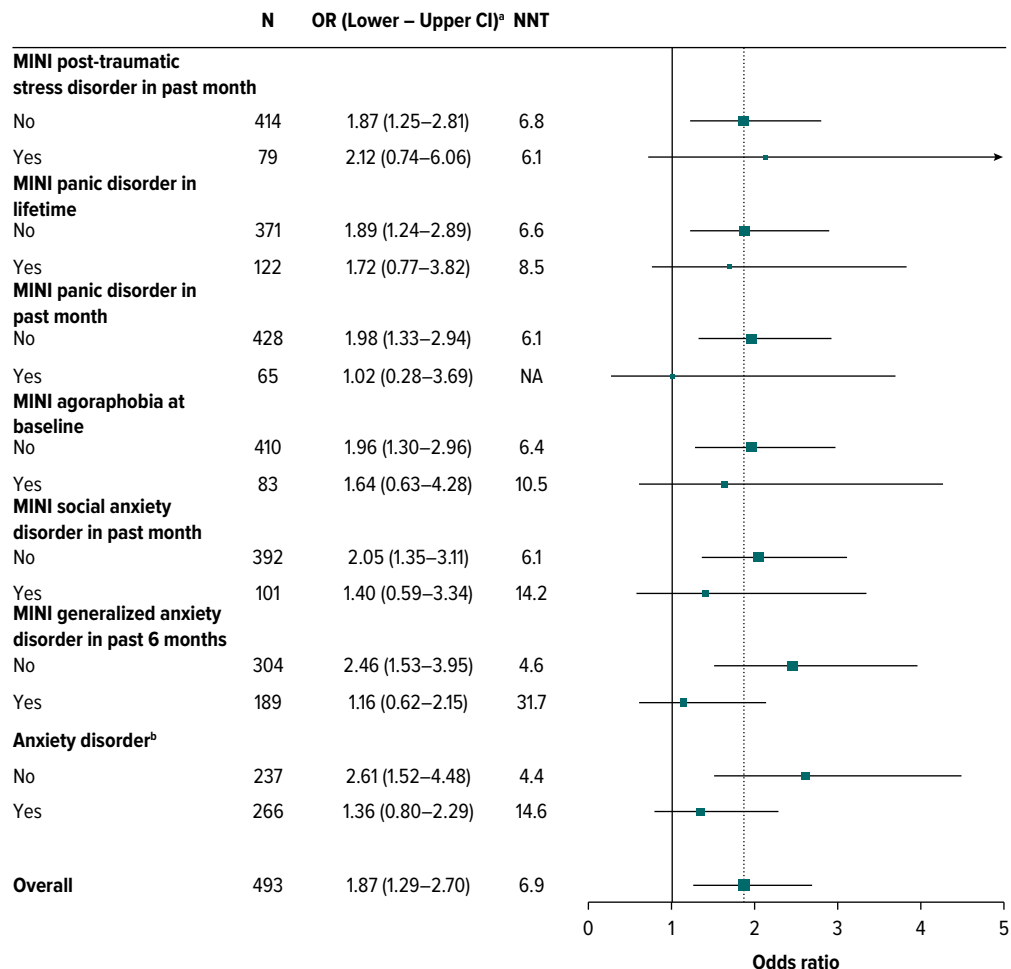
[a]ORs indicate the relative probability of response to the tripartite outcome comparing active VNS+TAU vs sham VNS+TAU at different values of the baseline covariates. ORs >1 favor active VNS+TAU. Dark vertical line is placed at OR of 1. Any subgroup with a lower bound (95% CI) >1 showed statistical separation favoring VNS over sham (ie, whether there was a statistical separation of the superiority of active VNS vs sham VNS for specific variables). Type 1 error was not controlled, and no adjustments were made for multiple comparisons. Light vertical line is placed at odds ratio of 1.87. Any subgroup with an OR point estimate >1.87 had an arithmetically higher observed treatment effect compared to entire modified intent-to-treat (mITT) sample.

[b]Anxiety disorder is based on generalized anxiety disorder, panic disorder (in lifetime), agoraphobia (in current major depressive episode), or social anxiety disorder (in current major depressive episode).

Abbreviations: MINI = Mini-International Neuropsychiatic Interview, N = number of study participants in sample, NNT = number needed to treat, OR = odds ratio, TAU = treatment as usual, VNS = vagus nerve stimulation.

interventions. For example, patients in the active VNS group had similar rates of positive outcome regardless of exposure to TMS or ECT, whereas the sham VNS group with prior interventional treatment had an especially poor outcome.

DISCUSSION

This sample of MDD patients was among the most chronically ill, treatment-resistant, and functionally impaired ever studied with any intervention, averaging 18 years duration for the current depressive episode, history of an average of 13 *failed* lifetime antidepressant treatments, and with 75% unemployed. These marked TRD patients, as a group, were unexposed to relatively few available treatment options, other than VNS at study entry. In this marked TRD sample, we sought to identify the baseline patient features that predicted course of the illness with or without treatment with adjunctive VNS (prognostic predictors) and the patient features that

Figure 3.

