Title Page

Two-year Outcome of Vagus Nerve Stimulation (VNS) in Treatment-resistant Depression

Malek Bajbouj, MD[1,2]*; Angela Merkl, MD[1]*; Thomas E. Schlaepfer, MD[3,4,5]; Caroline Frick, MD[3]; Astrid Zobel, MD[3]; Wolfgang Maier, MD[3]; Veronica O'Keane, MD[6]; Ciaran Corcoran, MD[6]; Rolf Adolfsson, MD[7]; Michael Trimble, MD[8]; Harald Rau, MD; Hans-Joachim Hoff, MD[9]; Frank Padberg, MD[10]; Florian Müller-Siecheneder, MD[10]; Kurt Audenaert, MD[11]; Dirk van den Abbeele, MD[11]; Keith Matthews, MD[12]; David Christmas, MD[12]; Sam Eljamel, MD[12]; and Isabella Heuser, MD[1]

1. Department of Psychiatry, Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany; 2. Freie Universität Berlin, Cluster of Excellence "Languages of Emotion"; Dahlem Institute of Neuroimaging of Emotion (DINE); 3 Department of Psychiatry and Psychotherapy, University Hospital, Bonn, Germany; 4. Department of Psychiatry, University Hospital, Bern, Switzerland; 5. Departments of Psychiatry and Mental Health, The Johns Hopkins University, Baltimore, MD, USA; 6. Jonathan Swift Clinic, St. James Hospital, Dublin, Ireland; 7. University Hospital Umea, Umea, Sweden; 8. National Hospital for Neurology and Neurosurgery, Department of Neuropsychiatry and Neurology, London, UK; 9. Evangelisches Krankenhaus Bielefeld, Bielefeld, Germany; 10. Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany; 11. University Hospital Gent, Gent, Belgium; 12. Centre for Neuroscience, University of Dundee, Ninewells Hospital and Medical School, UK
* both authors contributed equally

Address for correspondence and reprints: Malek Bajbouj, MD, Department of Psychiatry; Charité – Universitätsmedizin Berlin; Campus Benjamin Franklin; Eschenallee 3; 14050 Berlin; Germany; phone: +49 30 8445 8622; fax: +49 30 8445 8233; Email: malek.bajbouj@charite.de

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Running title: Long-term VNS in Depression

ABSTRACT

One of the major goals of antidepressant treatment is a sustained response and remission of depressive symptoms. Some of the previous studies of vagus nerve stimulation (VNS) have suggested antidepressant effects. Our naturalistic study assessed the efficacy and safety of VNS in 74 European patients with therapy-resistant major depressive disorder. Psychometric measures were obtained after 3, 12, and 24 months of VNS. Mixed model repeated measures ANOVA revealed a significant reduction ($p \leq 0.05$) at all 3 time points in the Hamilton Rating Scale for Depression ($HRSD_{28}$), the primary outcome measure. After 2 years, 53.1% (26/49) patients fulfilled response criteria (≥50% reduction in $HRSD_{28}$ scores from baseline) and 38.9% (19/49) fulfilled remission criteria ($HRSD_{28}$ scores ≤10). The proportion of patients who fulfilled remission criteria remained constant as the duration of VNS treatment increased. Voice alteration, cough, and pain were the most frequently reported adverse effects. Two patients committed suicide during the study; no other deaths were reported. No statistically significant differences were seen in the number of concomitant antidepressant medications. The results of this 2-year open-label trial suggest a clinical response and a comparatively benign adverse effect profile among patients with treatment-resistant depression.

Key words: clinical trial; Hamilton Rating Scale for Depression; major depressive disorder; depression, vagus nerve stimulation

INTRODUCTION

The necessity for comparably safe, effective, and well tolerated, long-term treatments for chronic and treatment-resistant depression is well recognized. Although a broad range of effective treatments is available, a considerable proportion of patients do not respond adequately [1]. Patients who have experienced recurrent depressive episodes often relapse and do not achieve full remission despite treatment with conventional therapies [2-3]. Given that 'remission' status predicts better functioning and a more favourable prognosis for this group of patients, achievement of remission should be the goal for both treatment and clinical trials [4]. However, achieving sustained response and remission remains a major challenge in the long-term management of patients with depression.

Treatment resistance is one of the common principal indications for stimulation techniques, such as electroconvulsive therapy, vagus nerve stimulation (VNS) or, currently only in the context of research investigations, deep brain stimulation [5]. The rationale for the use of VNS as a long-term treatment in patients with chronic depression has been based on clinical findings in epilepsy patients as well as in neuroimaging findings in both epilepsy and depression patients showing alterations in medial and prefrontal limbic regions associated with neurotransmitters that have a role in anticonvulsive actions [6, 7]. Consequently, VNS was approved by the US Food and Drug Administration in 2005 for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments. The approval required the manufacturer to conduct 2

additional studies, which are underway in the United States. The efficacy studies of VNS for treatment-resistant depression are summarized here.

Results from previous naturalistic studies assessing the antidepressant effect of VNS after 12 months of active treatment in patients with treatment-resistant depression have suggested an improvement in primary outcome scores [8-10]. Response rates of 29.8% and remission rates of 17.1% have been reported after 1 year of VNS in a naturalistic setting [8]; however, in a 10-week acute, sham-controlled, randomized trial of adjunctive VNS compared with stable medication, the Hamilton Depression Rating Scale ($HRSD_{24}$) response rates were as low as 15.2% for the active group versus 10.0% for the sham group, with statistically significant improvement in depressive symptoms only for secondary outcome measures [11]. Although the 12-month outcome of a VNS-treated group has been compared with treatment as usual, efficacy and the time course for antidepressant effects remain unclear [10].

We investigated symptomatic outcomes in a cohort of patients with treatment-refractory mood disorders treated with VNS over a 24-month period in this open-label, uncontrolled, European multicenter trial. Results of the first 3 months (acute phase) and the first 12 months (long-term phase) of this study have been reported [12]. Specifically, we were interested to know whether depression severity improved at 24-month follow-up; whether improvements in depressive symptoms were sustained beyond the 12-month period; and whether VNS was tolerated over a 2-year period.

PATIENTS AND METHODS

Patients

Independent Ethics Committees at each study site approved the protocol, and all patients gave written informed consent before enrollment in the study.

Patient eligibility requirements for the study included diagnosis of a major depressive episode (MDE) according to DSM-IV, a chronic (2 years or more) current MDE or a history of recurrent MDEs (at least 4 lifetime MDEs including the current MDE). During the current MDE, at least 2 adequate trials of antidepressant treatments measured with the Antidepressant Treatment History Form (ATHF) [13] had failed to bring about a meaningful clinical response. Additional main eligibility requirements included a trial of at least 6 weeks of psychotherapy, a score of ≥20 on the 24-item Hamilton Rating Scale of Depression ($HRSD_{24}$), and stable psychopharmacological medication for at least 4 weeks before baseline. Exclusion criteria included atypical depression, psychotic symptoms, schizophrenia, schizoaffective disorder, delusional disorder, rapid cycling bipolar disorder; secondary diagnosis of or signs of delirium, dementia, amnestic, or other cognitive disorders per DSM-IV; failure at antidepressant resistance rating (ARR) score ≥3 of 7 or more antidepressant treatments during the current depressive episode; suicide attempt requiring medical treatment within the previous 12 months, 2 or more suicide attempts during the previous 12 months, or suicidal tendencies; alcohol or substance dependence within the previous 12 months or abuse during the previous 6 months other than nicotine; participation in other investigational trials; significant cardiac or pulmonary conditions, or likelihood of requiring whole-body magnetic resonance imaging (MRI) after implantation.

Study Device

Vagus Nerve Stimulation Therapy (Cyberonics, Houston, Texas) is a nonpharmacologic treatment that involves the surgical implantation of a small pulse generator subcutaneously in the left thoracic region. Electrodes attached to the left cervical vagus nerve are connected to the pulse generator by a lead, which is tunneled under the skin. After the clinician programs the device, it delivers chronic intermittent electrical stimulation to the vagus nerve.

