Repetitive transcranial magnetic stimulation (rTMS) is a safe and effective alternative treatment for patients suffering from various psychological and medical conditions (George et al., 2001; Sampson, Rome, & Rummans, 2006; Seibner, Rossmeier, Mentschel, Pienemann, & Conrad, 2000). Specifically, previous research shows patients suffering from treatment-resistant depression achieve benefit from rTMS and report a decrease in symptomology (O’Reardon et al., 2007). This is especially important given up to 40% of patients do not benefit from traditional forms of treatment, namely, psychotherapy and psychotropic medication (Gredden, 2001). During treatment, a coil delivering a time-varying magnetic pulse placed over the scalp penetrates the skull, resulting in clinical improvement. There were 47 patients and three distinct treatment groups found: 10 Hz, 20 Hz, and a separate group who received both frequencies (10/20 Hz). The primary outcome indicator was the difference in Beck Depression Inventory–II (BDI-II) scores. Secondary outcomes included categorical indicators of remission, response, and partial response rates as assessed with the BDI-II. In all 3 groups, the majority of patients had depression that remitted, with the highest rate occurring in the 20 Hz group. There were similar response rates in the 10 Hz and 20 Hz groups. There were no patients in the 10/20 Hz group whose depression responded and the highest partial response and nonresponse rates occurred in this group. Although within-group differences were significant from baseline to end of treatment, there were no between-group differences.

Keywords
TMS, depression, left DLPFC, 10 Hz, 20 Hz
difference among the treatments, which again leaves uncertainty regarding treatment recommendations.

This article examines the progress of patients treated using high-frequency rTMS of 10 Hz and/or 20 Hz. We performed a retrospective chart review of outcome measures completed by patients while receiving rTMS to the left DLPFC for depression. Specifically, the Beck Depression Inventory—II (BDI-II) served as one of several indicators of treatment progress and appropriateness for continuation. Given that the literature reflects contradictory results, this exploration is deemed necessary.

Method

Participants

Patients included in the retrospective chart review met Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; American Psychiatric Association, 1994) diagnostic criteria for a Mood Disorder, which a psychiatrist confirmed during a diagnostic interview. Most patients also had other concurrent Anxiety disorders. All patients previously failed a minimum of one antidepressant trial of adequate dosage and duration. Furthermore, all were on their psychotropic medications prior to entering treatment, and there were no changes to medications while undergoing rTMS. Patients continued with rTMS in the acute phase until it was appropriate to taper due to improvement in symptomatology. There were no exclusionary criteria to begin rTMS.

Materials and Procedure

This study is a retrospective chart review of patients who received rTMS between March 2009 and April 2011. Treatments occurred at three offices of a psychiatric facility in South Florida. Prior to beginning rTMS, patients met with a psychiatrist for a 90-min clinical interview to determine diagnoses and appropriateness for treatment. There were two phases to the treatment: the acute phase in which patients received daily treatment 5 days per week and the taper phase in which treatments reduced over a 3-week period. Based on recommendations in the literature, we suggested patients complete at least 20 sessions with treatments occurring over 4 weeks (Avery et al., 2008). In addition, patients attended weekly follow-up appointments with the psychiatrist to monitor progress and determine whether changes needed to be made to their protocol. This retrospective study received Institutional Review Board (IRB) Exemption (Sterling Institutional Review Board, Atlanta, Georgia) based on its examination of existing documents and records. Specifically, the study was done in such a manner that participants could not be identified (e.g., random number assignment, using birth year only). Thus, no informed consent process was necessary given the nature of patient information utilized.

Treatment parameters and device. Patients received treatment delivered from the Neuronetics Therapy TMS system, which utilizes a figure-8 coil (Neuronetics Inc., Malvern, Pennsylvania). Stimulation of the finger muscles of the right hand helped determine each patient’s observed motor threshold (MT) and was continually verified throughout treatment using visual observation of hand movement. The Neuronetics system contained each patient’s coordinates so that treatment occurred in the same location during each session. Each treatment delivered 3,000 pulses to the left DLPFC at a fixed dose of 120% MT. Treatment intensity could be lowered during the 1st week of the acute phase for the patient to build tolerance. Initially, when the practice began administering rTMS, patients received 10 Hz treatment; however, those who started their treatment protocol at a later date received 20 Hz. Regardless of which protocol patients received, stimulation occurred for a 4- or 5-s duration with the minimum interval allowed by the machine.

