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5 Hz repetitive transcranial magnetic stimulation to left prefrontal cortex for major depression

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Abstract

Background—Repetitive transcranial magnetic stimulation (rTMS) to left prefrontal cortex at 10 Hz is the most commonly utilized protocol for major depressive disorder (MDD). Published data suggests that left sided 5 Hz rTMS may be efficacious and well tolerated.

Objective—We analyzed outcomes in a naturalistic cohort of MDD patients who could not tolerate 10 Hz rTMS and were routinely switched to 5 Hz. We hypothesized that the efficacy of 5 Hz rTMS would be equivalent to 10 Hz.

Methods—Records were reviewed for patients (n=98) who received 15 or more acute rTMS treatments. The sample was split based upon the frequency (10 or 5 Hz) at which the majority of treatments were delivered. The Inventory of Depressive Symptoms (IDS-SR) and 9-Item Patient Health Questionnaire (PHQ-9) were used to evaluate outcomes.

Results—Baseline IDS-SR was higher in the 5 Hz (n=27) than in the 10 Hz (n=71) group ($p < .05$), as was frequency of comorbid anxiety ($p = .002$). Depression outcomes did not differ between groups, and there were no differences in response or remission rates (all $p > .1$). Statistical power was sufficient to detect small group differences ($d = .26$).

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CONFLICT OF INTEREST

In the last two years, Drs. Noah Philip, Linda Carpenter, Audrey Tyrka and Lawrence Price have received support for research from Neuronetics Inc., NeoSync Inc., and Cervel Neurotech Inc., through clinical trial contracts. Dr. Linda Carpenter reports a consulting relationship with Magstim, Naurex and Taisho. Ms. Carpenter, Dr. Ridout, Mr. Sanchez and Ms. Albright have no relevant disclosures.

CONTRIBUTORS

Drs. Philip and Carpenter designed the study and wrote the manuscript. Ms. Carpenter and Albright drafted the manuscript and managed the literature searches. Dr. Ridout assisted with study design and data analysis. Mr. Sanchez gathered the data and assisted with data analysis. Drs. Tyrka and Price contributed to study conceptualization and design. All authors contributed to, and have approved, the final manuscript.

Limitations—Open-label data in a naturalistic setting.

Conclusion—Outcomes associated with 5 Hz rTMS did not differ from 10 Hz, despite higher baseline depressive symptom severity and anxiety in 5 Hz patients. 5 Hz stimulation may be an alternative treatment option for patients unable to tolerate 10 Hz rTMS.

Keywords

repetitive transcranial magnetic stimulation; major depression; anxiety

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation treatment for major depressive disorder (MDD) that has emerged as a standard of care therapy for pharmacoresistant or -intolerant patients (APA Guidelines, 2010). Clinical outcomes from randomized controlled trials and naturalistic studies have confirmed that rTMS is an effective monotherapy or adjunct therapy to medications in the treatment of MDD (O'Reardon et al., 2007; Carpenter et al., 2012). There is a large range of rTMS parameters that determine the quality and quantity of energy delivered in a noninvasive manner to the human brain during this therapy (e.g., intensity of each pulse relative to motor threshold, frequency of pulses, total number of pulses delivered per treatment session, total number of treatments in an acute series), and the relative merits of variations in these parameters has not been systematically explored. It is reasonable to assume that changes in certain parameters may impact the likelihood of relieving individual patient symptoms or optimizing rTMS tolerability.

The delivery of stimulation at different pulse frequencies has been the focus of considerable research. Both low frequency (1 Hz, typically delivered to right prefrontal cortex [PFC]) and high frequency (5–20 Hz, typically delivered to the left PFC) rTMS have been found efficacious for the treatment of MDD (Berlim et al., 2013; Berlin et al., 2014). Neurophysiological research suggests that pulsing the magnetic field at lower and higher frequencies may have opposite effects (inhibitory and excitatory, respectively) on cortical activity (Speer et al., 2000; Cao et al., 2013).

