Chronic Vagus Nerve Stimulation Significantly Improves Quality of Life in Treatment-Resistant Major Depression

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ABSTRACT

Objective: To compare quality-of-life (QOL) change associated with treatment as usual (TAU, any antidepressant treatment) versus adjunctive vagus nerve stimulation treatment (VNS + TAU) in a population of patients with treatment-resistant depression (TRD) for 5 years.

Methods: Self-reported QOL assessments, using the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), were gathered in a multicenter, longitudinal registry (January 2006–May 2015) comparing the antidepressant efficacy of VNS + TAU versus TAU in TRD. All depressed patients (N = 599), with either unipolar or bipolar depression, met *DSM-IV-TR* major depressive episode criteria and failed at least 4 adequate antidepressant trials. The Montgomery-Asberg Depression Rating Scale (MADRS) was administered by blinded raters. Q-LES-Q-SF scores in the treatment arms were compared via linear regression; linear regression was employed to compare QOL differences with percent decrease in MADRS. A subanalysis comparing Q-LES-Q-SF functional domain change was performed.

Results: 328 VNS + TAU and 271 TAU patients with TRD were compared. On average, VNS + TAU demonstrated a significant, comparative QOL advantage over TAU (as demonstrated via non-overlapping 95% confidence bands) that began at 3 months and was sustained through 5 years and was reinforced using a clinical global improvement measure. Patients receiving VNS + TAU, but not TAU alone, demonstrated a clinically meaningful QOL improvement (34% MADRS decrease) well below the classically defined antidepressant response (50% MADRS decrease). Exploratory post hoc subanalysis demonstrated that VNS + TAU had a significant advantage in multiple Q-LES-Q domains.

Conclusion: Compared to TAU, adjunctive VNS significantly improved QOL in TRD, and this QOL advantage was sustained. Further, TRD patients treated with VNS experienced clinically meaningful QOL improvements even with depression symptom reduction less than the conventional 50% reduction used to ascribe "response."

J Clin Psychiatry 2018;79(5):18m12178

To cite: Conway CR, Kumar A, Xiong W, et al. Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. *J Clin Psychiatry.* 2018;79(5):18m12178.

To share: https://doi.org/10.4088/JCP.18m12178

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In 2005, the United States Food and Drug Administration approved the use of adjunctive vagus nerve stimulation (VNS) treatment for treatment-resistant major depression (TRD) not responsive to 4 antidepressant treatment trials. VNS involves intermittent electrical stimulation of the left cervical vagus nerve using an implanted electrical stimulator. Since approval, additional studies have further demonstrated the efficacy of VNS for TRD.[1,2]

Recently, Aaronson et al[3] published the report of the longest and largest treatment trial of VNS use in TRD to date. The investigators demonstrated that VNS, combined with treatment as usual (ie, any treatment available to psychiatrists, including electroconvulsive therapy [ECT]), was superior to treatment as usual without VNS, achieving greater response (50% reduction in depressive symptoms) and remission rates and lowering overall suicide rates. During the course of studying VNS in TRD and epilepsy, the treatment has also been hypothesized to positively affect factors beyond depression, including anxiety and alertness,[4–7] pain perception,[8] and cognition.[9,10] The effects of VNS on long-term quality of life (QOL) have yet to be examined.

Over the past 20 years, there has been emerging recognition that measuring antidepressant response based solely on standardized depressive symptom scales (eg, Hamilton Depression Rating Scale) does not adequately assess improvements in QOL or daily functioning seen with resolution of clinical depressive syndromes.[11] That is, effective depression treatment should improve the patient's depressive symptomatology as well as overall QOL and functioning across multiple life domains. Research on the "minimal clinically important difference" [MCID] has attempted to address this very issue by examining the smallest degree of change in a clinical outcome measure that is clinically meaningful. While there is no established MCID for QOL improvement in unipolar depression, Endicott et al[12] previously determined the MCID for a standardized measure of QOL, the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF).[13]

This report examines the effects of VNS on QOL in patients with unipolar and bipolar TRD using longitudinally collected data concomitantly with depression scale data as part of a 5-year VNS clinical registry. On the basis of previous evidence of beneficial effects of VNS on anxiety, alertness, cognition, and other symptoms often comorbid with depression, we

hypothesized that VNS would improve QOL beyond standard antidepressant treatments. We also proposed that this QOL advantage may be sustained over time during the 5 years of study observation. We conducted an additional post hoc subanalysis to elucidate potentially specific QOL factors enhanced with sustained VNS in TRD. Finally, we compared the change in QOL via the Q-LES-Q-SF occurring with adjunctive VNS using the MCID Endicott et al[12] reported for a bipolar depression population in our combined bipolar and unipolar TRD population.

Clinical Points

- When assessing therapeutic treatment outcomes for treatment-resistant depression (TRD), changes in depression rating scale scores may not be an adequate measure (ie, depression scales may not capture the totality of the patient-perceived clinical benefit).
- Results from this study suggest that the cumulative therapeutic effects of some treatments—in this case, vagus nerve stimulation—may be more accurately assessed using quality of life measures.
- For TRD patients receiving adjunctive vagus nerve stimulation, it is important to assess for improvements not only in clinical depression symptoms (sleep, appetite, energy, etc) but also in other aspects of overall quality of life functioning (ability to fulfill roles, family and social relationships, overall well-being, etc).

METHODS

Overview

As part of a large 5-year clinical registry (the overall time span for the study was January 2006–May 2015; see Aaronson et al[3] for details), quality of life data were collected on all patients at established intervals using the Q-LES-Q-SF,[13] a 14-item scale that measures improvements across a wide range of life areas including physical health, mood, work, economic situation, and social relationships. Detailed data on baseline demographics and clinical features, including duration of illness, number of failed antidepressant trials, and number of lifetime depressive episodes, were obtained in the registry. The 61 sites were selected based on significant experience with TRD and VNS for TRD; the vast majority of sites (60 [98%] of 61) contributed both treatment-as-usual (TAU) subjects and subjects with TAU plus adjunctive VNS (VNS + TAU). Subjects were recruited into the registry based on a history of highly refractory TRD (ie, minimal failure of 4 more adequate antidepressant trials, diagnosis of major depressive episode using *DSM-IV-TR*,[14] and the commitment that their symptom and treatment course would be followed by experienced staff for 5 years). Because this registry followed the natural treatment course of TRD, no restrictions were placed on the treatments for the TAU group; patients could receive any psychopharmacologic, neurostimulation (including ECT), or psychotherapeutic intervention for the 5-year duration.