Proportion of Patients Experiencing Response at Month 12 on the Tripartite Measure in Active VNS Vs Sham VNS Groups Based on History of Exposure to Interventional Psychiatric Treatments[a]
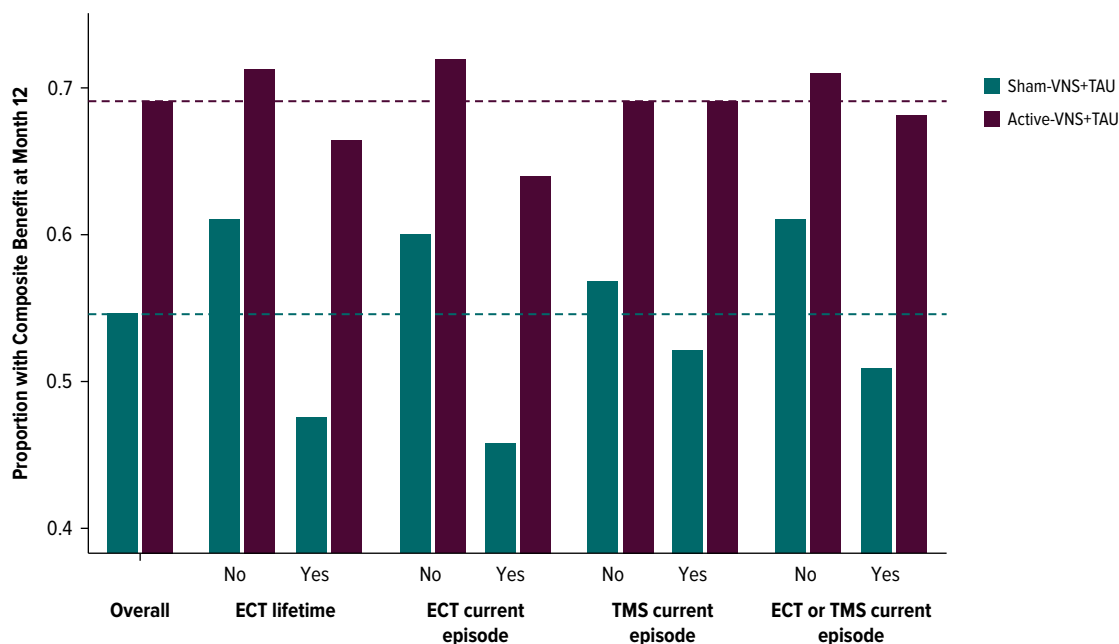
[a]Horizontal dotted lines represent the overall values for each group.
Abbreviations: ECT = electroconvulsive therapy, TAU = treatment as usual, TMS = transcranial magnetic stimulation, VNS = vagus nerve stimulation.

specifically predicted greater benefit from active vs sham VNS (prescriptive predictors).

Treatment history features had consistent and robust prognostic and prescriptive associations with clinical outcome despite requiring a minimum of 4 failed antidepressant trials in the current episode for study entry. Specifically, patients with previous ECT or TMS (interventional psychiatry) treatments had poorer outcomes in the overall population and especially in the sham VNS group (Table 1) (prognostic prediction). The mechanisms underlying this pattern are not known. However, in patients with TRD, ECT, and TMS each exert greater efficacy than further medication trials.[44–46] These treatment failures likely represent a greater degree of or different types of treatment resistance that ordinarily portend poor prognosis that can be ameliorated with VNS. These same patients, however, had superior benefit with active vs sham VNS (Figure 1) (prescriptive prediction). In essence, receipt of these interventional psychiatry treatments identified a subgroup especially likely to show lower levels of improvement on the tripartite outcome metric during the trial. However, this poorer outcome as a function of treatment history, while pronounced in the sham VNS group, was largely absent in the active VNS group (Figure 3). Essentially, active VNS appeared to mitigate the adverse/negative prognostic effects of history of treatment with ECT or TMS. Thus,

the patient subgroups manifesting the poorest clinical outcome during this trial, such as those with a lifetime history of ECT exposure or failure of TMS or ECT in the current episode, were also the same subgroups that reliably benefited more from active VNS than sham VNS, with NNTs of about 5 to 6.

Another set of patient features showed both prognostic and prescriptive associations. The presence of *DSM-5-TR* classified anxiety disorders (including panic disorder and generalized anxiety disorder) at baseline was linked to superior clinical outcomes during the trial (Table 1). Additionally, the absence of a comorbid anxiety disorder was prescriptive of superior outcome with active vs sham VNS. These findings are consistent with a large body of research indicating inferior clinical outcomes with pharmacologic treatments of MDD among patients with comorbid anxiety disorders.[47,48] The prognostic associations, linking these comorbid conditions to superior outcomes independent of the VNS intervention, suggest that these subgroups, at least in the context of marked TRD, indicate greater nonspecific therapeutic change than patients without a comorbid anxiety disorder.