Findings from sham-controlled pilot studies in clinical samples suggest that left-sided 5 Hz rTMS to the PFC is safe and as efficacious as higher frequency left-sided 20 Hz rTMS in reducing depressive symptoms. In a study of 30 depressed patients with MDD or bipolar depression, George et al. (2000) found significantly more responders in patients receiving two weeks of active 5 Hz or 20 Hz rTMS, compared to a sham control group. Similar outcomes were reported by Su et al., (2005) where no significant difference was observed between the lower (5 Hz) and higher (20 Hz) frequency groups, and a trend emerged for superiority of 5 Hz compared to sham after two weeks of rTMS. Rumi et al., (2005) delivered sham-controlled 5 Hz rTMS to patients after 1 week of receiving amitriptyline, and found that 5 Hz rTMS, compared to sham, resulted in significant reductions in depressive symptoms during the first week of rTMS. These antidepressant effects lasted for the duration of the 4-week rTMS trial. The principal limitations of these 5 Hz clinical studies were modest sample sizes ($n = 30\text{--}40$) and the delivery of relatively low cumulative

doses of rTMS. In these pilot studies, the cumulative dose of rTMS was comprised of only 10–20 treatment sessions, with a total of 16,000–25,000 pulses delivered for the entire course of treatment, representing delivery of less net energy when compared to the now-standard 36-session course of rTMS that includes at least 108,000 pulses (O'Reardon et al., 2007). The relatively lower “dose” of rTMS used in the published 5 Hz clinical trials may have been insufficient to produce the maximal clinical efficacy signal in these studies (Gross et al., 2007). These prior studies also focused on evaluating 5 Hz rTMS against 20 Hz, or 5 Hz vs. sham, providing little data on potential comparisons between 5 Hz and the now-standard 10 Hz rTMS for MDD.

Based on the published efficacy data supporting the use of 5 Hz rTMS to the left PFC for MDD, we systematically administered 5 Hz rTMS therapy to all patients in our clinic who were unable to tolerate a standard course of rTMS initiated at 10 Hz. We operationally defined intolerance as present when a patient reported anxiety, insomnia, or psychomotor agitation that emerged (or worsened, relative to baseline levels) during a course of rTMS therapy delivered at 10 Hz. Our practice of switching the protocol from 10 Hz to 5 Hz stimulation reflected our desire to deliver high frequency stimulation, keep other parameters stable (i.e., laterality, field intensity, total number of pulses per session), avoid the addition of anxiolytic/hypnotic medications (especially benzodiazepines, which can change the motor threshold upon which treatment intensity is calibrated), and remain within accepted safety guidelines (Rossi et al., 2009). Other additional benefits of this frequency modification would be a theoretically reduced likelihood for an rTMS-induced seizure with slower rTMS pulsing (Rossi et al., 2009).

Standardized depression assessment scales are serially administered in our clinic at baseline, weekly, and following the final treatment in the series. We evaluated data gathered from our rTMS clinical practice to summarize clinical outcomes associated with 5 Hz rTMS therapy in a naturalistic treatment setting and to compare the results obtained with the standard 10 Hz rTMS. We hypothesized that 5 Hz rTMS would be comparable in efficacy to 10 Hz rTMS.

MATERIALS AND METHODS

Participants

A retrospective chart review was performed to gather data on adult outpatients who received clinical rTMS at Butler Hospital, Providence, RI, from January 2009 through July 2014. The Butler Hospital Institutional Review Board approved the study. Inclusion criteria were broad in order to best represent the clinical rTMS treatment population, and included: (1) a primary diagnosis of MDD (single or recurrent episode without psychotic features, consistent with DSMIV criteria) determined by a licensed psychiatrist, (2) completion of an acute course of 15 or more rTMS treatments to left PFC, (3) being naïve to rTMS therapy prior to the acute course administered in our clinic, and (4) serial completion of standardized symptom assessments with data available at both pre-rTMS baseline and at the end of the series. All patients in our clinic demonstrated resistance to one or more trials of antidepressant medication before starting rTMS therapy; the great majority met insurance coverage criteria, i.e., resistance to, or intolerance of, four or more medications from

multiple pharmacological classes. rTMS was routinely delivered as an adjunct to the ongoing psychotropic medication regimen.