At all participating sites, the registry was approved by an institutional review board, and written informed consent was obtained from all study patients after the procedures had been fully explained. Depression assessments were obtained by offsite blinded raters using the Montgomery-Asberg Depression Rating Scale (MADRS).[15]

Statistical Analyses

A slightly different sample from that reported in the Aaronson et al study[3] was used for the analysis presented in this article (see Supplementary Figure 1 for a CONSORT diagram detailing patient selection for the analysis). Specifically, patients who rolled over from a previous VNS dose-finding study[2] were excluded so that both TAU and VNS + TAU patients had the same follow-up period; patients in the dose-finding study did not have post-baseline Q-LES-Q-SF assessments until the 18-month visit. Further, patients who were not depressed at baseline (MADRS score of < 10) were also removed from the analysis. Thus, analyses in this report used data from 328 patients treated with VNS + TAU and 271 patients treated with TAU. Data from all visits were incorporated. For paired data analyses, such as the change in Q-LES-Q-SF score against percentage change in MADRS score, data were paired by the assigned visit number: paired MADRS and Q-LES-Q-SF ratings were obtained quarterly (ie, every 3 months) for the first year and biannually (every 6 months) for the remaining 4 years. Of note, the Q-LES-Q-SF and MADRS assessments for a particular month may have taken place on separate visits (visit window was ± 45 days until 1 year of follow-up and ± 90 days afterward) and, hence, different dates. Any missing data were excluded from analyses if one of the observations in a pair was missing.

All post-baseline data collected in the 5-year follow-up were used except the missing-pair data previously referenced. Separate models were developed for VNS + TAU and TAU. For the longitudinal comparative QOL assessment of VNS + TAU versus TAU, a linear regression model was fit with the change in Q-LES-Q-SF percentage maximum possible score (percent max score) from baseline as the dependent variable and months after baseline visit as the predictor. Q-LES-Q-SF percent max score was used instead of raw score so that results could be compared with the MCID value obtained by Endicott et al.[12] The analysis was subsequently repeated in unipolar and bipolar groups separately. Stochastic error terms for the linear models are assumed to follow normal distribution. Within-patient variability was accounted for using a first-order autoregressive covariance structure. The best covariance structure was picked using the Akaike Information Criterion.[16] To compare the change in QOL for TRD patients receiving VNS + TAU versus TAU for similar drops in MADRS score, a linear regression model was fit with the change in Q-LES-Q-SF percent max score from baseline as the dependent variable and the percentage change in MADRS score from baseline as the predictor.

Since both patient-reported QOL measured using Q-LES-Q-SF score and clinician-reported improvement

Table 1. Baseline Demographics and Clinical Features of Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive VNS

	VNS Group (n = 328)		Treatment-as-Usual Group (n = 271)	
Characteristic or Measure	n	%	n	%
Female	225	68.6	192	70.8
White	318	97.0	246	90.8
DSM-IV-TR primary diagnosis				
Major depressive disorder	231	70.4	212	78.2
Bipolar I disorder, most recent episode depressed	65	19.8	28	10.3
Bipolar II disorder, most recent episode depressed	32	9.8	31	11.4
	Mean	SD	Mean	SD
Age, y	48.8	10.37	50.0	10.80
Age at initial onset of depression, y	20.8	12.12	21.4	11.54
Lifetime no. of failed treatments for depression	8.0	3.04	7.4	2.93
Lifetime no. of diagnosed depressive episodes	15.1	24.34	11.7	24.56
Lifetime no. of suicide attempts	2.0	4.35	1.2	2.32
Baseline score				
Montgomery-Asberg Depression Rating Scale	33.2	7.67	29.5	6.40
Clinical Global Impressions–Severity of Illness scale	5.2	0.78	4.7	0.72
Quick Inventory of Depressive Symptomatology–Self Report	18.3	4.67	15.8	4.92
Q-LES-Q-SF percentage of possible maximum score	38.4	14.97	40.8	15.77

Abbreviations: *DSM-IV-TR* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; VNS = vagus nerve stimulation.

in QOL measured using Clinical Global Impressions–Improvement scale (CGI-I)[17] score were available, a similar analysis on CGI-I data was conducted to determine if the results from the two QOL measures concurred. Although the CGI-I and Q-LES-Q-SF are not identical measures, the CGI-I has previously been used as a means of validating QOL. Similar analyses of Q-LES-Q-SF and CGI have been done in other work.[12] A response on the CGI-I post-baseline was defined as a rating of 1 or 2.[17] Dichotomized outcomes (ie, response or no response) on the CGI-I was then used to fit a logistic regression model with the CGI-I response as the dependent variable and the percentage change in MADRS score from baseline as the predictor for all 5-year follow-up data. Again, separate models were developed for VNS + TAU and TAU, and within-patient variability was accounted for using a first-order autoregressive covariance structure.

Finally, an exploratory post hoc subanalysis of the 14 functional domains of the Q-LES-Q-SF was performed to analyze which domains differentiated VNS + TAU from TAU. A statistical model similar to the one previously described was employed, except the change in Q-LES-Q-SF percent max score from baseline was replaced with the change in Q-LES-Q-SF domain score from baseline as the response. A range of percent changes in MADRS were selected a priori for these domain subanalyses: 50% was chosen as this is the historical definition of antidepressant response, 10% was chosen as a point at which we would expect to observe only minimal change in quality of life (Q-LES-Q-SF score), and 30% as an intermediate value approximating the 34% MADRS decrease determined to be consistent with an improvement in QOL.