It was noteworthy that, of the 66 variables examined, no subgroup demonstrated better outcomes in the VNS-sham group. Furthermore, we restricted the identification of prescriptive variables to those having significant prognostic value. As seen in Supplementary

Table 3, several variables that lacked prognostic significance had prescriptive value, particularly those indicative of more severe illness at baseline, such as higher depression rating scores and a history of a suicide attempt or suicidal ideation. This suggests that adjunctive VNS therapy may have particularly better efficacy with more severe illness.

This study used a novel tripartite metric to classify clinical outcomes using conjoint measures of depressive symptoms, psychosocial function, and QoL. We previously reported that the 3 components (QIDS-C PR, Mini Q-LES-Q, and WPAI Item 6) in the tripartite measure each showed significant separation of the active VNS vs sham VNS groups.[16,28,49] These findings supported the rationale for constructing a composite measure using the 3 components simultaneously. We showed that this composite identified the largest group of patients as having meaningful benefit and strongly covaries with clinician global judgment.[22]

This patient-centric metric has been validated against blinded clinician ratings based on the Clinical Global Impression-Improvement, and is sensitive to between-treatment group differences in the trial.[22] An analogous tripartite metric based on symptoms, function, and quality of life, when applied to the data from the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study,[1] was a better predictor of relapse during continuation phase treatment with citalopram than any single domain.[50] By capturing improvement in any of 3 critical domains, an advantage of the tripartite metric is that it classifies a larger number of patients as obtaining positive clinical outcome than any single domain measures. The tripartite metric may be advantageous in marked TRD patients in whom small, but clinically meaningful changes, may be more reasonable outcome measures.[3,4] Furthermore, this method may be more reflective of the benefit patients perceive since improvements in function and QoL are often prioritized by patients over symptom change.[51]

This report revealed that the tripartite measure was useful in identifying patient subgroups with the best long-term course and those most likely to benefit from VNS.

Limitations

This study was exploratory. It screened 66 demographic, diagnostic, symptomatic, and treatment history features to identify prognostic and prescriptive predictors. No correction for multiple comparisons was applied to the data, yet the findings were largely consistent with identifying 2 main sets of variables—treatment history and comorbid anxiety disorders—as having consistent prognostic and prescriptive associations with outcomes. The analyses tested the statistical significance of each patient feature in prognostic prediction (Table 1). However, we did not require a significant interaction between treatment group and the levels of the patient feature covariate when identifying prescriptive predictors. The aim was to identify the subgroups that showed reliably greater benefit from active vs sham VNS. This does not entail that the different levels of a feature (eg, positive vs negative history of ECT) differed in terms of outcomes. The prognostic and prescriptive predictors we identified derive from treatment of marked TRD patients and may not apply to other samples.

CONCLUSIONS

In a marked TRD sample, patients with a history of treatment with either ECT or TMS had especially poor outcomes when receiving sham VNS with TAU for 1 year. Active VNS appeared to mitigate this negative prognostic effect, as these same subgroups showed significant differential benefit with adjunctive active VNS relative to sham VNS. The absence of a comorbid anxiety disorder was also linked to superior benefit in the active VNS group vs sham VNS group. These prognostic and prescriptive predictors may help guide clinical decision-making when considering VNS.

Author Affiliations: Institute for Advanced Diagnostics and Therapeutics, Sheppard Pratt Health System, Baltimore, Maryland (Aaronson); Department of Psychiatry, Washington University in St. Louis, St. Louis, Missouri (Conway, Hristidis, Brown, Kriedt); LivaNova PLC (or a subsidiary), London, Great Britain, United Kingdom (Gordon, Lee, Tran, Bunker); Brain Stimulation Division, Department of Psychiatry, Medical University of South Carolina, Charleston, South Carolina (George); Ralph H. Johnson VA Medical Center, Charleston, South Carolina (George); Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, Illinois (Zajecka); Psychiatric Medicine Associates, LLC, Skokie, Illinois (Zajecka); Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia (Riva-Posse); Center for Anxiety and Depression, Mercer Island, Washington (Dunner); Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington (Dunner); UAB Depression and Suicide Center, Department of Psychiatry and Behavioral Neurobiology, Heersink School of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama (Macaluso); Department of Psychiatry and Health Behavior, Medical College of Georgia at Augusta University, Augusta, Georgia (Rosenquist); Department of Psychiatry, University Neuropsychiatric Institute, University of Utah, Salt Lake City, Utah (Mickey); Department of Anesthesiology, University of Utah, Salt Lake City, Utah (Mickey); Department of Psychiatry, University of Michigan, Ann Arbor, Michigan (Mickey); Center for Neuromodulation in Depression and Stress, Department of Psychiatry and Behavioral Sciences, Department of Radiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania (Sheline); Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina (Sackeim); Duke-NUS Medical School, Singapore (Rush); Curbstone Consultant LLC, Dallas, Texas (Rush).