TMS Device and Treatment Parameters

Prior to the first treatment session, the motor threshold (MT) was ascertained in order to determine treatment intensity using the NeuroStar TMS Therapy System (Neuronetics, Inc.), with rTMS treatments subsequently administered using the same device. Treatments were delivered at 120% of MT over the left prefrontal cortex, with the coil over the approximate position of F3 using standard EEG 10/20 positioning coordinates. MT was generally kept stable for treatment, however following clinic practices it could be re-checked at any time during the course of rTMS as indicated by clinical circumstances. Two stimulation protocols were used for treatment: standard “on-label” 10 Hz rTMS protocol (4-second stimulation train, 26-second inter-train interval, 3000 pulses per session) or 5 Hz rTMS (4-second stimulation train, 12-second inter-train interval, 3000 pulses per session). All patients were started on the 10 Hz protocol, with change to 5 Hz rTMS implemented according to clinical judgment as needed at any point during the treatment series to address the emergence or worsening of insomnia, anxiety, or psychomotor agitation. Coil position remained unchanged during this treatment modification. Consistent with common clinical practice, the total number of pulses per daily treatment session could be increased to 4000, and this was usually done if patients had not demonstrated substantial clinical improvement after the third week of rTMS therapy (George et al., 2010). The sample was split into two groups based on the rTMS frequency (5 Hz or 10 Hz) at which >50% of total pulses in the treatment series were delivered.

Outcome Measures

Baseline and endpoint reports of depressive symptom severity were compared using the Inventory of Depressive Symptoms-Self Report (IDS-SR)(Rush et al., 2006) and the 9-Item Patient Health Questionnaire (PHQ-9)(Kroenke et al., 2001). Clinical response was defined as 50% reduction of baseline scores on the IDS-SR or PHQ-9. Remission was defined by scores less than 15 on the IDS-SR and less than 5 on the PHQ-9. The primary outcomes for this study were the percent changes in baseline to endpoint scores on the IDS-SR and PHQ-9 scales.

Statistical Analyses

All analyses were conducted using the last observation carried forward (LOCF) method. Paired samples t-tests were conducted to evaluate baseline to endpoint change on the IDS-SR and PHQ-9 for the entire sample. Independent t-tests were conducted to compare treatment groups (5 Hz vs. 10 Hz) on baseline and endpoint measures of symptom severity and on percent change. Treatment group remission and response rates were compared with chi-square analyses. Clinical and demographic variables included for comparison between groups were those known to affect treatment outcomes of efficacy, including severity of baseline depression, antidepressant exposure (defined as the number of antidepressant trials used in the current MDD episode, broadly inclusive of standard antidepressants and those used for augmentation, application of specific criteria for adequacy), early life stress assessed by the Childhood Trauma Questionnaire (Bernstein and Fink, 1998), and presence

of anxiety symptoms. Presence of anxiety was operationally defined by regular daytime use of anxiolytic medications at the start of the treatment series. Analysis of covariance (ANCOVA) was performed to evaluate the impact of any continuous variable that differed between groups at baseline on primary outcomes (percent change). Statistical significance for all tests was defined as two-tailed $p < .05$, using SPSS Statistics 20 (IBM Corporation, Armonk, NY).

RESULTS

Demographic and clinical characteristics

Ninety-eight patients met inclusion criteria for analysis. Clinical and demographic characteristics are summarized in Table 1. The majority of patients were female (72%) and mean $\pm$ SD age of the total sample was 51 ± 12.8 years. Fifty-two percent of the total sample had a past history of hospitalization for MDD and 23% reported a past suicide attempt. Demographic variables did not differ between the 5 Hz ($n=27$) and 10 Hz ($n=71$) groups (all $p > .1$). Both groups had equivalent exposure to early life stress ($p = .96$), but patients receiving 5 Hz were more likely to have comorbid anxiety compared to patients in the 10 Hz group (85% versus 51%, $\chi^2 = 9.7$, $p = .002$). There was also a statistical trend toward greater exposure to antidepressant medications during the current major depressive episode in the 5 Hz group (6.6 ± 4.6 vs. 4.9 ± 4 medication trials in the 5 Hz and 10 Hz groups, respectively, $p = .069$). For the total sample, baseline measures of depressive symptoms reflected moderately severe depression symptom burden prior to rTMS (IDS-SR and PHQ-9 mean scores, 48.1 ± 9.3 and 18.9 ± 4.9 , respectively). The mean baseline IDS-SR score was significantly higher in the 5 Hz group (51.6 ± 8.0) than in the 10 Hz group (46.8 ± 9.6 ; $p = .024$), but baseline PHQ-9 scores did not differ (19.2 ± 4.2 vs. 18.9 ± 5.2 for 5 Hz and 10 Hz groups, respectively, $p = .785$).