Throughout this article, estimated response curves with 95% confidence bands are provided for both VNS + TAU and TAU. Non-overlapping 95% confidence bands imply statistically significantly different responses in the two arms.[18] Further, overlapping confidence bands may or may not imply significant difference and hence are assumed to give inconclusive results throughout the article.

Comparison to Previously Established MCID

In a large clinical trial (N = 542) of individuals with non–treatment-resistant bipolar depression receiving two different doses of quetiapine, Endicott et al[12] determined the MCID for the Q-LES-Q-SF to be an 11.89% max increase from baseline. This value represents the change in Q-LES-Q-SF percent max score (ie, a raw score of 14–70 rescaled to 0–100) associated with a CGI-I assessment of at least "minimally improved" (ie, score of 1–3). We decided a priori to use this predetermined MCID value to compare effect sizes observed with adjunctive VNS versus TAU, despite the differences in the two study populations. Notably, the TRD patients receiving VNS in this study were slightly more ill: patients had mean baseline scores of 33.2 on the MADRS and 5.2 on the CGI–Severity of Illness scale (CGI-S) versus 30 and 4.5, respectively, in the study by Endicott et al,.[12]

RESULTS

Sample Demographics and Disease Characteristics

For a full description of patient demographics, please see the article by Aaronson et al.[3] Table 1 summarizes the key demographics of the subset of patients used for this report. MADRS and Q-LES-Q-SF assessments were not necessarily performed on the same day for many patients; however, the time difference between these measures (median of 4 weeks) was similar between the two cohorts.

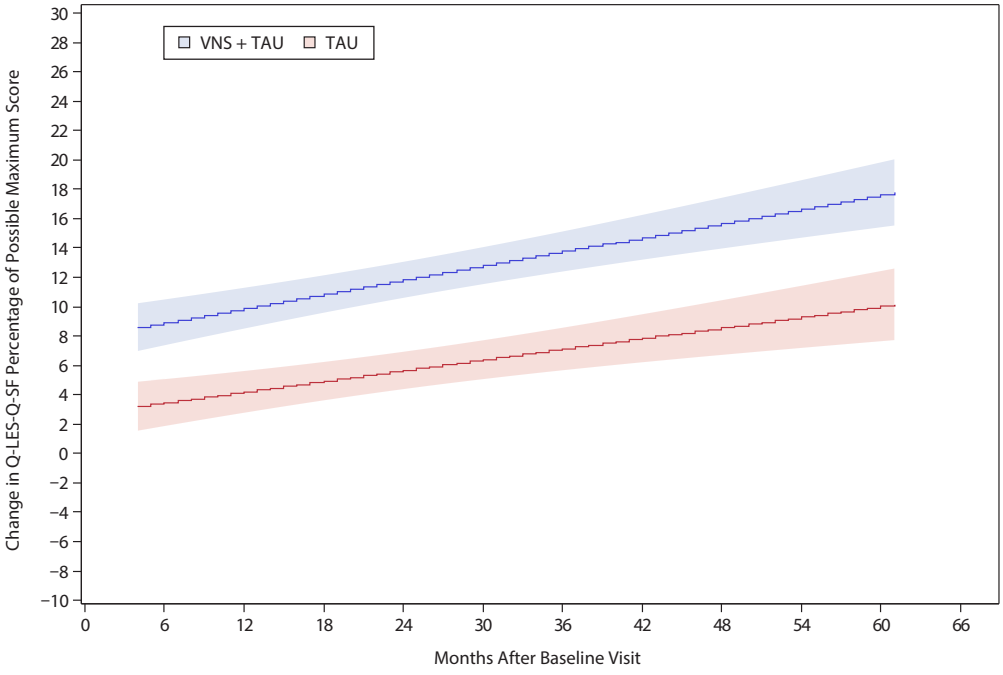
Longitudinal QOL Changes: VNS + TAU versus TAU

The estimated longitudinal curve for the change in Q-LES-Q-SF percent max score from baseline is shown in Figure 1. On average, there was a comparative QOL advantage observed for the VNS + TAU group as early as 3 months, which was sustained throughout the entire 5-year duration of the study.

Change in QOL From Baseline for TRD Patients Receiving Adjunctive VNS + TAU Versus TAU for Similar Drop in MADRS Score From Baseline

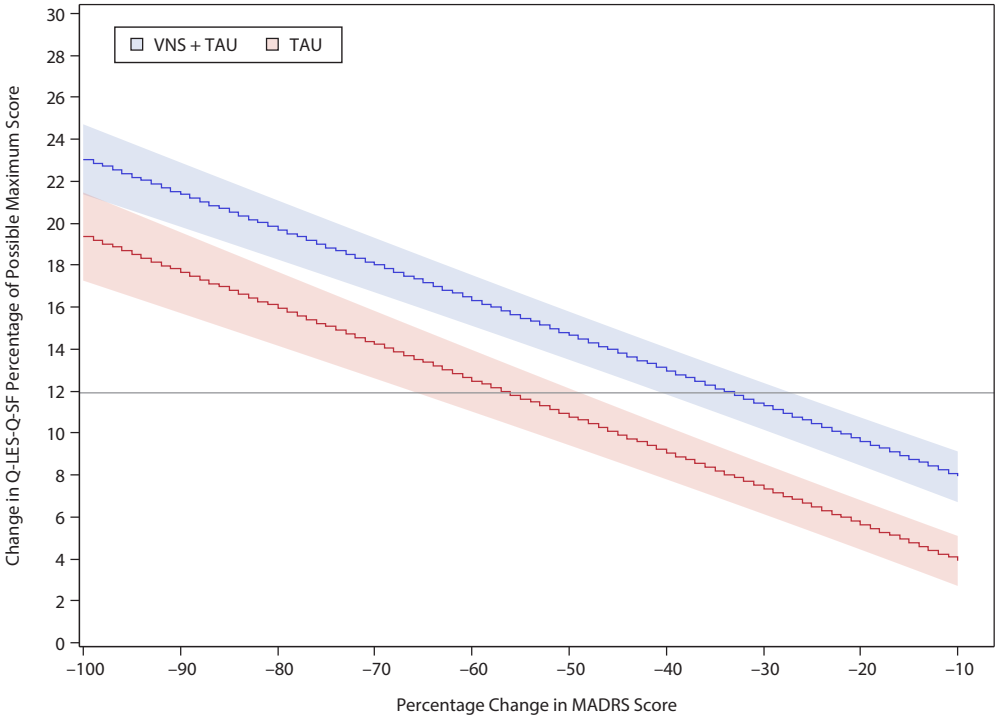
Figure 2 shows a significantly larger improvement in Q-LES-Q-SF percent max score from baseline in the VNS group (VNS + TAU) compared to the TAU group for the same drop in MADRS score. Since estimated lines are approximately parallel, a combined linear regression