Corresponding Author: Scott T. Aaronson, MD, Institute for Advanced Diagnostics and Therapeutics, Sheppard Pratt Health System, 6501 N. Charles St, Baltimore, MD 21204 (saaronson@sheppardpratt.org).

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1. Patient demographic, clinical, and treatment history features tested for significant prognostic outcomes in the total group, sham VNS group, and active VNS group in Months 3-12.

Variable[a]	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value
Baseline age (years), <65 vs ≥65	1.06 (0.80, 1.41)	0.699	0.89 (0.60, 1.32)	0.564	1.26 (0.83, 1.91)	0.278
Age at MDD diagnosis (years), <25 vs ≥25	1.17 (0.89, 1.55)	0.259	1.04 (0.71, 1.53)	0.846	1.29 (0.86, 1.95)	0.216
Sex, female vs male	1.16 (0.88, 1.54)	0.290	1.21 (0.82, 1.78)	0.337	1.05 (0.69, 1.61)	0.809
MADRS, <34 vs ≥34	1.12 (0.85, 1.47)	0.408	1.21 (0.83, 1.76)	0.327	1.06 (0.71, 1.58)	0.770
QIDS-C, ≥17 vs <17	1.16 (0.84, 1.60)	0.365	0.90 (0.57, 1.40)	0.630	1.47 (0.92, 2.35)	0.104
QIDS-SR, ≥18 vs <18	1.00 (0.75, 1.35)	0.974	0.79 (0.52, 1.21)	0.275	1.32 (0.86, 2.02)	0.207
CGI-S, <6 vs ≥6	1.09 (0.81, 1.47)	0.578	1.12 (0.74, 1.71)	0.586	1.05 (0.67, 1.63)	0.842
Prior episode of depression, No vs Yes	1.21 (0.92, 1.58)	0.166	1.42 (0.97, 2.07)	0.067	1.04 (0.70, 1.54)	0.847
EQ-5D VAS, ≥51 vs <51	1.16 (0.89, 1.52)	0.277	1.52 (1.04, 2.22)	**0.030**	0.88 (0.59, 1.30)	0.513
Mini-QLES-Q, <29 vs ≥29	1.16 (0.87, 1.54)	0.313	1.02 (0.69, 1.50)	0.934	1.28 (0.84, 1.94)	0.253
WHODAS, <50 vs ≥50	1.03 (0.78, 1.36)	0.836	1.05 (0.71, 1.55)	0.810	1.06 (0.71, 1.57)	0.782
WPAI Item 6, ≥8 vs <8	1.08 (0.82, 1.42)	0.592	1.22 (0.83, 1.79)	0.306	0.94 (0.63, 1.40)	0.751
Baseline employment status, Yes vs No	1.08 (0.78, 1.48)	0.645	0.90 (0.56, 1.44)	0.668	1.27 (0.81, 1.99)	0.292
Duration of current depressive episode (years), ≥12 vs <12	1.17 (0.89, 1.53)	0.257	1.33 (0.91, 1.93)	0.141	1.06 (0.72, 1.57)	0.760

Variable[a]	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value
Duration of lifetime depressive episodes (years), ≥27 vs <27	1.05 (0.79, 1.38)	0.746	1.31 (0.89, 1.93)	0.165	0.81 (0.54, 1.20)	0.289
Number of prior hospitalizations for mood disorders, ≥1 vs 0	1.07 (0.81, 1.40)	0.631	0.94 (0.64, 1.36)	0.730	1.10 (0.73, 1.66)	0.631
Prior suicide attempt, Yes vs No	1.12 (0.85, 1.48)	0.412	1.33 (0.90, 1.96)	0.146	0.90 (0.60, 1.34)	0.594
Suicide ideation at baseline, No vs Yes	1.31 (0.98, 1.75)	0.069	1.40 (0.93, 2.11)	0.102	1.23 (0.81, 1.87)	0.338
Number of failed pharmacotherapies in lifetime, ≤10 vs >10	1.12 (0.85, 1.47)	0.435	1.05 (0.71, 1.54)	0.810	1.20 (0.81, 1.79)	0.364
Number of failed treatments in lifetime, ≤10 vs >10	1.32 (1.01, 1.73)	**0.043**	1.31 (0.90, 1.92)	0.158	1.33 (0.89, 1.98)	0.160
ECT exposure in lifetime, No vs Yes	1.56 (1.19, 2.05)	**0.001**	1.76 (1.21, 2.56)	**0.003**	1.42 (0.95, 2.11)	0.086
ECT exposure in lifetime, Response vs Non-Response	1.30 (0.83, 2.04)	0.252	1.61 (0.84, 3.05)	0.147	1.07 (0.54, 2.10)	0.848
ECT exposure in current episode, No vs Yes	1.65 (1.25, 2.18)	**<0.001**	1.79 (1.22, 2.63)	**0.003**	1.56 (1.03, 2.35)	**0.034**
TMS exposure in current episode, No vs Yes	1.36 (1.04, 1.77)	**0.025**	1.64 (1.13, 2.39)	**0.010**	1.15 (0.78, 1.70)	0.467
Esketamine exposure in current episode, No vs Yes	1.14 (0.83, 1.57)	0.404	1.01 (0.66, 1.54)	0.963	1.34 (0.82, 2.18)	0.241
ECT or TMS exposure in current episode, No vs Yes	1.69 (1.27, 2.25)	**<0.001**	1.93 (1.30, 2.88)	**0.001**	1.51 (0.99, 2.29)	0.054
MINI post-traumatic stress disorder in past month, No vs Yes	1.04 (0.72, 1.52)	0.824	0.93 (0.56, 1.54)	0.782	1.08 (0.61, 1.91)	0.801