rTMS Exposure

The mean number of treatment sessions for individual patients was 35.4 ± 7.2 , comprising an average cumulative total of $120,673 \pm 29,819$ pulses delivered over the entire series. A subset of 72 (73.5%) patients underwent optimization of their sessions with increase to 4000 pulses per session (per our clinical protocol as described above). Total number of treatment sessions and total number of pulses in the series did not differ between the 5 and 10 Hz groups ($p = .545$ and $p = .343$, respectively). The average motor threshold was $1.01 \pm .17$ SMT (standardized motor threshold units) for the entire sample and did not differ between groups ($p = .216$). The 5 Hz group received 24 ± 6 treatments at 5 Hz, whereas the 10 Hz group received few or no treatments (i.e., 3 ± 5) pulsed at 5 Hz.

Treatment Outcomes

Treatment outcomes are summarized in Table 2. There were no between-groups differences in primary outcome measures (44.7 ± 26.9 vs. 46.4 ± 28.6 percent for the IDS-SR, $p = .78$, and 52.0 ± 29.9 vs. 54.0 ± 34.1 percent for the PHQ-9, for the 5 Hz and 10 Hz groups, respectively). Controlling for baseline depression severity in the ANCOVA did not change these results; effect of treatment group was not significant ($p = .53$ and $p = .98$ for IDS-SR and PHQ-9, respectively). Within each group, there was a significant baseline-to-endpoint

improvement on both the IDS-SR and PHQ-9 scales (all $p < .001$). Endpoint depression severity scores were similar (for 5 and 10 Hz groups, respectively, mean $\pm$ SD IDS-SR scores were 26.3 ± 14.2 and 28.8 ± 14.9 , $p = .283$; PHQ-9 scores were 8.9 ± 5.4 and 9.2 ± 7.1 , $p = .833$). There were no statistically significant differences between groups on categorical outcomes (all $p > .1$). In the 5 Hz group, 48.1% of patients were responders and 18.5% were remitters (per IDS-SR criteria). Application of the same IDS-SR criteria for categorical outcomes in the 10 Hz group revealed that 54.9% achieved clinical response and 32.4% remitted ($p = .548$, and $.174$ for group comparisons in IDS-SR response and remission rates, respectively). Similarly, no significant differences in clinical outcomes were observed when utilizing the PHQ-9.

Because there were some patients in the 10 Hz group who received one or more of their rTMS treatment sessions delivered at 5 Hz, a linear regression model examined whether the number or percent of treatments or pulses delivered at 5 Hz was a predictor of clinical improvement (as measured by baseline-to-endpoint percent change in IDS-SR). The results of these analyses confirmed that the delivery of 5 Hz stimulation (in any quantity) was not associated with superior or inferior therapeutic outcomes (effects all $p > .1$). To determine whether our negative results were due to a lack of statistical power, we conducted a post-hoc power calculation with power ($1-\beta$) set at .80 and two-tailed α set at .05. We found that we had sufficient power for the primary analysis to detect small differences between groups (Cohen's $d = .26$).

DISCUSSION

Naturalistic treatment results from our clinic suggest that acute antidepressant outcomes achieved with 5 Hz rTMS are similar to those achieved with the standard “on-label” 10 Hz protocol. It is important to note that assignment to 5 Hz was not random, but rather systematically implemented for patients unable to tolerate 10 Hz rTMS therapy as a result of treatment-emergent activation or anxiety. We found no significant differences in response or remission rates when comparing our patients who had received the majority of their rTMS treatments delivered at 5 Hz rTMS with those who had all, or nearly all, of their treatments pulsed at a rate of 10 Hz. Both groups demonstrated significant improvement in baseline to endpoint scores, and the magnitude of improvement did not differ between the 5 Hz and 10 Hz groups. These results suggest that 5 Hz rTMS is not inferior to the standard protocol with regard to efficacy when patient tolerance may limit treatment, and suggest that 5 Hz may provide an important treatment option in patients who cannot tolerate standard 10 Hz rTMS or have treatment-emergent anxiety. A randomized controlled trial would be needed to draw definitive conclusions about relative tolerability and efficacy of the two pulse frequencies.