Figure 1. Months After Baseline Visit Plotted Against Estimated Change (With 95% Confidence Bands) in Q-LES-Q-SF Percentage Maximum Possible Score From Baseline



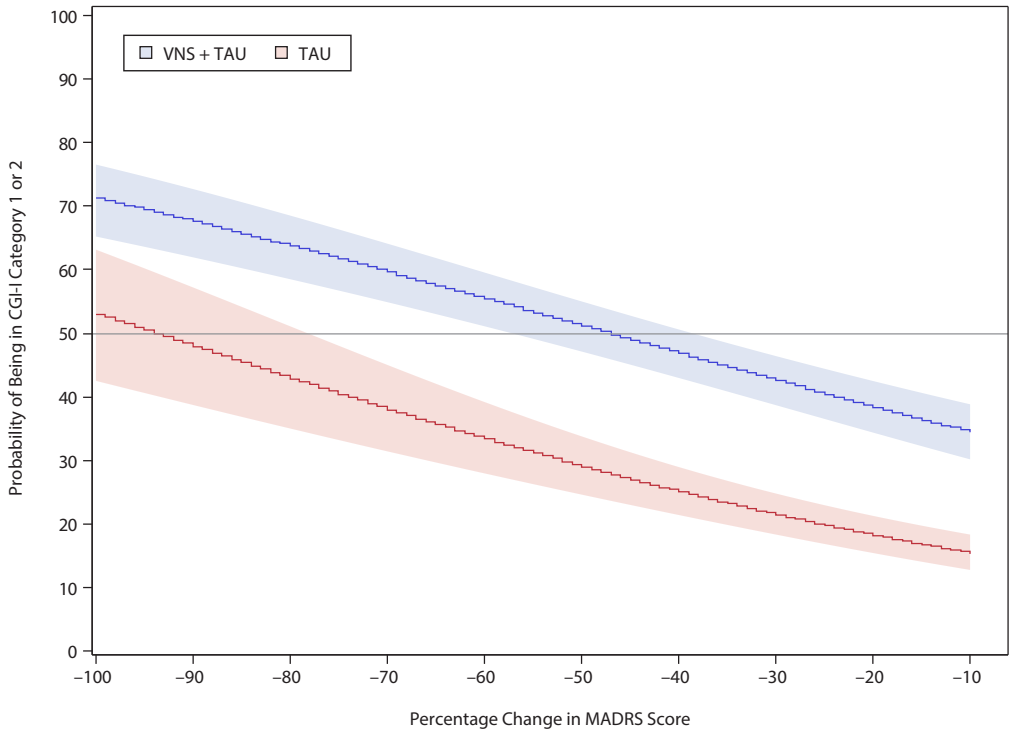
Abbreviations: Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS and any antidepressant treatments.

Figure 2. Percentage Change in MADRS Score From Baseline for VNS + TAU and TAU Plotted Against Estimated Change (With 95% Confidence Band) in Q-LES-Q-SF Percentage Maximum Possible Score From Baseline[a]



[a]The horizontal line denotes the clinically significant change in Q-LES-Q-SF percentage of possible maximum score.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS and any antidepressant treatments.

Figure 3. Estimated Probability (With 95% Confidence Band) of a Patient's Being in CGI-I Category 1 or 2 Plotted Against Percentage Change in MADRS Score From Baseline for VNS + TAU and TAU[a]



[a]The horizontal line denotes a 50% chance of reaching CGI-I category 1 or 2.
Abbreviations: CGI = Clinical Global Impressions–Improvement scale, MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS and any antidepressant treatments.

model with the change in Q-LES-Q-SF percent max score as the response, percentage change in MADRS score as the predictor, and a dummy treatment variable (VNS + TAU = 1 and TAU = 0) as the covariate can be used to estimate the additional improvement in VNS + TAU (via estimating the treatment coefficient). Results from this new model demonstrated that a VNS + TAU patient is expected to have an additional mean improvement in Q-LES-Q-SF percent max score of 3.96 (95% CI, 2.32 to 5.61) compared to a TAU patient for the same drop in MADRS score. The trend observed is maintained in both unipolar and bipolar depression patients when the analysis was repeated separately for each subgroup. However, the result for bipolar depression patients was inconclusive due to greater variance stemming from a smaller sample size.

Furthermore, the individual model for VNS + TAU also estimated that, on average, VNS + TAU patients could achieve a clinically meaningful increase in Q-LES-Q-SF percent max score of 11.89 (horizontal line in Figure 2) when the MADRS drop from baseline is at least 34%—a level that is well below the "standard" 50% drop typically used to define antidepressant treatment response. Note that, on average, the TAU patients achieved the same clinically meaningful increase in Q-LES-Q-SF percent max score when the MADRS drop from baseline is much higher (at least 56%).