Variable[a]	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value
MINI panic disorder in lifetime, Yes vs No	1.56 (1.14, 2.14)	**0.006**	1.57 (0.99, 2.47)	0.054	1.55 (0.99, 2.43)	0.053
MINI panic disorder in past month, Yes vs No	2.15 (1.42, 3.25)	**<0.001**	2.29 (1.26, 4.15)	**0.006**	1.97 (1.09, 3.56)	**0.025**
MINI agoraphobia at baseline, No vs Yes	1.25 (0.88, 1.79)	0.217	1.43 (0.83, 2.46)	0.197	1.20 (0.73, 1.96)	0.472
MINI social anxiety disorder in past month, No vs Yes	1.02 (0.74, 1.43)	0.885	0.92 (0.59, 1.45)	0.728	1.08 (0.65, 1.77)	0.767
MINI generalized anxiety disorder in past 6 months, Yes vs No	1.28 (0.97, 1.69)	0.079	1.42 (0.96, 2.08)	0.078	1.14 (0.76, 1.70)	0.533
Anxiety disorder[c], Yes vs No	1.25 (0.95, 1.63)	0.111	1.36 (0.93, 1.99)	0.113	1.13 (0.77, 1.67)	0.531

[a]Median values are used as cut-off for numerical variables.

[b]OR indicates the relative probability of response to the tripartite outcome comparing two levels of a baseline covariate within the specified population. The odds of response for the first level of the baseline covariate shown (e.g., <65) is divided by the odds of response for the second level shown (e.g., ≥65).

[c]Anxiety disorder is based on generalized anxiety disorder, panic disorder (in lifetime), agoraphobia (in current major depressive episode), or social anxiety disorder (in current major depressive episode).

Abbreviations: CGI-S=clinical global impression-severity, ECT=electroconvulsive therapy, EQ-5D-VAS=EuroQoL-5 Dimensions Visual Analog Scale, MDD=major depressive disorder, MADRS=Montgomery-Åsberg Depression Rating Scale, MINI=Mini International Neuropsychiatric Interview, Mini-QLES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, OR=odds ratio, QIDS-C=Quick Inventory of Depressive Symptomatology-Clinician Rated, QIDS-SR=Quick Inventory of Depressive Symptomatology-Self Rated, TMS=transcranial magnetic stimulation, VNS=vagus nerve stimulation, WHODAS=World Health Organization Disability Assessment, WPAI=work productivity and activity impairment.

Supplementary Table 2. Patient demographic, clinical, and treatment history features tested for significant prognostic outcomes in the total group, sham VNS group, and active VNS group in Month 12.

Variable[a]	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value
Baseline age (years), ≥65 vs <65	1.12 (0.76, 1.66)	0.575	1.26 (0.73, 2.17)	0.406	1.01 (0.56, 1.83)	0.961
Age at MDD diagnosis (years), <25 vs ≥25	1.34 (0.92, 1.97)	0.132	1.21 (0.72, 2.06)	0.470	1.47 (0.83, 2.63)	0.189
Sex, female vs male	1.12 (0.76, 1.64)	0.569	1.15 (0.68, 1.95)	0.609	0.99 (0.54, 1.79)	0.966
MADRS, <34 vs ≥34	1.12 (0.78, 1.63)	0.535	1.36 (0.81, 2.27)	0.248	0.93 (0.53, 1.62)	0.784
QIDS-C, <17 vs ≥17	1.00 (0.64, 1.55)	0.999	1.63 (0.88, 3.02)	0.123	0.63 (0.32, 1.21)	0.161
QIDS-SR, <18 vs ≥18	1.01 (0.67, 1.52)	0.949	1.13 (0.63, 2.00)	0.680	0.85 (0.46, 1.55)	0.585
CGI-S, <6 vs ≥6	1.00 (0.66, 1.52)	0.990	0.84 (0.47, 1.50)	0.564	1.19 (0.64, 2.20)	0.586
Prior episode of depression, No vs Yes	1.09 (0.76, 1.59)	0.630	1.51 (0.90, 2.54)	0.119	0.78 (0.45, 1.36)	0.380
EQ-5D VAS, ≥51 vs <51	1.04 (0.72, 1.51)	0.829	1.47 (0.87, 2.46)	0.148	0.72 (0.41, 1.26)	0.251
Mini-QLES-Q, <29 vs ≥29	1.10 (0.75, 1.63)	0.616	1.08 (0.63, 1.84)	0.790	1.07 (0.59, 1.94)	0.813
WHODAS, <50 vs ≥50	1.15 (0.79, 1.68)	0.472	1.23 (0.72, 2.10)	0.457	1.15 (0.66, 2.02)	0.627
WPAI Item 6, <8 vs ≥8	1.17 (0.80, 1.70)	0.419	0.94 (0.55, 1.58)	0.802	1.48 (0.84, 2.62)	0.173
Baseline employment status, Yes vs No	1.26 (0.81, 1.96)	0.306	0.91 (0.48, 1.73)	0.768	1.72 (0.89, 3.35)	0.109
Duration of current depressive episode (years), ≥12 vs <12	1.14 (0.79, 1.65)	0.478	1.57 (0.94, 2.64)	0.087	0.84 (0.49, 1.46)	0.538