Overall response and remission rates from this clinic are consistent with results seen in a larger, multi-site naturalistic study by Carpenter et al., (2012). While we observed no group differences in treatment outcomes, several features of the 5 Hz group might have predicted poor prognosis at the start of rTMS therapy: the patients in that group had more severe depressive symptoms at baseline, greater prevalence of comorbid anxiety, and were nominally more medication resistant. Dunner et al., (2014) recently reported that patients receiving anxiolytic medications were the least likely to achieve response or remission after

an acute 6-week course of 10 Hz rTMS. Taken together, these findings raise the possibility that patients with comorbid or treatment-emergent anxiety may respond better to rTMS delivered at 5 Hz than at 10 Hz.

Our choice of 5 Hz stimulation as a second-line protocol in our clinic was informed by previous work that had demonstrated preliminary antidepressant efficacy and safety. As is the case for rTMS therapy pulsed at 1 Hz or 10 Hz, the putative mechanism by which 5 Hz rTMS produces antidepressant effect is not yet known. Anecdotally, we observed anxiolytic effects in most patients who switched from 10 Hz to 5 Hz, and this has led us to speculate whether the intervention allowed a better “match” for those patients, perhaps such that rTMS better targeted intrinsic oscillatory brain rhythms relevant to the individual’s psychiatric symptoms and underlying pathological brain function. Neuronal rhythms oscillating at a frequency of 5 Hz are found in the theta band signals (i.e., 4-7 Hz) on electroencephalogram (EEG). Theta activity is thought to be responsible for frontal activation during attention (Ishii et al., 1999) and emotion processing (Mitchell et al., 2008). Changes in theta indices have been linked to GABA systems (Hoeller et al., 2008; Hsiao et al., 2013) and are implicated in modulation of anxiety states (McNaughton et al., 2013). Several anxiety disorders are characterized by abnormal theta activity, including posttraumatic stress disorder (Cohen et al., 2013), obsessive-compulsive disorder (Ischebeck et al., 2014), and generalized anxiety disorder (Suetsugi et al., 2000).

The standard 10 Hz “on label” rTMS protocol corresponds to pulsing at a frequency found within the EEG alpha band (7-13 Hz), and a number of EEG studies have identified abnormalities in indices of alpha activity in depressed patients relative to healthy controls (e.g., Bruder et al., 1997; Debener et al., 2000; Leuchter et al., 2013). Matching rTMS therapy pulse frequency with individual EEG alpha rhythms has also been proposed as a novel approach to improve the efficacy of rTMS (Arns et al., 2010). EEG recordings are not performed as part of routine care in our clinic, so we do not have data to explore potential relationships between pulse frequency, symptoms, and alpha or theta band signals.

Limitations

This retrospective study of outcome data was conducted with a modest sample size, but there was sufficient power to detect small differences between the two groups, supporting the assertion of non-inferiority of 5 Hz rTMS relative to the 10 Hz standard. The data are limited by their retrospective nature and also by the fact that rTMS was given as an adjunct to ongoing pharmacotherapy and, in some cases, psychotherapy. There was no systematic control of time spent in patient-clinician exposure, so the more severely ill patients in the 5 Hz group may have received more staff attention. However, our requirement for hearing protection through use of earplugs or earbud headphones effectively discouraged discourse during the treatments themselves. It is possible that interactions between 10 Hz rTMS and certain psychiatric medications were related to the treatment-emergent activation/anxiety, or otherwise related to the outcomes we measured. In regulatory trials conducted by rTMS device manufacturers, 10 Hz stimulation has been investigated as a monotherapy rather than as an adjunct to various psychotropic medications, and patients who are not able to tolerate the treatments are typically withdrawn from the study rather than subjected to change in

stimulation parameters. It is not possible to know whether patients we switched to 5 Hz would have gone on to achieve better or worse outcomes if we had persisted with 10 Hz stimulation and prescribed additional sedative/hypnotic drugs to manage rTMS-emergent activation. Despite these limitations and caveats, the use of naturalistic data from real-life clinic populations does offer advantages for identifying and addressing issues such as treatment tolerability, as well as generating results that are generalizable to clinical practice.