Association of QOL With CGI-I Scores

Similar to the patterns observed with Q-LES-Q-SF, using a logistics model, VNS + TAU patients were estimated to have a significantly higher probability of having a response, as defined by a CGI-I score of 1 or 2,[17] compared to TAU patients (Figure 3). On average, a MADRS drop of at least 48% is sufficient for a VNS + TAU patient to have a 50% chance of reaching CGI-I category 1 or 2, whereas a MADRS drop of at least 95% is needed for a TAU patient to have a 50% chance of reaching a CGI-I score of 1 or 2. Because the estimated curves are approximately parallel, a combined model can estimate the odds ratio for VNS + TAU patients' achieving a response compared to TAU patients for the same drop in MADRS score. The estimated odds ratio is 2.78 (95% CI, 2.17 to 3.57), providing further empirical evidence that the greater self-perceived improvement in QOL observed for VNS + TAU over TAU patients (using the Q-LES-Q-SF) is simultaneously being identified by clinician assessment of overall improvement. These improvements, as measured by Q-LES-Q or CGI-I, are greater for the VNS + TAU patients than for the TAU patients for the same drop in MADRS score.

Subanalysis of QOL Domains Influenced by VNS + TAU Versus TAU

An analysis was done to determine which Q-LES-Q-SF domains differentiated VNS + TAU from TAU. Table 2

Table 2. Estimated Change in Q-LES-Q-SF Domain Score From Baseline With 95% Confidence Interval at Selected Levels of MADRS Percent Change From Baseline (10, 30, and 50)

Q-LES-Q-SF Subscale	MADRS Percentage Change	VNS + TAU	TAU
Physical Health			
	−50	0.22 (0.14 to 0.31)	0.24 (0.13 to 0.34)
	−30	0.13 (0.06 to 0.21)	0.14 (0.04 to 0.23)
	−10	0.05 (−0.04 to 0.13)	0.03 (−0.06 to 0.13)
Mood[a]			
	−50	1.00 (0.92 to 1.07)	0.74 (0.65 to 0.83)
	−30	0.75 (0.68 to 0.83)	0.50 (0.42 to 0.58)
	−10	0.50 (0.42 to 0.59)	0.25 (0.18 to 0.33)
Work			
	−50	0.82 (0.71 to 0.93)	0.66 (0.53 to 0.8)
	−30	0.65 (0.54 to 0.76)	0.50 (0.37 to 0.62)
	−10	0.47 (0.36 to 0.59)	0.33 (0.21 to 0.46)
Household activities[a]			
	−50	0.80 (0.73 to 0.88)	0.54 (0.45 to 0.63)
	−30	0.65 (0.58 to 0.73)	0.40 (0.32 to 0.48)
	−10	0.50 (0.42 to 0.58)	0.25 (0.17 to 0.33)
Social relationship			
	−50	0.75 (0.67 to 0.83)	0.58 (0.48 to 0.68)
	−30	0.57 (0.49 to 0.65)	0.40 (0.32 to 0.49)
	−10	0.40 (0.31 to 0.48)	0.23 (0.15 to 0.31)
Family relationship			
	−50	0.54 (0.45 to 0.62)	0.35 (0.25 to 0.44)
	−30	0.42 (0.34 to 0.5)	0.23 (0.15 to 0.32)
	−10	0.30 (0.21 to 0.4)	0.12 (0.04 to 0.2)
Leisure activity[a]			
	−50	0.83 (0.75 to 0.91)	0.54 (0.44 to 0.64)
	−30	0.65 (0.57 to 0.73)	0.38 (0.28 to 0.47)
	−10	0.47 (0.38 to 0.55)	0.21 (0.12 to 0.3)
Ability to function[a]			
	−50	0.89 (0.82 to 0.96)	0.62 (0.54 to 0.71)
	−30	0.69 (0.63 to 0.76)	0.42 (0.34 to 0.5)
	−10	0.50 (0.43 to 0.57)	0.22 (0.14 to 0.3)
Sex drive			
	−50	0.49 (0.41 to 0.58)	0.35 (0.25 to 0.45)
	−30	0.40 (0.32 to 0.49)	0.26 (0.18 to 0.34)
	−10	0.32 (0.23 to 0.4)	0.17 (0.09 to 0.25)
Economic status			
	−50	0.18 (0.1 to 0.25)	0.32 (0.23 to 0.41)
	−30	0.12 (0.05 to 0.2)	0.24 (0.15 to 0.32)
	−10	0.07 (−0.01 to 0.15)	0.15 (0.07 to 0.24)
Living/housing situation			
	−50	0.24 (0.16 to 0.32)	0.15 (0.06 to 0.24)
	−30	0.17 (0.09 to 0.25)	0.07 (−0.01 to 0.15)
	−10	0.11 (0.02 to 0.19)	−0.01 (−0.09 to 0.07)
Ability to get around			
	−50	0.10 (0.01 to 0.19)	0.01 (−0.08 to 0.11)
	−30	0.05 (−0.04 to 0.13)	−0.06 (−0.14 to 0.03)
	−10	−0.01 (−0.1 to 0.09)	−0.12 (−0.21 to −0.04)
Ability to do work			
	−50	0.42 (0.32 to 0.53)	0.27 (0.15 to 0.38)
	−30	0.31 (0.21 to 0.41)	0.18 (0.08 to 0.28)
	−10	0.20 (0.1 to 0.31)	0.09 (−0.01 to 0.19)
Overall well-being[a]			
	−50	0.92 (0.84 to 0.99)	0.68 (0.59 to 0.78)
	−30	0.70 (0.63 to 0.77)	0.49 (0.41 to 0.57)
	−10	0.48 (0.4 to 0.56)	0.29 (0.21 to 0.38)

[a]Additional improvement in the domain score for the VNS + TAU group compared to the TAU group is statistically significant (without any multiplicity adjustment). Significance was determined by absence of overlap of confidence intervals between groups (TAU + VNS vs TAU) when comparing the regression of a given Q-LES-Q-SF domain at each MADRS percent decrease (without multiple comparisons).

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q-SF = Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS + any antidepressant treatment(s).

provides the estimated change in the domain scores from baseline with the 95% CIs for both VNS + TAU and TAU for a selected percentage change in MADRS score. A graph similar to Figure 2 for the individual domains is provided in Supplementary Figures 2 and 3. Results show that VNS + TAU patients achieve greater improvements on mood, household activities, leisure activity, ability to function, overall well-being domains, social relationships, family relationships, and sex drive domains. TAU patients, on the other hand, do better on the economic status domain. Both groups were similar for the remaining domains. Because this subanalysis was post hoc and exploratory, the values in Table 2 were not adjusted for multiple comparisons.