Variable[a]	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value
Duration of lifetime depressive episodes (years), ≥27 vs <27	1.03 (0.71, 1.51)	0.866	1.25 (0.74, 2.12)	0.409	0.81 (0.46, 1.41)	0.449
Number of prior hospitalizations for mood disorders, 0 vs ≥1	1.01 (0.69, 1.46)	0.971	1.24 (0.74, 2.07)	0.419	0.94 (0.53, 1.68)	0.843
Prior suicide attempt, Yes vs No	1.09 (0.74, 1.58)	0.668	0.93 (0.55, 1.57)	0.773	1.22 (0.69, 2.16)	0.486
Suicide ideation at baseline, No vs Yes	1.03 (0.69, 1.53)	0.883	1.38 (0.79, 2.42)	0.251	0.74 (0.41, 1.36)	0.333
Number of failed pharmacotherapies in lifetime, ≤10 vs >10	1.03 (0.71, 1.51)	0.866	0.99 (0.59, 1.68)	0.984	1.09 (0.62, 1.92)	0.753
Number of failed treatments in lifetime, ≤10 vs >10	1.26 (0.87, 1.83)	0.226	1.18 (0.70, 1.98)	0.540	1.33 (0.76, 2.33)	0.319
ECT exposure in lifetime, No vs Yes	1.46 (1.01, 2.12)	**0.046**	1.68 (1.00, 2.82)	0.051	1.29 (0.74, 2.26)	0.373
ECT exposure in lifetime, Response vs Non-Response	1.89 (0.99, 3.61)	0.055	2.05 (0.83, 5.06)	0.119	1.96 (0.69, 5.59)	0.206
ECT exposure in current episode, No vs Yes	1.59 (1.09, 2.33)	**0.016**	1.73 (1.02, 2.94)	**0.041**	1.48 (0.83, 2.64)	0.178
TMS exposure in current episode, No vs Yes	1.09 (0.75, 1.57)	0.659	1.22 (0.73, 2.04)	0.449	1.01 (0.58, 1.74)	0.982
Esketamine exposure in current episode, No vs Yes	1.05 (0.68, 1.62)	0.812	0.81 (0.45, 1.45)	0.477	1.44 (0.73, 2.82)	0.292
ECT or TMS exposure in current episode, No vs Yes	1.30 (0.87, 1.92)	0.196	1.47 (0.85, 2.53)	0.169	1.15 (0.64, 2.07)	0.629
MINI post-traumatic stress disorder in past month, Yes vs No	1.41 (0.83, 2.39)	0.200	1.58 (0.79, 3.20)	0.197	1.53 (0.64, 3.65)	0.331
MINI panic disorder in lifetime, Yes vs No	1.55 (1.00, 2.41)	0.052	1.69 (0.90, 3.19)	0.105	1.40 (0.74, 2.67)	0.301
MINI panic disorder in past month, Yes vs No	2.98 (1.56, 5.71)	**0.001**	4.41 (1.69, 11.50)	**0.003**	1.96 (0.80, 4.80)	0.143

Variable[a]	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[b]	P-value
MINI agoraphobia at baseline, Yes vs No	1.08 (0.66, 1.77)	0.764	1.27 (0.60, 2.68)	0.537	0.86 (0.43, 1.71)	0.670
MINI social anxiety disorder in past month, No vs Yes	1.00 (0.64, 1.58)	0.992	0.76 (0.41, 1.42)	0.389	1.24 (0.63, 2.48)	0.531
MINI generalized anxiety disorder in past 6 months, Yes vs No	1.48 (1.01, 2.18)	**0.045**	2.15 (1.25, 3.71)	**0.006**	0.97 (0.55, 1.71)	0.919
Anxiety disorder[c], Yes vs No	1.44 (0.99, 2.09)	0.055	2.06 (1.21, 3.51)	**0.008**	0.98 (0.57, 1.70)	0.942

[a]Median values are used as cut-off for numerical variables.

[b]OR indicates the relative probability of response to the tripartite outcome comparing two levels of a baseline covariate within the specified population. The odds of response for the first level of the baseline covariate shown (e.g., <65) is divided by the odds of response for the second level shown (e.g., ≥65).