In summary, we found comparable clinical outcomes when utilizing 5 Hz rTMS in patients with poor tolerability of standard left-sided prefrontal 10 Hz treatment. These results offer preliminary insights about the role of specific rTMS parameters such as pulse frequency, and emphasize the value of future work aimed at exploring ways in which this and other neuromodulatory therapies may be individually customized to produce the best results for patients manifesting different symptom constellations.

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Highlights

- Patients who were unable to tolerate standard 10Hz rTMS were switched to 5Hz rTMS
- Higher baseline levels of depression and anxiety were found in 5Hz patients
- 5Hz rTMS provided the same clinical outcomes as 10Hz rTMS
- Power was sufficient to detect small differences between groups

Table 1

Demographic and clinical characteristics of study population (N=98) split into two groups based on pulse frequency used for majority of treatments.

	5 Hz (N=27)	10 Hz (N=71)	<i>p</i>
Demographic variables			
Age, Mean $\pm$ <i>SD</i> years	50.44 $\pm$ 11	51.7 $\pm$ 13.4	ns
Range	22 – 70	23 – 79	
Gender, % (N) Female	74.1 (20)	71.8 (51)	ns
Disease history			
Age of onset of first depressive symptoms, Mean $\pm$ <i>SD</i> years	23.0 $\pm$ 13.1	20.0 $\pm$ 10.9	ns
Co-morbid Anxiety % (N)	85.2 (23)	50.7 (36)	.002
History of childhood trauma % (N)	66.7 (18)	67.1 (47)	ns
History of psychiatric hospitalization % (N)	59.3 (16)	49.3 (34)	ns
History of prior VNS/ECT % (N)	44.4 (12)	28.5 (20)	ns
Antidepressant trials, Mean $\pm$ <i>SD</i>	6.6 $\pm$ 4.6	4.9 $\pm$ 4	.069
Range	1 – 17	0 – 18	
Baseline symptom scores			
IDS-SR total score, Mean $\pm$ <i>SD</i>	51.6 $\pm$ 8.0	46.8 $\pm$ 9.6	.024
PHQ-9 total score, Mean $\pm$ <i>SD</i>	19.2 $\pm$ 4.2	18.8 $\pm$ 5.2	ns

SD, standard deviation; MDE, major depressive episode; ECT, electroconvulsive therapy; VNS, vagus nerve stimulation; IDS-SR, Inventory of Depressive Symptoms-Self Report; PHQ-9, Patient Health Questionnaire

Table 2

Summary of treatment parameters, cumulative rTMS “dose” (per patient), and treatment outcomes.

	5 Hz (N=27)	10 Hz (N=71)	<i>p</i>
Treatment parameters and cumulative rTMS “dose” (Mean ± SD)			
Motor Threshold	1.04 ± 0.16	0.99 ± 0.17	0.216
Total number of treatment sessions	36.0 ± 5.4	35.0 ± 7.8	0.545
Total pulses delivered	125333 ± 20612	118901 ± 32600	0.343
Number of treatment sessions at 4000 pulses	19.4 ± 8.0	21.8 ± 9.2	0.204
Percent of total pulses delivered at 5 Hz	70.7 ± 12.2	9.0 ± 15.0	< .001
Treatment outcomes			
IDS-SR			
Total endpoint score, Mean ± SD	28.8 ± 14.2	25.3 ± 14.9	0.283
Percent change from baseline, Mean ± SD	44.7 ± 26.9	46.4 ± 28.6	0.780
Response rate % (N)	48.1 (13)	54.9 (39)	0.548
Remission rate % (N)	18.5 (5)	32.4 (23)	0.174
PHQ-9			
Total endpoint score, Mean ± SD	9.2 ± 5.4	8.3 ± 7.1	0.833
Percent change from baseline, Mean ± SD	52 ± 29.9	54 ± 34.1	0.794
Response rate % (N)	57.7 (15)	59.4 (38)	0.883
Remission rate % (N)	19.2 (5)	32.8 (21)	0.198

SD, standard deviation; IDS-SR, Inventory of Depressive Symptoms-Self Report; PHQ-9, Patient Health Questionnaire. Note: PHQ-9 endpoint data was missing for 10 patients.