Study Design

The study was designed to extend the findings of a pilot study conducted in the United States [6, 9] in an open-label, non-randomized, single-arm, longitudinal, multicenter design that evaluated the use of VNS in patients with unipolar or bipolar depression. The study was conducted at 11 study sites located in 6 European countries (Belgium, Germany, Ireland, Sweden, Switzerland, and the United Kingdom) between 2000 and 2005. Further study details have been described elsewhere (12).

Outcome Measures

Effectiveness

The primary outcome measure was improvement from baseline values over time in the scores of the 28-item Hamilton Rating Scale for Depression ($HSRD_{28}$). The secondary outcome measures were changes in scores on the Montgomery-Åsberg Depression Rating Scale (MADRS), the Inventory of Depressive Symptoms-Self Report ($IDS\text{-}SR_{30}$), Clinical Global Impression Scale Severity (CGI-S), and the Clinical Global Impressions Improvement (CGI-I). We report the results of testing at 3, 12, and 24 months.

'Response' was defined *a priori* as a 50% or greater reduction in the $HRSD_{28}$ scores compared with the mean score of 2 baseline visits. For secondary outcomes, response was defined as a reduction of 50% or more in the score compared with baseline for the MADRS or the IDS-SR_{30}. 'Remission' was defined *a priori* as a score ≤10 for the $HRSD_{28,}$ ≤10 for the MADRS, or ≤14 for the IDS-$SR_{30.}$

Safety

Safety was assessed by reports of adverse events.

Concomitant Medications

The number of concomitant psychotropic antidepressant and antipsychotic medications taken at baseline were compared with those taken after 3, 12, and 24 months of VNS.

Sustained Response Analysis

Data listings for response and remission were analyzed to determine the number of patients who met criteria for response and/or remission at all 3 end points (3 months, 12 months, and 24 months). In addition, an analysis determined the number of patients who met criteria for response or response and remission at both 12 months and 24 months.

Statistical Analysis

Simple descriptive statistics (mean, standard deviation) were obtained for patients' demographic and baseline clinical characteristics. Both observed cases (OC) and last observation carried forward (LOCF) values were provided for outcomes measures. Longitudinal profiles for mean improvement, mean percent improvement from baseline, and mood medications, consisting of 3-, 12-, and 24-month follow-up visits, were

analyzed for significant temporal trends using mixed model repeated measures (MMRM) analysis of variance methodology as implemented in the SAS GLIMMIX procedure (SAS V9); normally distributed errors and a compound symmetric variance-covariance matrix were assumed. MMRM also were used in a longitudinal analysis of the binary outcomes response, remission, and CGI-I; a binomial error distribution was assumed in conjunction with the logit link function and compound symmetric variance-covariance matrix. A p-value ≤ 0.05 was considered statistically significant; p-values were not adjusted for multiplicity of comparisons. Analyses were performed on both the OC and imputed data using the LOCF approach.

RESULTS

Patients

A total of 74 patients met the inclusion criteria and had the VNS generator implanted. Of these 74, 70 (94.6%) entered the long-term follow up, with 60 (81.1%) patients evaluable at 12 months, and 49 (66.2%) patients evaluable at 24 months (Figure 1). One patient for whom results were not available at 12 months did have results at 24 months. Of the 24 patients who exited the study before the 24-month endpoint, 8 (33.3%) patients had met the criteria for response at the end point before their exit, and 5 (20.8%) had also met the criterion for remission. Reasons for study exit included consent withdrawal, death, lack of efficacy, and adverse events. Patients were not explanted at the 24-month follow up. In the 24-month analysis, long-term data for the OC sample were analyzed for $HRSD_{28}$ (n = 49), MADRS (n = 49), $IDS\text{-}SR_{30}$ (n = 46), and CGI-S (n = 49). For all assessments under LOCF, the sample size was 74.

**Insert figure 1 about here **

Mean age of patients was 47.4 ± 11.7 years (median 46.5; range 23.0 to 78.0). One patient, age 78 years, was older than the 75 years specified as the upper limit in the inclusion criteria. Women comprised 68% of the cohort. Most had MDD (54 patients, 73%), and more than half of the patients (41 patients, 55.4%) had recurrent MDD, 13 patients (17.6%) had a single major depressive episode, and 20 (27%) had bipolar disorder (9/74 bipolar I and 11/74 bipolar II). Further demographic and clinical data are summarized in Table 1.

Insert table 1 about here

Effectiveness

Results for the primary and secondary efficacy measures at 3, 12, and 24 months are provided in Table 2 and Figure 2a and 2b. Table 3 compares improvement in the scores of primary and secondary efficacy measures between follow-up intervals. The improvement in the primary efficacy measure, the $HRSD_{28}$ score, was statistically significant for OC and LOCF in the 3-month versus 12-month comparison ($p = 0.003$, OC; $p = 0.018$, LOCF) and 3-month versus 24-month comparison ($p = 0.010$, OC; $p = 0.016$, LOCF) assessments only. In the secondary efficacy measures, comparisons of improvement in the scores were significant for the MADRS at 3 versus 24 months ($p = 0.013$, OC; $p = 0.014$, LOCF); for the $IDS\text{-}SR_{30}$ at 3 versus 12 months ($p = 0.047$, OC) and 3 versus 24 months ($p = 0.025$, OC; $p = 0.020$, LOCF); and for the CGI-S at 3 versus 12 months ($p = 0.024$, OC) and 3 versus 24 months ($p = 0.007$, OC; $p = 0.009$, LOCF). None of the CGI-I comparisons were significant.

Insert table 2 and table 3 about here

Insert figure 2a and 2b about here

Figure 3 shows the percentages of patients who met the criteria for response on the $HRSD_{28}$, as well as the secondary measures of the MADRS and the $IDS\text{-}SR_{30}$. Table 4 lists pairwise comparisons of percentages of responders for the same efficacy measures. Comparisons of percentages of responders were statistically significant for 3 versus 12 months for the $HRSD_{28}$ ($p = 0.046$, OC), 3 versus 24 months for the MADRS ($p = 0.042$, OC), and 3 versus 12 months for the IDS-SR ($p = 0.035$, OC).

Insert table 4 about here

Insert figure 3 about here

Figure 4 shows the percentages of patients who met the criteria for remission at each time point. In the OC sample, 27.1% of the initial 70 patients were remitters after 24 months. For the LOCF $HRSD_{28}$ sample, the percentage of remitters increased across time: from 17.6% (13/74) to 29.7% (22/74) to 32.4% (24/74) at 3, 12, and 24 months, respectively. The IDS-SR percentage of remitters also more than doubled from 3 months to 24 months for both the OC and LOCF samples. Table 5 lists pairwise comparisons of the percentage of patients who met the requirements for remission. Differences were statistically significant for the $HRSD_{28}$ at 3 months versus 12 months ($p = 0.023$, OC; $p = 0.042$, LOCF) and at 3 months versus 24 months ($p = 0.013$, OC; $p = 0.015$, LOCF). None of the comparisons were statistically significant for the MADRS. Differences were significant for the $IDS\text{-}SR_{30}$ at 3 versus 12 months ($p = 0.035$, LOCF) and 3 versus 24 months ($p = 0.029$, OC, $p = 0.020$, LOCF).

Insert table 5 about here

Insert figure 4 about here

Concomitant Medications

No statistically significant differences were found at 3, 12, or 24 months for the number of concomitant antidepressant drugs (p = 0.62; mean/median 3-months = 1.3/1.0; 12-months = 1.3/1.0; 24-months = 1.2/1.0) or antipsychotic drugs (p = 0.90; mean/median 3-months = 1.5/1.0; 12-months = 1.3/1.0; 24-months = 1.3/1.0) (data not shown).

Safety

The most common adverse events reported at 3 months (acute phase) were voice alteration (24.1%), cough (10.7%), pain (20.8%), and dyspnea (5.1%) (data not shown). At 12 and 24 months (long-term phase), the most commonly reported adverse events were voice alteration (24.8%), pain (10.7%), and depression (5.6%) (data not shown). Two patients discontinued the study because of an adverse event and 2 patients were explanted, one because of aggravation of illness. Twenty-seven patients reported 39 serious adverse events that resulted in hospitalization, including worsening of depression (13/39, 33.3%); infection (3/39, 7.7%); suicide attempt (2/39, 5.1%); overdose (2/39, 5.1%); mixed state (1/39, 2.6%); and manic reaction (1/39, 5.1%). Two patients (2/74; 2.7%), both women, died on study by suicide within the first year of treatment. One woman, age 48 years, who completed suicide had not responded to VNS and had no prior suicide attempts. The other woman, age 40 years, who completed suicide had responded to VNS and had 18 life-time suicide attempts. Both had been diagnosed with Major Depressive Disorder, Recurrent.