Efficacy assessments. Patients completed the BDI-II (Beck, Steer, & Brown, 1996) at baseline and during subsequent weeks to assess outcome. At the time of treatment, this measure was viewed as the best way to help patients quantify their own progress, as well as aid the psychiatrist in determining change in symptomology. In terms of scoring, a complete or near complete absence of symptoms, determined by a scale specific score of 0 to 13, categorized remission. At least a 50% reduction in symptoms defined a response to treatment, and at least a 20% reduction in symptoms defined a partial response. Patients had no response to treatment if their BDI-II score reduced by <20%.

Safety measures. Hearing loss may occur if there is inadequate ear protection during treatment, as the rTMS coil creates a clicking sound during stimulation (Loo et al., 2001). Thus, patients and administrators wore earplugs throughout each treatment session.

Statistical methods. Patients included in the final analyses of scores obtained from our chart review had a BDI-II score at the beginning of treatment and at least one postbaseline measure. In addition, patients considered needed at least 10 rTMS treatments. The primary outcome measure was within-group differences between BDI-II scores from the beginning to the end of treatment using the last observation carried forward (LOCF). Tests of normality using the Shapiro–Wilk test indicated that the data deviated from a normal distribution. Therefore, the Wilcoxon Signed Ranks test using PASW Statistics 18.0 software (SPSS Inc., Chicago, Illinois) determined level of significance for within-subjects analyses. Between-subjects comparisons were made using the Kruskal-Wallis test. In addition, the secondary outcome was categorical classification of change in BDI-II scores.

Results

Sample Characteristics

A total of 62 patients received rTMS of the left DLPFC for depression. The final chart analyses excluded 15 patients from the original 62, leaving a total of 47 patients (75.8%).
Figure 1 indicates the breakdown of reasons for exclusion and discontinuation. Specifically, we excluded those who completed less than 10 rTMS treatments, which occurred with 7 patients, and 8 patients lacked sufficient data to determine treatment progress.

In terms of treatment discontinuation, there were more patients who discontinued who received 10 Hz rTMS ($n=8$) than those who received 20 Hz ($n=4$). Three patients received both 10 and 20 Hz treatment and discontinued before their protocol finished. In addition, there were 11 patients who discontinued during the 1st week of treatment and 4 patients who discontinued during the 2nd week.

The composition breakdown between patients in the 10 Hz and 20 Hz groups showed an additional group of patients who received both 10 Hz and 20 Hz treatments. These patients began receiving rTMS at 10 Hz or 20 Hz and were given the opportunity to switch parameters at some point in their protocol if it was determined by the physician and patient to be appropriate. The average time of switch occurred during the 3rd week of treatment. Those who chose to do so subsequently began receiving the alternate protocol in case switching would increase response and minimize the treatment benefit plateau.

The three treatment groups were similar in size; however, some differences in composition were present (see Table 1). Specifically, there were more females in the 10 Hz group. The average number of treatments completed among the groups was similar and there was no significant difference found, $\chi^2(2, N=47) = 0.907, p = .635$.

The majority of patients received a diagnosis of Major Depressive Disorder (MDD), Recurrent Episode. As indicated in Table 1, there also were several patients with comorbid diagnoses, such as an Anxiety Disorder. Despite any differences in treatment group composition, there was no significant difference in severity on the BDI-II among groups at the beginning of treatment, $\chi^2(2, N=47) = 0.105, p = .949$. In addition, there was no minimum severity score needed to begin rTMS. Thus, four patients already had minimal depression at the start of treatment, with BDI-II scores ≤13.

**Outcome Measures**

BDI-II scores during two time points at the beginning and end of treatment using the LOCF measured progress. Examining score differences within groups showed significance. Specifically, there was a significant difference among BDI-II scores in the 10 Hz group between the beginning (median = 27.00) and the end of rTMS (median = 10.00), $Z = 2.87, p = .004$. There was also significance for the 20 Hz group, $Z = 3.73, p < .001$. Before treatment, patients’ median score was 25.75, and at the end of treatment the median score was 5.00.

