

## Supplementary Material

**Article Title:** Prognostic and Prescriptive Predictors of Treatment Response to Adjunctive VNS Therapy in Major Depressive Disorder: A RECOVER Trial Report

**Authors:** Scott T. Aaronson, MD; Charles R. Conway, MD; Charles Gordon, MSc; Ying Chieh (Lisa) Lee, MSc; 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

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### **DISCLAIMER**

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

**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.**

	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
Variable <sup>a</sup>	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	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)	<b>0.030</b>	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

	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
Variable <sup>a</sup>	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value
Duration of lifetime depressive episodes (years), $\geq 27$ 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, $\geq 1$ 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, $\leq 10$ 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, $\leq 10$ vs $> 10$	1.32 (1.01, 1.73)	<b>0.043</b>	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)	<b>0.001</b>	1.76 (1.21, 2.56)	<b>0.003</b>	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)	<b>&lt;0.001</b>	1.79 (1.22, 2.63)	<b>0.003</b>	1.56 (1.03, 2.35)	<b>0.034</b>
TMS exposure in current episode, No vs Yes	1.36 (1.04, 1.77)	<b>0.025</b>	1.64 (1.13, 2.39)	<b>0.010</b>	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)	<b>&lt;0.001</b>	1.93 (1.30, 2.88)	<b>0.001</b>	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

	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
Variable <sup>a</sup>	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value
MINI panic disorder in lifetime, Yes vs No	1.56 (1.14, 2.14)	<b>0.006</b>	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)	<b>&lt;0.001</b>	2.29 (1.26, 4.15)	<b>0.006</b>	1.97 (1.09, 3.56)	<b>0.025</b>
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 <sup>c</sup> , 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

<sup>a</sup>Median values are used as cut-off for numerical variables.

<sup>b</sup>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).

<sup>c</sup>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.**

	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
Variable <sup>a</sup>	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value
Baseline age (years), $\geq 65$ 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 $\geq 25$	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 $\geq 34$	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 $\geq 17$	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 $\geq 18$	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 $\geq 6$	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, $\geq 51$ 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 $\geq 29$	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 $\geq 50$	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 $\geq 8$	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), $\geq 12$ 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

	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
Variable <sup>a</sup>	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value
Duration of lifetime depressive episodes (years), $\geq 27$ 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 $\geq 1$	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, $\leq 10$ 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, $\leq 10$ 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)	<b>0.046</b>	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)	<b>0.016</b>	1.73 (1.02, 2.94)	<b>0.041</b>	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)	<b>0.001</b>	4.41 (1.69, 11.50)	<b>0.003</b>	1.96 (0.80, 4.80)	0.143

	Total Sample (N=493)		Sham VNS (N=244)		Active VNS (N=249)	
Variable <sup>a</sup>	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	P-value	OR (95% CI) <sup>b</sup>	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)	<b>0.045</b>	2.15 (1.25, 3.71)	<b>0.006</b>	0.97 (0.55, 1.71)	0.919
Anxiety disorder <sup>c</sup> , Yes vs No	1.44 (0.99, 2.09)	0.055	2.06 (1.21, 3.51)	<b>0.008</b>	0.98 (0.57, 1.70)	0.942

<sup>a</sup>Median values are used as cut-off for numerical variables.

<sup>b</sup>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).

<sup>c</sup>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 <sup>a</sup>	N	GLMM Odds Ratio <sup>b</sup>	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



<b>Variable<sup>a</sup></b>	<b>N</b>	<b>GLMM Odds Ratio<sup>b</sup></b>	<b>Proportion benefit Sham VNS</b>	<b>Proportion benefit Active VNS</b>	<b>NNT</b>
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

<b>Variable<sup>a</sup></b>	<b>N</b>	<b>GLMM Odds Ratio<sup>b</sup></b>	<b>Proportion benefit Sham VNS</b>	<b>Proportion benefit Active VNS</b>	<b>NNT</b>
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 <sup>c</sup> , No	237	2.61 (1.52, 4.48)	47%	69%	4.4
Anxiety disorder <sup>c</sup> , Yes	256	1.36 (0.80, 2.29)	62%	69%	14.6

<sup>a</sup>Median values are used as cut-off for numerical variables.

<sup>b</sup>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.

<sup>c</sup>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.