Sustained Response Analysis

Figure 5 shows the progression of patients who met or did not meet the criteria for response at the 3-month assessment and their response status at the 12- and 24-month

assessments. In the OC sample, of the 26 patients who met the criteria for response at the 3-month assessment, 15 (58%) patients were responders at both 3 and 12 months, and 10 (38%) patients were responders at 3, 12, and 24 months (Figure 5a). Also in the OC sample, of the 13 patients who met the criteria for remission at the 3-month assessment, 5 (38%) patients were remitters at both 3 and 12 months, and 4 (31%) were remitters at 3, 12, and 24 months (data not shown). In the LOCF sample, of the 26 patients who met the criteria for response at the 3-month assessment, 16 (62%) patients were responders at both 3 and 12 months, and 13 (50%) patients were responders at 3, 12, and 24 months (Figure 5b). Also in the LOCF sample, of the 13 patients who met the criteria for remission at the 3-month assessment, 6 (46%) patients were remitters at both 3 and 12 months, and 5 (38%) were remitters at 3, 12, and 24 months (data not shown).

DISCUSSION

The results of this study suggest an improvement in depression severity after treatment for 24 months with the addition of VNS to existing medication regimens in a population of patients with chronic treatment-refractory depression. Importantly, more than half of the patients (OC) met the criteria for response and more than one-third met the criteria for remission after 2 years of treatment with VNS. Also, the percentage of patients who met the requirements for response as well as remission increased continuously with the increasing duration of treatment. In addition, the analysis for sustained response showed that 38% of the patients who met criteria for response and 31% who met criteria for remission after 3 months of VNS also met those criteria after both 12 and 24 months.

Although VNS failed to show relevant acute antidepressant effects in the only sham-controlled trial published to date [11], other noncontrolled studies [8, 12] have reported response rates between 27% and 53% after 1 year. In another study, response rates were 42% and remission rates 22% after 2 years of treatment [9]. Within the group of responders in this latter study, more than 60% had substantial and durable clinical benefit after 12 and 24 months of treatment [9].

The observation that more than 50% (26/49, OC) of the patients in our study met criteria for response after 2 years of treatment suggests a sustained response to VNS for many patients. Comparisons with other antidepressant interventions are difficult because long-term data rarely are available, particularly in a population of patients with treatment-resistant depression. It is noteworthy; that our overall responses are better compared to previously reported VNS Therapy US long term follow studies.

In theory, at least, 4 factors may account for the relatively high percentage of responders seen after 2 years of treatment in our study: effects of VNS, placebo effects, natural course, and concomitant medication. Usually, placebo response is characterized with a certain response pattern with stronger effects in patients with less severe and short depressive episodes as well as an early onset and nonpersistent response [14-16]. This explanation is unlikely owing to the demographics of the patients and timing of response. The influence of the natural course and concomitant medication cannot be ruled out, although participation in a study may have certain antidepressant effects. However, in a study investigating the course of patients treated with VNS and patients treated with therapy as usual in a comparable sample, VNS was associated with a more profound antidepressant effect after 12 months [10].

The second finding of an increasing percentage of patients who met remission criteria over time, is of interest. Compared with nonresponse and response, remission (referred to as the absence clinically significant depressive symptoms [4]) has been linked to a lower likelihood of relapse and recurrence [17], a better level of functioning [18], a better prognosis [19], and a more stable course [20]. Although treatment resistance is a factor that negatively influences time to and likelihood of achieving remission [1,13], our data indicate that chronic VNS may be capable of achieving long-term clinical remission in some patients.

With regard to maintenance of response, 10 of the patients followed in this study (OC analysis) were responders at all 3 follow-up intervals, 3, 12, and 24 months. Of 17 patients whose response was first recorded at 12 months, 9 were also responders at 24 months. Four patients who responded at 3 months but did not meet response criteria at 12 months regained response at 24 months. Four patients met remission criteria at all follow-up intervals. In comparison, a follow-up study of 347 patients who received ECT in community settings reported remission rates of 30.3% to 46.7% (depending on criteria) and a relapse rate of 64.3% during 24 weeks of follow-up [21]. Comparisons with reports of sustained response with antidepressant medications are complicated by issues with adherence, differences in the degree of treatment resistance, and study duration. Follow-up during the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study showed that the relapse rate of patients who achieved remission increased and the time to relapse decreased as the number of treatment steps increased (Step 1: 33.5%, 4.4 months; Step 2: 47.4%, 4.5 months; Step 3: 42.9%, 3.9 months; Step 4: 50.0%, 2.5 months) [3].

Considering the severity and duration of the depressive illness among these patients receiving VNS, their rates of sustained response and remission are impressive.

An additional finding is that adverse effects notably weakened with increasing treatment duration. Albeit previously described in long-term studies in patients treated with antidepressant or anticonvulsant VNS, the good tolerability of VNS may have led to relatively good adherence rates: 66% of the initially included patients received VNS after the 24-month study ended. In this context, it is of importance that nonadherence remains one of the most common problems in the treatment of patients with depression. Nonadherence rates of up to 60% in depressive patients who were receiving psychopharmacological medication have been reported [22]. Beside lack of patient information and a poor quality of patient-physician relationship, the main reasons for discontinuing antidepressant therapy are unpleasant side effects and a complex intake regimen [23]. VNS has the advantage of being able to deliver sustained and active treatment independently of the factors normally associated with non-adherence to medication regimes.

The two suicides within the 24 months indicate a suicide prevalence rate of 3% which is above the range one would expect in patients with treatment-resistant depression [24].

Two suicides occurred during the first year of this study. Comparing the suicide prevalence rate with that of other antidepressive treatments is difficult because few studies report outcomes of patients with the degree of treatment resistance of the patients in the present study. Khan et al [25] studied suicide rates of patients who received selective serotonin reuptake inhibitors (SSRIs) or other antidepressants in FDA trials of

investigational antidepressants. These patients were described as having mild to moderate depression, and not being actively suicidal at the beginning of the trial. For patients receiving SSRIs, the suicide rate by patient exposure years was 0.59% (95% CI 0.31-0.87), 17 suicides in 2,864 exposure years, and for those receiving other antidepressants, it was 0.76% (CI 0.49-1.03), 31 suicides in 4,094 exposure years [25]. In the present study of patients with chronic or recurrent, treatment-refractory depression, the suicide rate by patient exposure years was 1.57%, 2 suicides in 127 exposure years. This percentage was derived by dividing the number of suicides (n=2) by the exposure, the cumulative number of months (converted to years) that patients received VNS. The exposure years were calculated from implantation to the last assessment date before exit. The rate in the present study of patients with treatment-resistant depression is 1.57%, which is about half again as much as the upper confidence interval (1.03%) of the "other antidepressant" group, who were characterized as mildly to moderately depressed.

This study presents both means with standard deviations and medians with ranges and interquartile ranges as well as both LOCF and OC outcomes. Given the skewed nature of these data, medians with ranges and interquartile ranges are more appropriate to describe central tendencies. However, a decision to report only medians with ranges and interquartile ranges in the present study, without also including means and standard deviations, would certainly frustrate any efforts for direct comparisons with the previous VNS studies, which presented means and standard deviations. The same reasoning, to allow for comparison and continuity, applies to the reporting of both LOCF and OC results. Previously published VNS analyses presented both OC and LOCF results and allowed readers to draw their own conclusions. A similar opportunity is accorded here.