DISCUSSION

In a very large sample of patients with highly treatment-resistant major depression, adjunctive VNS demonstrated a statistically significant greater improvement in quality of life than TAU. On average, this significant comparative QOL advantage of adjunctive VNS over TAU occurred as early as 3 months. An equally crucial finding is that this comparative QOL advantage was sustained throughout 5 years of observation. Hence, in comparison to the TAU cohort, as a group the QOL improvements with adjunctive VNS appear to persist in patients with TRD—a significant achievement, as the TRD population is notorious for exceedingly high symptomatic relapse.[19,20] This comparative advantage of VNS + TAU over TAU was both observed in self-reported QOL via the Q-LES-Q-SF and confirmed with clinician-reported global improvement as measured by the CGI-I.

Notably, this improvement in QOL observed in the VNS group occurred even when the total change in MADRS score from baseline was less than 50% (ie, the classical definition of depression response). In fact, on average, the QOL improvement for the VNS group was observed as long as there was a reduction in MADRS score of at least 34% from baseline. That is, using a previously published minimally clinically important difference for Q-LES-Q-SF of 11.89 max percent increase from baseline,[12] adjunctive VNS patients were making clinically significant improvements in QOL with MADRS score drops of as low as 34% from baseline.

These findings are potentially important for several reasons. First, as we begin to better understand TRD, it is becoming increasingly clear that depressed patients who do not respond adequately to a series of medications are at very low likelihood of responding to additional medications or to augmentation and combination pharmacologic strategies.[19,21] This observation suggests that "novel" treatments, acting

via mechanisms qualitatively different from those of standard antidepressant medications, may provide benefits beyond medications. Second, the data in this report suggest that adjunctive VNS may be associated with changes that provide enhancement of QOL in addition to benefits obtained with depressive symptom reduction alone. That is, patients with TRD receiving adjunctive VNS experience markedly higher improvements in QOL with considerably smaller reductions in depressive symptoms (34% reduction from baseline MADRS). This finding suggests that perhaps each individual antidepressant treatment modality may differentially affect QOL, and perhaps studies of this more virulent form of depression (TRD) should emphasize outcome measures other than simply depressive symptom scales. Lastly, the findings suggest that our "standard" measure of a treatment's success—a 50% reduction in depressive symptoms—may not be an adequate measure in patients with TRD. This suggestion is particularly compelling, as the population of depressed patients studied in this trial was more ill than the reference group.[12]

Perhaps not surprisingly, patients with TRD receiving adjunctive VNS self-reported the greatest improvements in the mood domain of the Q-LES-Q-SF when compared to TAU patients. This could potentially be explained by the unique electrochemical effects of VNS, which are provided around the clock, as the VNS stimulator device fires at set intervals throughout the day, which is notably not the case with other neurostimulatory treatments, such as ECT and repetitive transcranial magnetic stimulation (rTMS), which are characterized by relatively brief treatment sessions and transient antidepressant effects in TRD, particularly when treatment is stopped.[22,23] Brain imaging studies suggest that VNS may bring about its effects via changes in the prefrontal, cingulate, and insular cortex as well as the brain stem.[24–26] Furthermore, cerebrospinal fluid and brain imaging studies suggest that dopamine may play a key role in the antidepressant effects of VNS.[26,27] This involvement of the dopaminergic system may be critical, as most of the current antidepressants do not powerfully influence the dopaminergic brain pathways. In summary, our current understanding of the QOL improvement advantage observed with VNS + TAU vis-à-vis TAU is hypothetical; future studies that target the biological underpinnings of these advantages are warranted.

The post hoc subanalysis also revealed that VNS demonstrated a statistically significant advantage in multiple other functional domains measured on the Q-LES-Q-SF, including overall well-being, improvement in perceived ability to function, household activities, and leisure activities. This statistical significance may not be maintained with advantages seen in other Q-LES-Q-SF domains (eg, perceived physical health, ability to do work or get around). The advantage noted for adjunctive VNS in the sexual domain of the Q-LES-Q-SF is consistent with other (unpublished) data from the VNS registry (available from the authors), which demonstrated that patients receiving VNS, vis-à-vis TAU, showed greater improvements in sexual function using the Arizona Sexual Experience Scale.[28] Notably, two of the Q-LES-Q-SF domains that showed no differential advantage with adjunctive VNS were "work" and "ability to work."

It is important to keep in mind the constraints of the investigation when interpreting these results. First, the depression symptoms (MADRS) were assessed single-blinded via offsite central raters; patients receiving either TAU or adjunctive VNS knew which treatment they were receiving when they completed the Q-LES-Q-SF. Second, as shown in Supplementary Table 1, there were dropouts with further time progression in the study, particularly in years 4 and 5. However, the primary finding of the study—a differential improvement in QOL with adjunctive VNS in patients whose MADRS score reductions were well below 50%—would not be affected by this observed dropout; the sample size of interest is of patients with a particular MADRS drop, regardless of when that drop happened. Finally, the current sample consisted of patients with unipolar and bipolar TRD with severe treatment-resistant depression, whereas the population providing the Q-LES-Q-SF MCID benchmark[12] consisted only of patients with bipolar depression. Although the sex distribution of the patient treatment groups was consistent with the predicted 2:1 female-to-male ratio typically observed in major depressive disorder, the racial demographic of the group was highly skewed toward white individuals, with 97% and 91% of the VNS + TAU and TAU groups, respectively, being white. Another potential limitation of the study was that it was open label (ie, the treating clinicians knew which patients had VNS devices), which could potentially influence the aggressiveness of adjunctive pharmacotherapy. However, data collected during the registry (unpublished) indicate that over the course of the registry duration, there were more medication changes in the TAU group, supporting the opposite conclusion—more aggressive pharmacotherapy was applied in the TAU group.