[c]Anxiety disorder is based on generalized anxiety disorder, panic disorder (in lifetime), agoraphobia (in current major depressive episode), or social anxiety disorder (in current major depressive episode).

Abbreviations: CGI-S=clinical global impression-severity, ECT=electroconvulsive therapy, EQ-5D-VAS=EuroQoL-5 Dimensions Visual Analog Scale, MDD=major depressive disorder, MADRS=Montgomery-Åsberg Depression Rating Scale, MINI=Mini International Neuropsychiatric Interview, Mini-QLES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, OR=odds ratio, QIDS-C=Quick Inventory of Depressive Symptomatology-Clinician Rated, QIDS-SR=Quick Inventory of Depressive Symptomatology-Self Rated, TMS=transcranial magnetic stimulation, VNS=vagus nerve stimulation, WHODAS=World Health Organization Disability Assessment, WPAI=work productivity and activity impairment.

Supplementary Table 3. Evaluation of prescriptive predictors with a probability of benefit based on the treatment effect of active VNS versus sham VNS for the tripartite measure at Month 12.

Variable[a]	N	GLMM Odds Ratio[b]	Proportion benefit Sham VNS	Proportion benefit Active VNS	NNT
Overall	493	1.87 (1.29, 2.70)	55%	69%	6.9
Baseline age, <65 years	327	2.07 (1.31, 3.27)	52%	69%	6.0
Baseline age, ≥65 years	166	1.63 (0.85, 3.14)	59%	69%	9.5
Age at diagnosis of major mood disorder, <25 years	246	2.10 (1.22, 3.63)	56%	73%	6.0
Age at diagnosis of major mood disorder, ≥25 years	247	1.62 (0.96, 2.74)	53%	65%	8.3
Sex, female	325	1.76 (1.11, 2.78)	56%	69%	7.5
Sex, male	168	2.02 (1.05, 3.87)	53%	69%	6.0
MADRS, <34	217	1.52 (0.86, 2.68)	59%	68%	10.7
MADRS, ≥34	276	2.29 (1.38, 3.78)	51%	70%	5.4
QIDS-C, <17	218	1.12 (0.63, 1.97)	61%	64%	33.1
QIDS-C, ≥17	275	2.86 (1.72, 4.78)	48%	72%	4.2
QIDS-SR, <18	226	1.49 (0.86, 2.59)	58%	67%	10.8
QIDS-SR, ≥18	267	2.30 (1.38, 3.86)	52%	71%	5.3
CGI-S, ≤5	355	2.02 (1.30, 3.14)	53%	70%	6.1
CGI-S, ≥6	138	1.55 (0.76, 3.16)	57%	67%	10.3
Prior episode of depression, No	214	1.26 (0.71, 2.22)	60%	66%	17.7
Prior episode of depression, Yes	279	2.48 (1.50, 4.09)	50%	71%	4.6
EQ-5D VAS, <51	244	2.81 (1.63, 4.85)	49%	73%	4.3
EQ-5D VAS, ≥51	249	1.29 (0.77, 2.18)	60%	66%	16.9
Mini-QLES-Q, <29	289	1.99 (1.22, 3.26)	54%	70%	6.4
Mini-QLES-Q, ≥29	204	1.75 (0.97, 3.14)	55%	68%	7.6
WHODAS, <50	241	1.74 (1.01, 3.00)	58%	70%	8.0
WHODAS, ≥50	252	2.06 (1.23, 3.48)	51%	68%	5.9
WPAI Item 6, <8	234	2.29 (1.31, 4.00)	54%	73%	5.4
WPAI Item 6, ≥8	259	1.62 (0.97, 2.70)	55%	65%	9.3
Baseline employment status, No	368	1.64 (1.07, 2.51)	55%	66%	8.8
Baseline employment status, Yes	123	3.42 (1.46, 8.03)	53%	77%	4.3