The OC approach may overestimate the effect of an intervention because it does not account for the outcomes of study participants whose outcomes are unknown, (eg, lost to follow-up or withdrawn from the study). The LOCF approach, which involves imputation of values by carrying forward outcomes of patients no longer active in the study, may also have limitations associated with the reasons that study participants were lost to follow-up or withdrew. The MMRM predicts data for patients lost to follow-up by drawing on the actual patient data before dropout. Prakash et al [26] used data from an 8-month outpatient depression trial to compare analyses using LOCF, MMRM, and OC. They found that within-group mean changes were consistently underestimated with LOCF and overestimated by OC when they were compared with the more robust MMRM [26]. In simulation studies, Siddiqui et al [27] found inflated Type I error rates and substantial bias in estimated treatment effects with LOCF analysis. They characterized MMRM analysis under the ignorable missing data framework as a "sensible analytic choice" for efficacy evaluation because it seemed robust to estimate true treatment differences and control the number of Type I errors [27].

The encouraging data in this study must, however, be interpreted with appropriate caution in the light of two major design limitations. First, the lack of a control group makes it difficult to compare the clinical outcome with those of other psychopharmacological, psychotherapeutic, or brain stimulation interventions, and to disentangle the effects of VNS from the non-specific effects of study participation. This shortcoming has, to an extent, been considered in a previous study in which patients who received long-term treatment with VNS were matched with comparably ill patients who were receiving treatment as usual [10]. In this study, the authors described one-year

response rates that were comparable to the results of our study and, more interestingly, a superiority of VNS treatment compared with standard treatment.

The second major limitation of the present study is that neither stimulation parameters nor further antidepressant treatments were controlled, although the differences in the overall numbers of antidepressant and other psychotropic treatments did not differ significantly. Hence, it is important that future studies should control for these parameters and include a control group.

In summary, these data suggest that long-term VNS treatment in addition to medication can offer the possibility of meaningful and sustained clinical benefit for patients who have not achieved satisfactory response with conventional treatment. Additionally, VNS appears to have a comparatively benign adverse effect profile, and favorable adherence rates in a relevant proportion of patients with treatment-resistant depression. Future studies should closely evaluate possible changes in suicidality associated with VNS.

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Under the direction of the authors, John C. Allen, Jr., PhD, and Amara K. Jayewardene, MS, performed the statistical analysis for this report. Dr. Allen and Mr. Jayewardene were employees of Cyberonics, Inc., manufacturer of the VNS Therapy System, and Dr. Allen owns Cyberonics stock. Malek Bajbouj MD and Angela Merkl MD independently confirmed this analysis. Penny Clowe, RN, MA, MaryAnn Foote, PhD, and Susan E. Siefert, ELS, CBC, assisted with medical writing services during the development of this manuscript. Ms Clowe and Ms Siefert were employees of Cyberonics, and Ms Siefert owns Cyberonics stock. Dr. Foote was compensated by Cyberonics.

Table 1: Baseline Demographic and Clinical Data (n=74)

Characteristic	Value
Age at implant (years) (mean ± SD)	47.4 ± 11.7
Median (IQ) range	46.5 (17.0) 23.0, 78.0
Women:Men (%)	2.1:1 (67.6% women)
White (%)	98.65
MDD, recurrent (%)	55.41
MDD, single episode (%)	17.57
Bipolar disorder (%)[a]	27.0
Length of current MDE (years) (mean ± SD)	3.5 ± 6.3
Median (IQ) range	2.0 (2.9) 0.1, 46.7
Total duration of MDD (years) (mean ± SD)	19.1 ± 10.5
Median (IQ) range	17.5 (16.0) 3.0, 50.0
Age of onset of first MDE (years) (mean ± SD)	28.8 ± 12.0
Suicide attempts in lifetime (n) (mean ± SD)	1.1 ± 2.3
ECT in lifetime (n=37) (%)	50.0
ECT in current MDE (n=27) (%)	36.5
Baseline $HRSD_{28}$ score (mean ±SD) Lower, Upper 95% CI	34.0 ± 5.8; 32.7, 35.4
Median (IQ) range	34.0 (7.5) 23.5, 50.5
Baseline MADRS score (mean ±SD) Lower, Upper 95% CI	32.9 ± 6.4; 31.4, 34.4
Median (IQ) range	32.5 (9.0) 17.5, 46.0
Baseline IDS-SR_{30} score (mean ±SD) Lower, Upper 95% CI	47.6 ± 9.1; 45.4, 49.8
Median (IQ) range	48.0 (11.0) 27.0, 74.0
Baseline CGI Severity of Illness Score (mean ±SD) Lower, Upper 95% CI	5.5 ± 0.9; 5.3, 5.7
Median (IQ) range	6.0 (1.0) 3.0, 7.0
Unsuccessful ATHF-defined treatments in current MDE	3.5 ± 1.3
(mean ±SD) Median (IQ) range	3.0 (2.0) 2.0 7.0

a. Bipolar I, n = 9; bipolar II, n = 11

ATHF = Antidepressant Treatment History Form; CGI = Clinical Global Impression scale, Global Assessment of Functioning; ECT = electroconvulsive therapy; $HRSD_{28}$ = Hamilton Rating Scale for Depression; IDS-SR_{30} = Inventory of Depressive Symptoms- Self Report; MADRS = Montgomery Åsberg Depression Scale; MDD = major depressive disorder; MDE = major depressive episode

Table 2: Outcome Measures at Baseline, 3-, 12-, and 24-month Follow-up [a]

Outcome Measure	Baseline		3 Months		12 Months		24 Months	
	N	Score	N	Score	N	Score	N	Score
$HRSD_{28}$								
OC	74	34.0 ± 5.8	70	22.1 ± 11.5 [b]	60	16.4 ± 10.4 [b]	49	17.0 ± 11.9 [b]
LOCF	74	34.0 ± 5.8	74	22.8 ± 11.9 [b]	74	19.5 ± 12.4 [b]	74	19.5 ± 12.9 [b]
MADRS								
OC	74	32.9 ± 6.4	70	20.5 ± 11.7 [b]	57	16.2 ± 11.8 [b]	49	15.3 ± 12.1 [b]
LOCF	74	32.9 ± 6.4	74	21.1 ± 11.7 [b]	74	19.2 ± 12.6 [b]	74	17.6 ± 12.6 [b]
$IDS\text{-}SR_{30}$								
OC	71	47.6 ± 9.1	68	33.2 ± 15.9 [b]	58	27.8 ± 16.9 [b]	46	26.4 ± 17.8 [b]
LOCF	71	47.6 ± 9.1	74	34.2 ± 15.7 [b]	74	31.0 ± 17.5 [b]	74	29.6 ± 17.7 [b]
CGI-S								
OC	74	5.5 ± 0.9	70	3.9 ± 1.6	60	3.3 ± 1.6	49	3.2 ± 1.8
LOCF	74	5.5 ± 0.9	74	4.0 ± 1.6	74	3.7 ± 1.7	74	3.5 ± 1.8

a. All scores reported as mean ± SD; b. statistically significant from baseline $p \leq 0.05$

CGI = Clinical global Impression scale, Global Assessment of Functioning; $HRSD_{28}$ = 28-Item Hamilton Rating Scale for Depression; $IDS\text{-}SR_{30}$ = Inventory of Depressive Symptoms- Self Report; LOCF = last observation carried forward, MADRS = Montgomery Åsberg Depression Scale; OC = observed cases