In conclusion, adjunctive VNS resulted in greater improvements in quality of life that are well beyond what treatment as usual provides, and these improvements were sustained. Adjunctive VNS also demonstrated significant advantages in not only the mood domain, but also multiple other functional domains measured on the Q-LES-Q-SF. Using a pre-established MCID, quality-of-life improvements occurred with MADRS reductions far below the classical 50% improvement definition of depression response.

Submitted: February 9, 2018; accepted July 3, 2018.

Published online: August 21, 2018.

Potential conflicts of interest: **Dr Conway** has previously received research support from LivaNova and Bristol-Myers Squibb. He currently receives research support from the Stanley Medical Research Institute, the National Institute of Mental Health, NeoSync Inc, The Taylor Family Institute for Innovative Psychiatric Research, The August Busch IV Foundation, and the Barnes-Jewish Hospital Foundation. He previously received speaking fees from Bristol-Myers Squibb and Otsuka. He serves as a research design consultant to LivaNova. He is a part-time employee of the John Cochran Veterans Administration Hospital in St. Louis. **Drs Kumar** and **Bunker** are employees of LivaNova. **Dr Aaronson** has received consulting fees from Janssen, Genomind, Alkermes, Neuronetics and LivaNova; speaking fees from Otsuka, Neurocrine and Sunovion; and research funding from Neuronetics. **Dr Rush** has received consulting fees from Akili, Brain Resource, Compass,

Curbstone Consultant LLC, Emmes Corp, Liva-Nova, MindLinc,; Sunovion, Taj Medical, and Takeda USA; royalties from Guilford Publications and University of Texas Southwestern Medical Center at Dallas (for the Inventory of Depressive Symptoms and its derivatives); and speaking fees from LivaNova and is also the co-inventor on US Patent No. 7,795,033 and US Patent No. 7,906,283. **Dr Xiong** has no conflicts of interest to report.

Funding/support: Research reported in this publication was supported by Cyberonics, Inc. (LivaNova, PLC), Houston, Texas.

Role of the sponsor: LivaNova PLC (formerly Cyberonics, Inc.) sponsored the patient registry through contracts to investigative sites. The study sponsor collaborated on the design of the study. Statistical analyses were performed by the sponsor and reviewed by the senior author and other contributing authors. The sponsor also collaborated with the other authors in data interpretation. Although staff at LivaNova reviewed the manuscript, the decision to submit the manuscript was the collective decision of all of the authors.

Acknowledgments: The authors thank Bryan Olin, PhD, and Giacomo Mordenti, MS, both employees of LivaNova PLC, London, UK, for their statistical insights. They also thank Britt Gott, MS, for providing editorial comments, and Al Janski, PhD, for intellectual input. Both Ms Gott and Dr Janski are employees of Washington University in St Louis. Neither have any financial disclosures.

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Chronic Vagus Nerve Stimulation Significantly Improves Quality of Life in Treatment Resistant Major Depression

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DOI Number: https://doi.org/10.4088/JCP.18m12178

List of Supplementary Material for the article

1. Table 1 (Treatment and Number of Patients Per Visit)
2. Figure 1 (Flowchart of Patient Status During the Study)
3. Figure 2 (Change in Q-LES-Q-SF domain scores plotted against percentage change in MADRS score)
4. Figure 3 (Change in additional Q-LES-Q-SF domain scores plotted against percentage change in MADRS score)