Variable[a]	N	GLMM Odds Ratio[b]	Proportion benefit Sham VNS	Proportion benefit Active VNS	NNT
Duration of current episode, <12 years	246	2.59 (1.52, 4.41)	48%	71%	4.4
Duration of current episode, ≥12 years	247	1.36 (0.80, 2.31)	60%	67%	14.1
Duration of lifetime depressive episodes, <27 years	247	2.42 (1.41, 4.16)	51%	71%	5.0
Duration of lifetime depressive episodes, ≥27 years	246	1.46 (0.86, 2.49)	58%	67%	11.2
No prior hospitalizations for mood disorders	201	1.58 (0.87, 2.87)	58%	68%	9.4
≥1 prior hospitalizations for mood disorders	292	2.15 (1.32, 3.50)	52%	70%	5.7
Prior suicide attempt, No	297	1.66 (1.03, 2.68)	55%	67%	8.3
Prior suicide attempt, Yes	196	2.33 (1.27, 4.29)	53%	72%	5.4
Suicide ideation at baseline, No	299	1.42 (0.88, 2.29)	58%	67%	12.1
Suicide ideation at baseline, Yes	194	2.86 (1.55, 5.27)	48%	73%	4.1
Number of failed pharmacotherapies in lifetime, ≤10	300	1.90 (1.17, 3.06)	55%	70%	6.7
Number of failed pharmacotherapies in lifetime, >10	193	1.81 (0.99, 3.28)	54%	68%	7.2
Number of failed treatments in lifetime, ≤10	226	1.92 (1.09, 3.38)	57%	72%	6.8
Number of failed treatments in lifetime, >10	267	1.83 (1.10, 3.03)	53%	66%	7.2
ECT exposure in lifetime, No	266	1.60 (0.95, 2.69)	61%	71%	9.5
ECT exposure in lifetime, Yes	227	2.24 (1.29, 3.87)	47%	66%	5.3
ECT exposure in lifetime, non-responder	171	2.38 (1.26, 4.52)	44%	63%	5.2
ECT exposure in lifetime, responder	56	2.73 (0.73, 10.19)	59%	78%	5.2
ECT exposure in current episode, No	305	1.70 (1.05, 2.77)	60%	72%	8.4
ECT exposure in current episode, Yes	188	2.20 (1.20, 4.02)	46%	64%	5.5
TMS exposure in current episode, No	245	1.70 (1.00, 2.90)	57%	69%	8.1
TMS exposure in current episode, Yes	248	2.05 (1.21, 3.46)	52%	69%	5.9
Esketamine exposure in current episode, No	372	2.09 (1.36, 3.23)	53%	71%	5.8

Variable[a]	N	GLMM Odds Ratio[b]	Proportion benefit Sham VNS	Proportion benefit Active VNS	NNT
Esketamine exposure in current episode, Yes	121	1.39 (0.63, 3.07)	58%	64%	16.5
ECT or TMS exposure in current episode, No	171	1.57 (0.82, 3.01)	61%	71%	10.3
ECT or TMS exposure in current episode, Yes	322	2.08 (1.31, 3.29)	51%	68%	5.8
Interventional Treatment Flag, No	144	1.25 (0.62, 2.54)	63%	68%	20.6
Interventional Treatment Flag, Yes	349	2.21 (1.42, 3.45)	51%	70%	5.4
MINI post-traumatic stress disorder in past month, No	414	1.87 (1.25, 2.81)	53%	68%	6.8
MINI post-traumatic stress disorder in past month, Yes	79	2.12 (0.74, 6.06)	60%	76%	6.1
MINI panic disorder in lifetime, No	371	1.89 (1.24, 2.89)	52%	67%	6.6
MINI panic disorder in lifetime, Yes	122	1.72 (0.77, 3.82)	63%	74%	8.5
MINI panic disorder in past month, No	428	1.98 (1.33, 2.94)	51%	67%	6.1
MINI panic disorder in past month, Yes	65	1.02 (0.28, 3.69)	80%	80%	-
MINI agoraphobia at baseline, No	410	1.96 (1.30, 2.96)	54%	70%	6.4
MINI agoraphobia at baseline, Yes	83	1.64 (0.63, 4.28)	57%	67%	10.5
MINI social anxiety disorder in past month, No	392	2.05 (1.35, 3.11)	53%	70%	6.1
MINI social anxiety disorder in past month, Yes	101	1.40 (0.59, 3.34)	58%	65%	14.2
MINI generalized anxiety disorder in past 6 months, No	304	2.46 (1.53, 3.95)	48%	69%	4.6
MINI generalized anxiety disorder in past 6 months, Yes	189	1.16 (0.62, 2.15)	66%	69%	31.7
Anxiety disorder[c], No	237	2.61 (1.52, 4.48)	47%	69%	4.4
Anxiety disorder[c], Yes	256	1.36 (0.80, 2.29)	62%	69%	14.6

[a]Median values are used as cut-off for numerical variables.

[b]OR indicates the relative probability of response to the tripartite outcome comparing active-VNS+TAU versus sham-VNS+TAU at different values of the baseline covariates. OR >1 favor active-VNS+TAU.

[c]Anxiety disorder is based on generalized anxiety disorder, panic disorder (in lifetime), agoraphobia (in current major depressive episode), or social anxiety disorder (in current major depressive episode).

Abbreviations: CGI-S=clinical global impression-severity, ECT=electroconvulsive therapy, EQ-5D-VAS=EuroQoL-5 Dimensions Visual Analog Scale, GLMM=Generalized Linear Mixed Model, MADRS=Montgomery-Åsberg Depression Rating Scale, MINI=Mini International Neuropsychiatric Interview, Mini-QLES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, N=number of study participants in sample, NNT=number needed to

treat, QIDS-C=Quick Inventory of Depressive Symptomatology-Clinician Rated, QIDS-SR=Quick Inventory of Depressive Symptomatology-Self Rated, TMS=transcranial magnetic stimulation, VNS=vagus nerve stimulation, WHODAS=World Health Organization Disability Assessment, WPAI=work productivity and activity impairment.