Table 3: Pairwise Comparisons: Improvement in Score from Baseline

$HRSD_{28}$	Comparison	Lower 95% CI	Upper 95% CI	p-value
OC	3 month vs 12 month	1.81	8.41	0.003*
	3 month vs 24 month	1.12	8.19	0.010*
	12 month vs 24 month	-4.08	3.16	0.802
LOCF	3 month vs 12 month	0.57	6.04	0.018*
	3 month vs 24 month	0.62	6.10	0.016*
	12 month vs 24 month	-2.64	2.79	0.969
MADRS	Comparison			p-value
OC	3 month vs 12 month	-0.12	6.92	0.058
	3 month vs 24 month	1.00	8.40	0.013*
	12 month vs 24 month	-2.53	5.13	0.503
LOCF	3 month vs 12 month	-0.91	4.61	0.188
	3 month vs 24 month	0.72	6.24	0.014*
	12 month vs 24 month	-1.13	4.40	0.244
$IDS\text{-}SR_{30}$	Comparison			p-value
OC	3 month vs 12 month	0.06	9.52	0.047*
	3 month vs 24 month	0.74	11.00	0.025*
	12 month vs 24 month	-4.16	6.33	0.682
LOCF	3 month vs 12 month	-0.33	7.20	0.073
	3 month vs 24 month	0.73	8.26	0.020*
	12 month vs 24 month	-2.70	4.82	0.580
CGI-S	Comparison			p-value
OC	3 month vs 12 month	0.07	0.99	0.024*
	3 month vs 24 month	0.19	1.18	0.007*
	12 month vs 24 month	-0.35	0.66	0.537
LOCF	3 month vs 12 month	-0.04	0.72	0.083
	3 month vs 24 month	0.13	0.90	0.009*
	12 month vs 24 month	-0.21	0.56	0.365
CGI-I	Comparison			p-value
OC	3 month vs 12 month	-0.66	0.23	0.338
	3 month vs 24 month	-0.46	0.49	0.944
	12 month vs 24 month	-0.25	0.72	0.347
LOCF	3 month vs 12 month	-0.52	0.22	0.425
	3 month vs 24 month	-0.38	0.35	0.942
	12 month vs 24 month	-0.23	0.50	0.468

* = statistically significant difference ($p \leq 0.05$)
CGI-I = Clinical Global Impression-Improvement, CGI-S= Clinical Global Impression-Symptomology , $HRSD_{28}$ = 28-Item Hamilton Rating Scale for Depression; $IDS\text{-}SR_{30}$ = Inventory of Depressive Symptoms- Self Report; LOCF = last observation carried forward, MADRS = Montgomery Åsberg Depression Scale; OC = observed cases

Table 4: Pairwise Comparisons: Percent Responders

$HRSD_{28}$	Comparison	Lower 95% CI	Upper 95% CI	p-value
OC	3 month vs 12 month	0.01	1.26	0.046*
	3 month vs 24 month	-0.05	1.28	0.071
	12 month vs 24 month	-0.69	0.65	0.949
LOCF	3 month vs 12 month	-0.13	0.92	0.136
	3 month vs 24 month	-0.07	0.97	0.090
	12 month vs 24 month	-0.46	0.57	0.833
MADRS	Comparison			p-value
OC	3 month vs 12 month	-0.09	1.13	0.096
	3 month vs 24 month	0.02	1.32	0.042*
	12 month vs 24 month	-0.51	0.82	0.652
LOCF	3 month vs 12 month	-023	0.79	0.278
	3 month vs 24 month	-0.06	0.95	0.086
	12 month vs 24 month	-0.34	0.66	0.520
$IDS\text{-}SR_{30}$	Comparison			p-value
OC	3 month vs 12 month	0.05	1.40	0.035*
	3 month vs 24 month	-0.05	1.40	0.068
	12 month vs 24 month	-0.77	0.67	0.888
LOCF	3 month vs 12 month	-0.01	1.15	0.056
	3 month vs 24 month	-0.01	1.15	0.056
	12 month vs 24 month	-0.55	0.55	1.000

* = statistically significant difference ($p \leq 0.05$)

Response was ≥50% reduction from baseline assessment score

Abbreviations: $HRSD_{28}$ = 28-Item Hamilton Rating Scale for Depression; $IDS\text{-}SR_{30}$ = Inventory of Depressive Symptoms-Self Report; LOCF = last observation carried forward, MADRS = Montgomery Åsberg Depression Scale; OC = observed cases

Table 5: Pairwise Comparisons: Percent Remitters

$HRSD_{28}$	Comparison	Lower 95% CI	Upper 95% CI	p-value
OC	3 month vs 12 month	0.12	1.60	0.023*
	3 month vs 24 month	0.21	1.76	0.013*
	12 month vs 24 month	-0.60	0.85	0.721
LOCF	3 month vs 12 month	0.03	1.35	0.042*
	3 month vs 24 month	0.16	1.47	0.015*
	12 month vs 24 month	-0.46	0.72	0.672
MADRS	Comparison			p-value
OC	3 month vs 12 month	-0.39	1.03	0.375
	3 month vs 24 month	-0.31	1.18	0.250
	12 month vs 24 month	-0.64	0.87	0.768
LOCF	3 month vs 12 month	-0.49	0.77	0.668
	3 month vs 24 month	-0.29	0.95	0.294
	12 month vs 24 month	-0.42	0.80	0.533
$IDS\text{-}SR_{30}$	Comparison			p-value
OC	3 month vs 12 month	-0.05	1.78	0.063
	3 month vs 24 month	0.11	2.02	0.029*
	12 month vs 24 month	-0.66	1.06	0.642
LOCF	3 month vs 12 month	0.06	1.69	0.035*
	3 month vs 24 month	0.15	1.77	0.020*
	12 month vs 24 month	-0.60	0.77	0.807

* = statistically significant difference ($p \leq 0.05$)

Remission: $\leq$10 $HRSD_{28}$, $\leq$10 MADRS, $\leq$14 $IDS\text{-}SR_{30}$

Abbreviations: $HRSD_{28}$ = 28-Item Hamilton Rating Scale for Depression; $IDS\text{-}SR_{30}$ = Inventory of Depressive Symptoms- Self Report; LOCF = last observation carried forward, MADRS = Montgomery Åsberg Depression Scale; OC = observed cases

1 Figure 1: Patient Disposition

Figure 2: Least Squares Means. Panel A = Percent Improvement From Baseline for $HRSD_{28}$, MADRS, and $IDS\text{-}SR_{30}$. Panel B = Improvement From Baseline for CGI-S and CGI-I. LOCF = last observation carried forward; OC = observed cases

Abbreviations: CGI-I = Clinical Global Impression-Improvement, CGI-S= Clinical Global Impression-Symptomology , $HRSD_{28}$ = 28-Item Hamilton Rating Scale for Depression; $IDS\text{-}SR_{30}$ = Inventory of Depressive Symptoms- Self Report; LOCF = last observation carried forward, MADRS = Montgomery Åsberg Depression Scale; OC = observed cases

Figure 3: Responders Sample Percentages: $HRSD_{28}$, MADRS, and IDS-SR_{30}.

Abbreviations: $HRSD_{28}$ = 28-Item Hamilton Rating Scale for Depression; IDS-SR_{30} = Inventory of Depressive Symptoms- Self Report; LOCF = last observation carried forward, MADRS = Montgomery Åsberg Depression Scale; OC = observed cases

Figure 4: Remitters Sample Percentages: $HRSD_{28}$, MADRS, and IDS-SR_{30}.

Abbreviations: $HRSD_{28}$ = 28-Item Hamilton Rating Scale for Depression; IDS-SR_{30} = Inventory of Depressive Symptoms- Self Report; LOCF = last observation carried forward, MADRS = Montgomery Åsberg Depression Scale; OC = observed cases

Figure 5: Sustained Response Analysis. Panel A = Observed Cases. Panel B = Last Observation Carried Forward

Response was ≥50% reduction from baseline assessment score in the $HRSD_{28}$.