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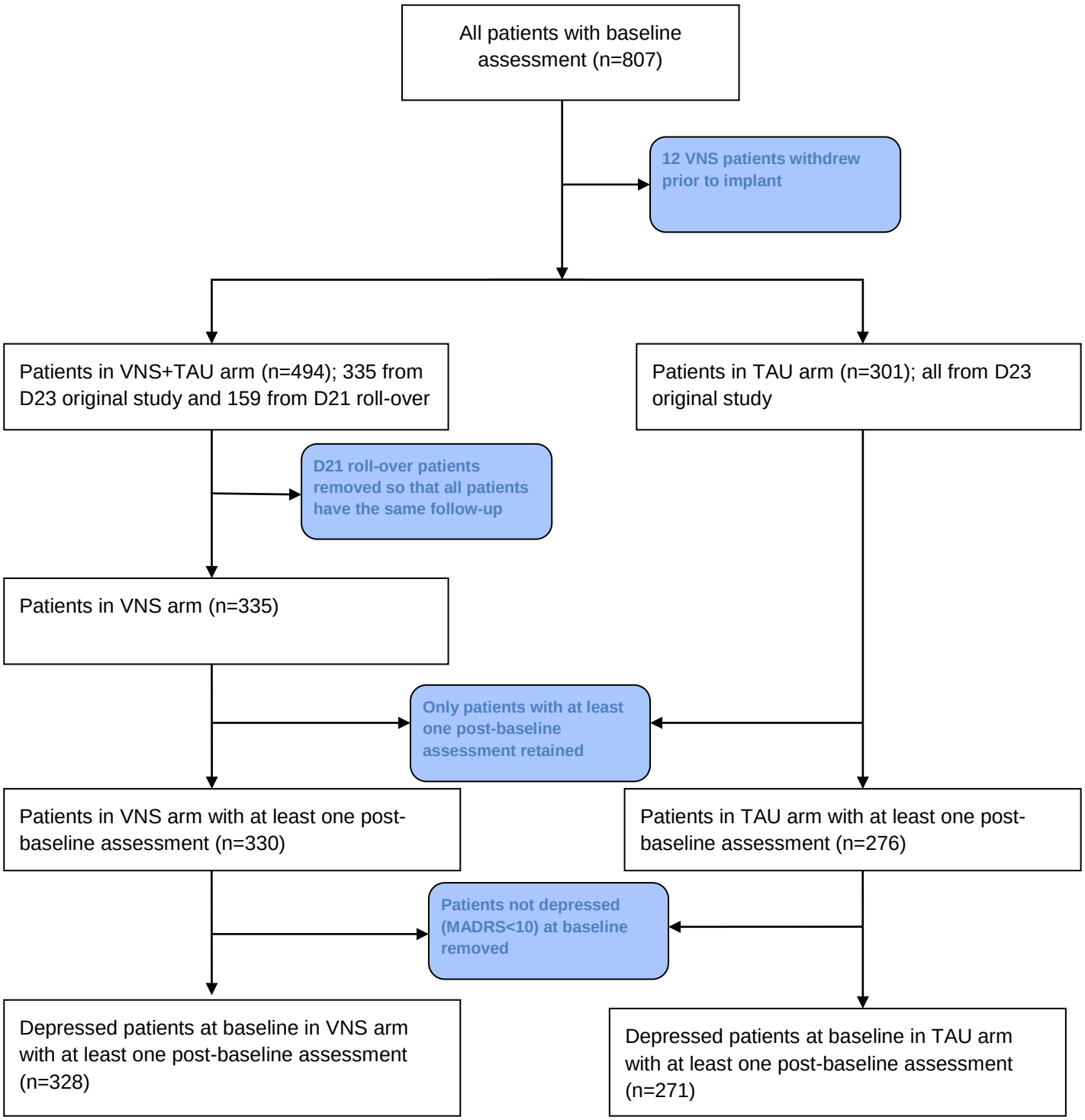
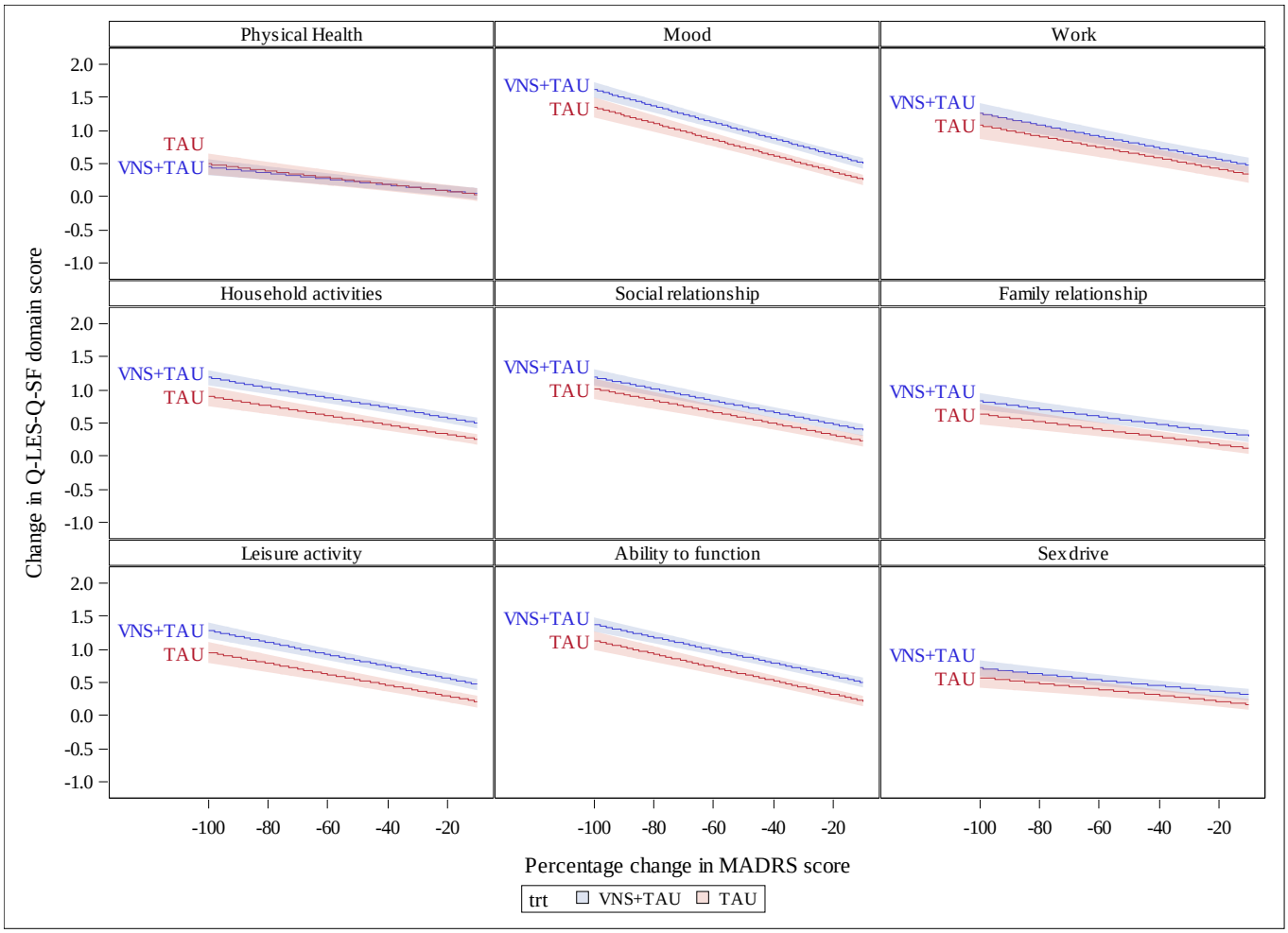
Supplementary Table 1

Treatment	Visit	N
VNS + TAU	3 month	320
VNS + TAU	6 month	295
VNS + TAU	9 month	266
VNS + TAU	12 month	260
VNS + TAU	18 month	254
VNS + TAU	24 month	229
VNS + TAU	30 month	209
VNS + TAU	36 month	204
VNS + TAU	42 month	180
VNS + TAU	48 month	165
VNS + TAU	54 month	146
VNS + TAU	60 month	161
TAU	3 month	256
TAU	6 month	237
TAU	9 month	214
TAU	12 month	209
TAU	18 month	178
TAU	24 month	158
TAU	30 month	146
TAU	36 month	148
TAU	42 month	140
TAU	48 month	127
TAU	54 month	126
TAU	60 month	128

Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3