Abbreviation: $HRSD_{28}$ = 28-Item Hamilton Rating Scale for Depression

Figures

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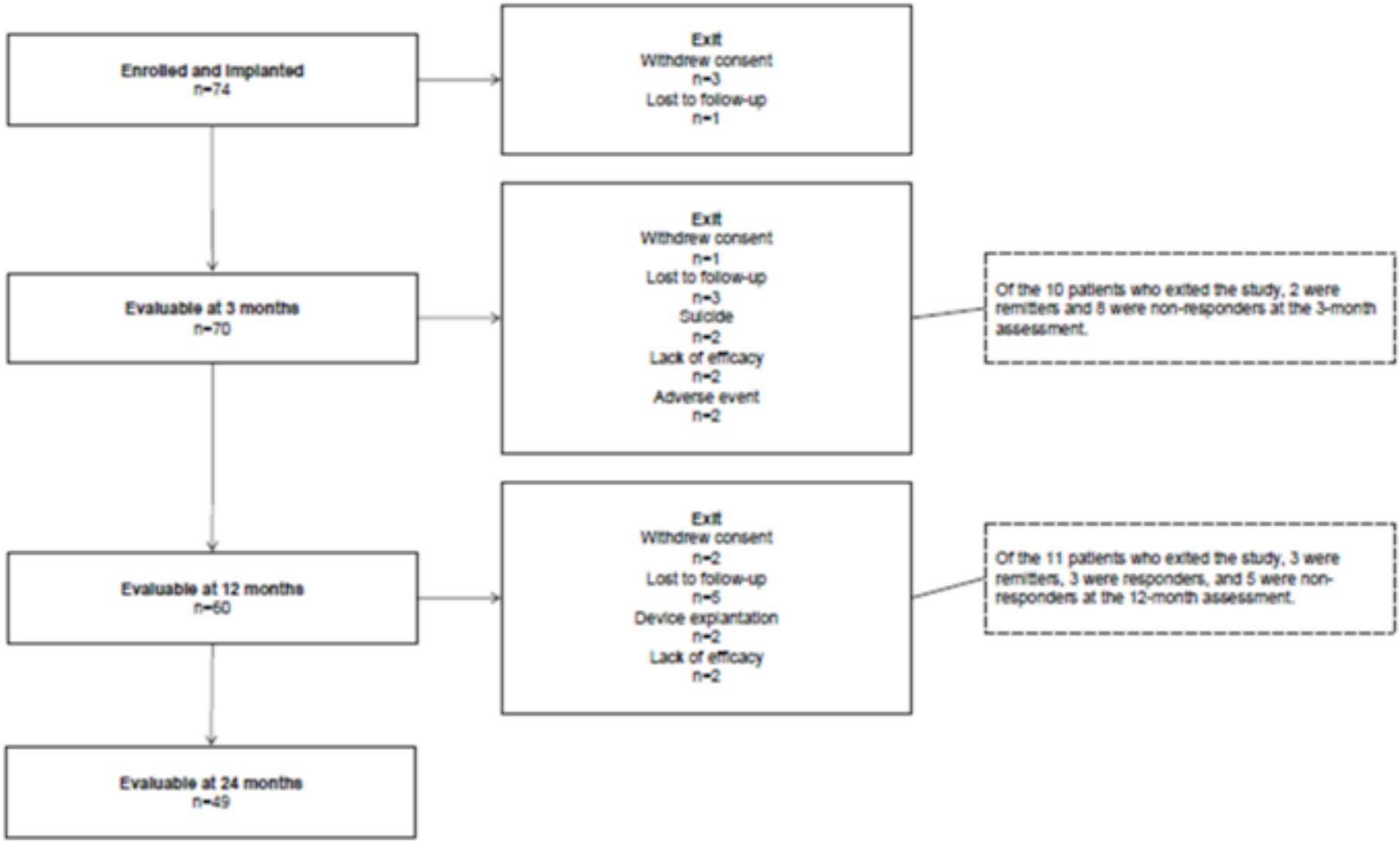
Figure 1. Patient Disposition



Figures

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Figure 2a. Least Squares Means: Percent Improvement From Baseline, HRSD-28, MADRS, IDS-SR

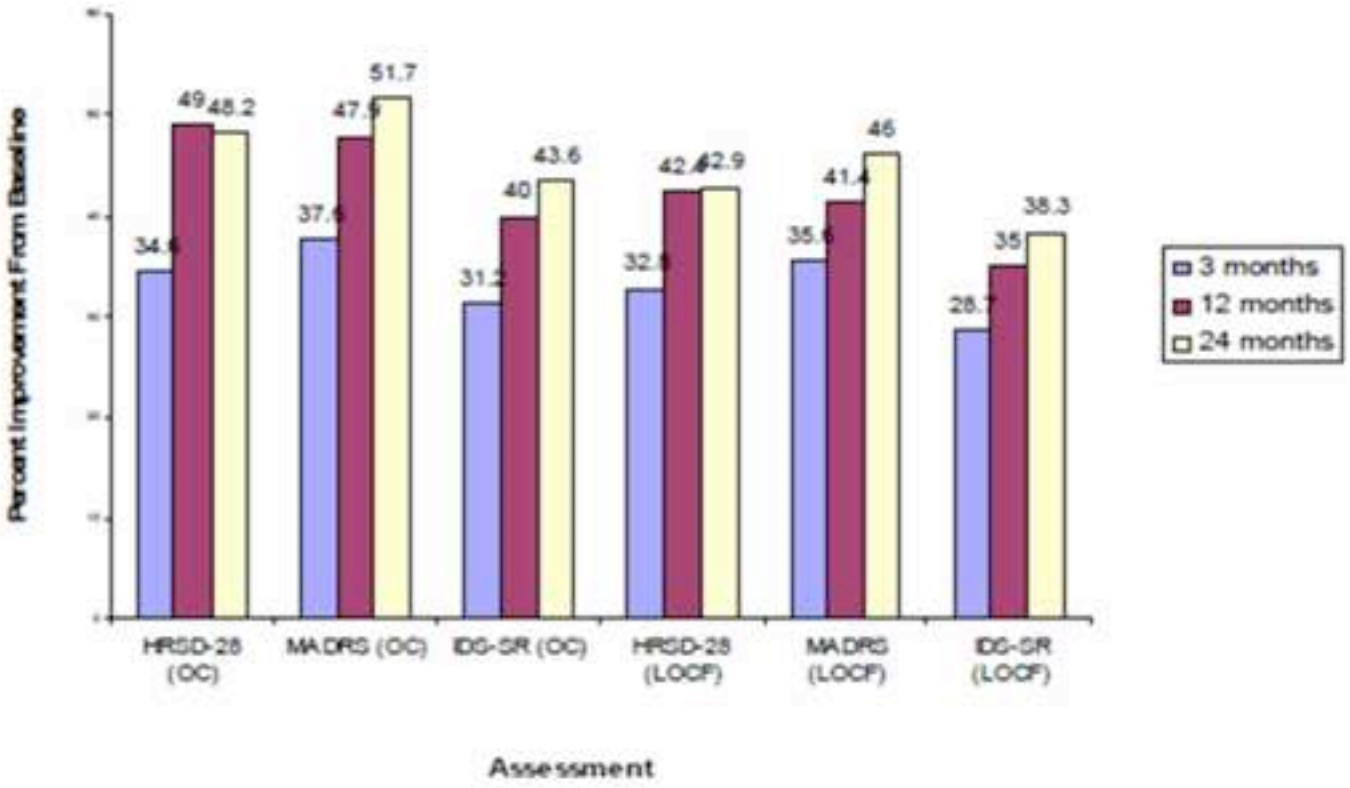

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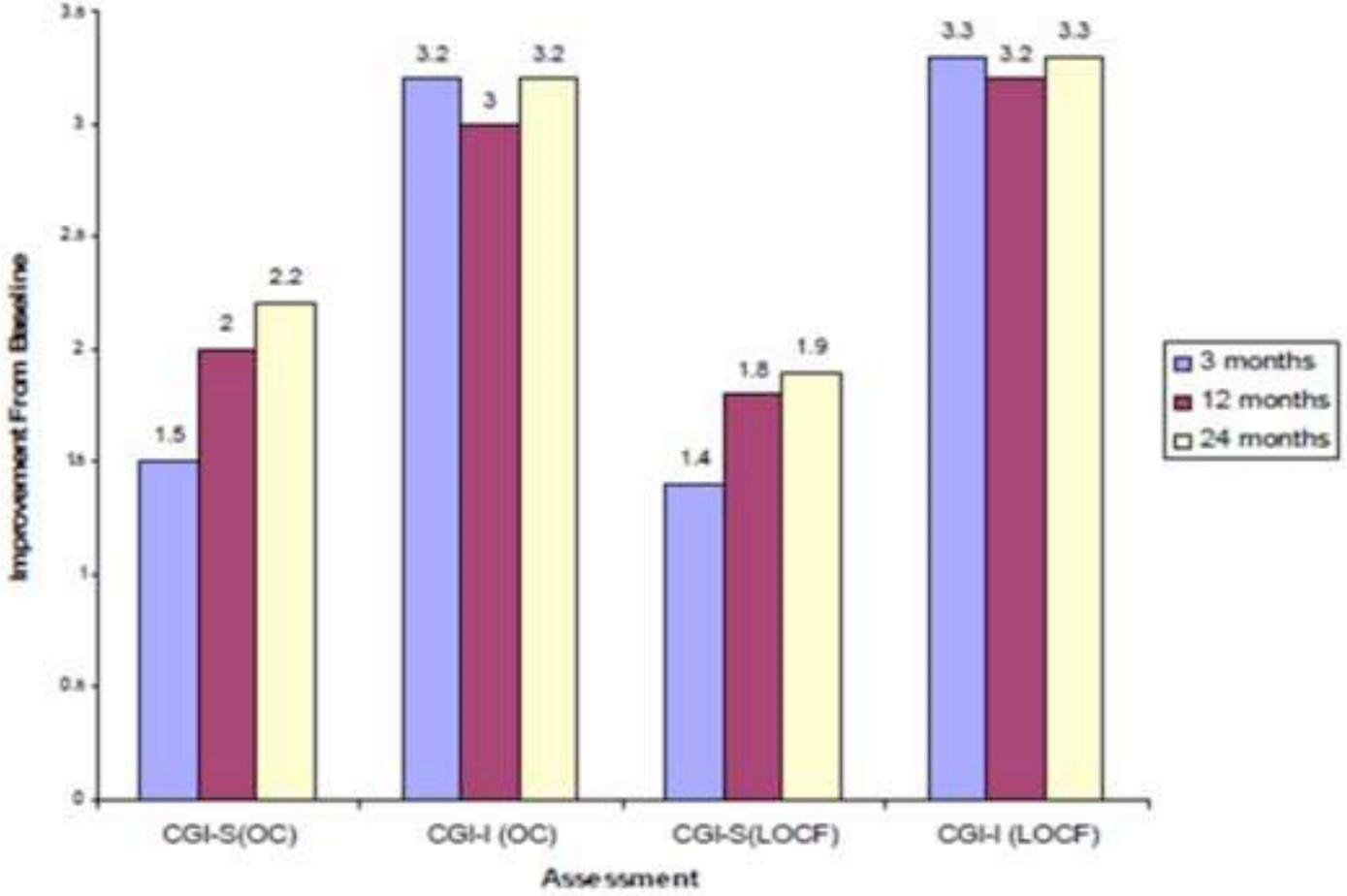
Figure 2b. Least Squares Means: Improvement From Baseline CGI-S and CGI-I



Figures

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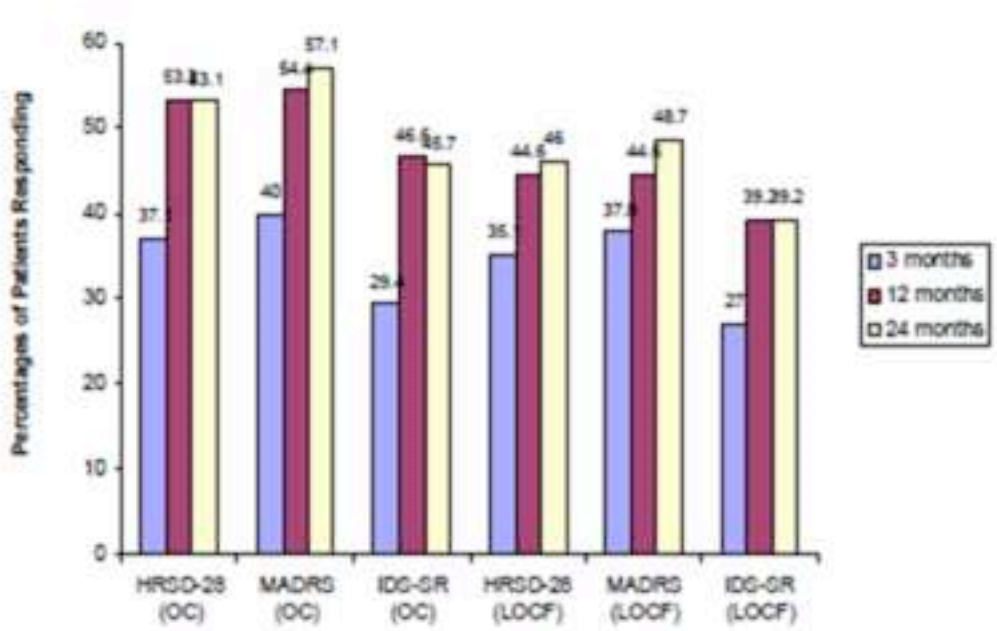
Figure 3. Percentages of Responders



Responders	OC			LOCF		
	HRSD-28	MADRS	IDS-SR-30	HRSD-28	MADRS	IDS-SR-30
3 mon	26/70	28/70	20/68	26/74	28/74	20/74
12 mon	32/60	31/57	27/58	33/74	33/74	29/74
24 mon	26/49	28/49	21/46	34/74	36/74	29/74

Figures

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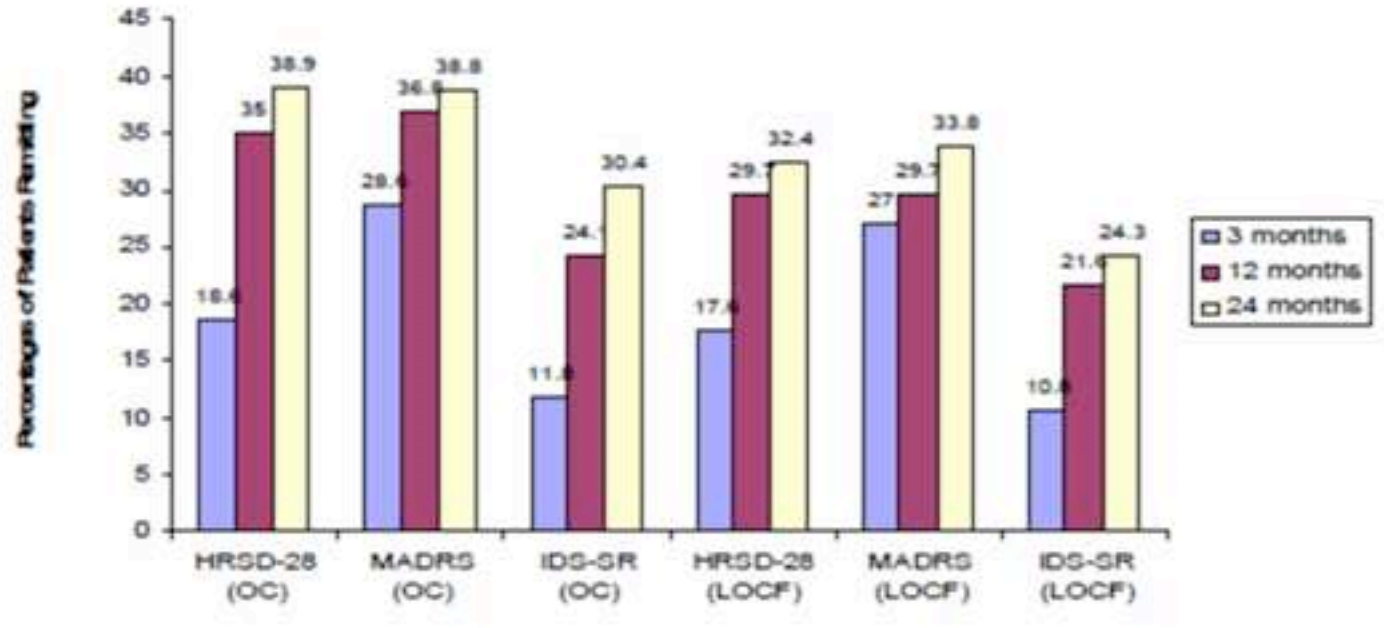
Figure 4. Percentages of Remitters



	Remitters					
	OC			LOCF		
	HRSD-28	MADRS	IDS-SR-30	HRSD-28	MADRS	IDS-SR-30
3 mon	13/70	20/70	9/68	13/74	20/74	8/74
12 mon	21/60	21/57	14/58	22/74	22/74	16/74
24 mon	19/49	19/49	14/48	24/74	25/74	18/74

Figures

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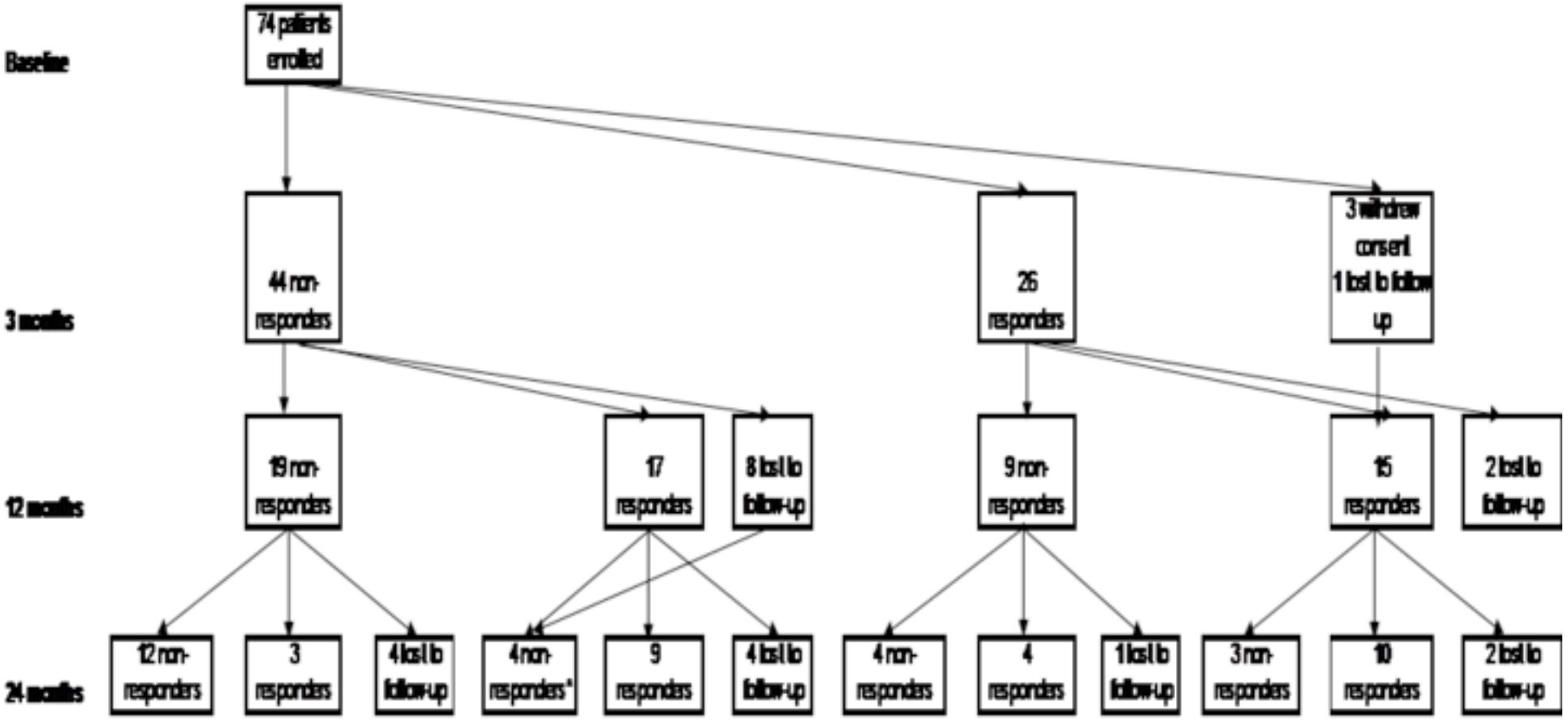
Figure 5a. Sustained Response (HRSD-28) Analysis: Observed Cases



* 1 patient who had no results from the 12-month visit did have results for the 24-month visit

Figures

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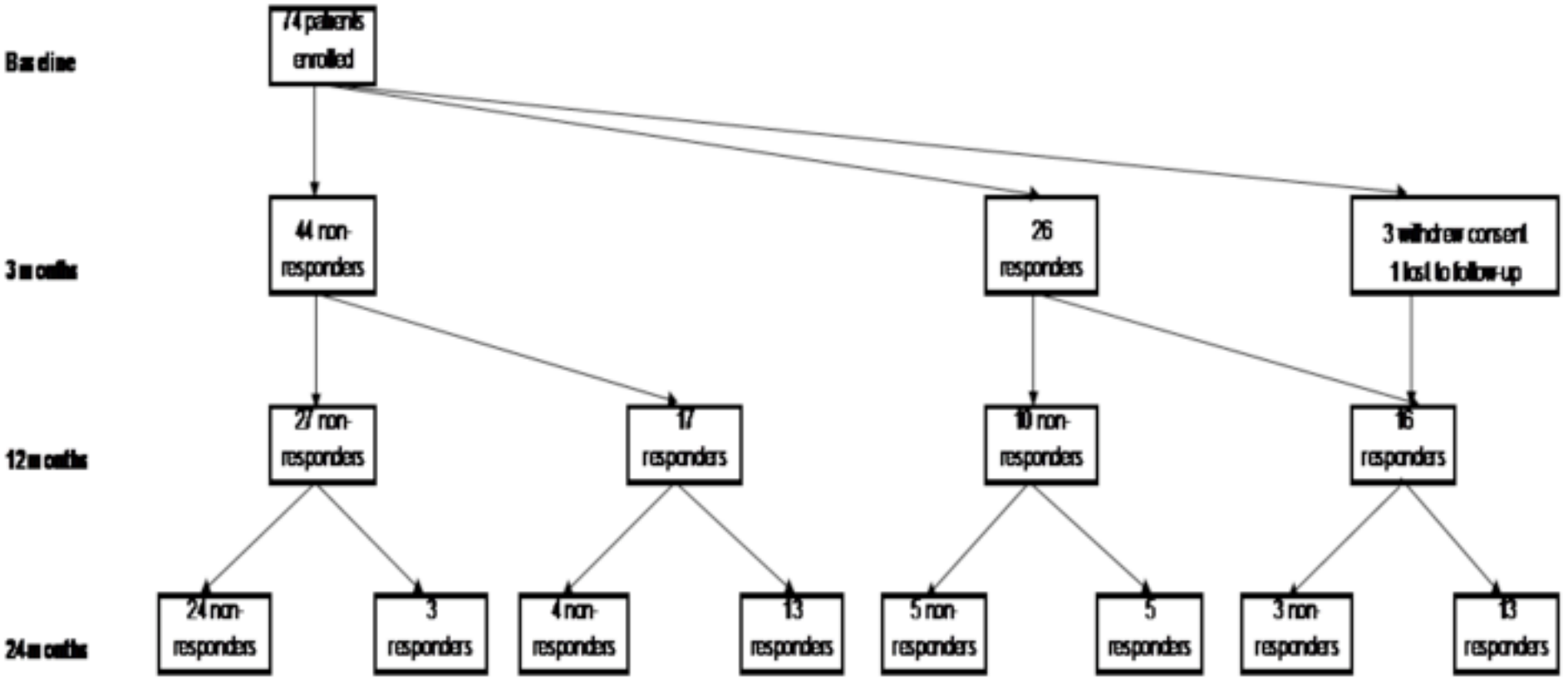
Figure 5b. Sustained Response (HRSD-28) Analysis: Last Observation Carried Forward



*Author Disclosures

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Under the direction of the authors, John C. Allen, Jr., PhD, and Amara K. Jayewardene, MS, performed the statistical analysis for this report. Dr. Allen and Mr. Jayewardene were employees of Cyberonics, Inc., manufacturer of the VNS Therapy System, and Dr. Allen owns Cyberonics stock. Malek Bajbouj MD and Angela Merkl MD independently confirmed this analysis. Penny Clowe, RN, MA, MaryAnn Foote, PhD, and Susan E. Siefert, ELS, CBC, assisted with medical writing services during the development of this manuscript. Ms Clowe and Ms Siefert were employees of Cyberonics, and Ms Siefert owns Cyberonics stock. Dr. Foote was compensated by Cyberonics.

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