As some patients received both 10 and 20 Hz parameters, it was important to analyze this group separately. This examination revealed significantly different scores on the BDI-II after undergoing rTMS from baseline (median = 24.00) to end of treatment (median = 13.25), $Z = 3.21, p = .001$. In addition, the progress of these patients prior to the switch revealed a significant change in scores from the first BDI-II measure (median = 24.00) to the last measure (median = 16.00), $Z = 3.11, p < .01$. However, when patients switched, there was no significant difference found in BDI-II scores (median = 12.25) from the first measure taken after the switch to the end of treatment (median = 13.25), $Z = 0.53, p = .593$. Tests to determine if there were significant between-group differences in the change in scores also did not reveal significant results, $\chi^2(2, N=47) = 1.910, p = .385$. 

![Figure 1. Reasons for participants’ discontinuation of treatment and exclusion from the study.](image-url)
As previously mentioned, there were four patients whose depression was in remission at the start of rTMS based on their beginning BDI-II score. Thus, further analyses helped determine if eliminating these patients would affect the results. This examination still revealed significance for the 10 Hz group between the beginning (median = 27.00) and end (median = 10.00), $Z = 2.87$, $p < .01$, as well as for the 20 Hz group, $Z = 3.52$, $p < .001$. The beginning median score was 28.00 and the end median score dropped to 6.50. In addition, no patient’s score was in remission prior to beginning rTMS for the 10/20 Hz group; therefore, these results did not change. The elimination of patients in remission at the start also did not affect between-group differences in progress, as there was still no significance found, $\chi^2(2, N = 43) = 2.733$, $p = .255$.

**Categorical Outcomes**

**Remission.** As seen in Figure 2, the majority of patients in all groups had depression in remission at the end of their rTMS. Specifically, 66.7% ($n = 10$) of patients in the 10 Hz group and 77.8% ($n = 14$) of patients in the 20 Hz group had depression considered to be in remission. In addition, when eliminating those patients whose scores began in remission, there was then 61.5% ($n = 8$) and 75.0% ($n = 12$) of patients in remission in the 10 Hz and 20 Hz groups, respectively. For those patients in the 10/20 Hz group, 57.1% ($n = 8$) of patients had depression in remission at treatment completion.

**Response.** As indicated by Figure 2, 6.7% ($n = 1$) of patients in the 10 Hz group had depression that responded to rTMS, as well as 5.6% ($n = 1$) of patients in the 20 Hz group. There were no patients in the 10/20 Hz group whose depression responded to treatment.

**Partial response.** Of those patients receiving 10 Hz treatment, 13.3% ($n = 2$) had a partial response to rTMS, as shown in Figure 2. In addition, 5.6% ($n = 1$) of patients in the 20 Hz group and 18.8% ($n = 3$) of patients in the 10/20 Hz group had a partial response.

**No response.** There were 13.3% ($n = 2$) of patients in the 10 Hz treatment group who did not receive benefit and 11.1% ($n = 2$) in the 20 Hz group who had no response. For those who received 10/20 Hz rTMS, 21.4% of patients ($n = 3$) failed to respond (see Figure 2).

**Safety Outcomes**

No adverse events occurred as a result of rTMS in any of the groups. No patients discontinued as a result of discomfort during treatment. In addition, patients reported no change in hearing, although they did not undergo a formal hearing test.

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**Table 1. Demographic Features, Clinical Indicators, and BDI-II Scores**

| Demographic features | 10 Hz ($n = 15$) | 20 Hz ($n = 18$) | 10/20 Hz ($n = 14$) | $p$ value$^a$ |
|----------------------|-----------------|-----------------|-------------------|---------------|
| Female, $n$ (%)      | 12 (80.0)       | 9 (50.0)        | 8 (57.1)          | .200          |
| Age in years, $M$ ($SD$) | 45.0 (16.0) | 46.0 (13.0) | 44.0 (16.0) | .949          |
| Ethnic origin, $n$ (%) |                |                 |                   | .529          |
| Caucasian            | 14 (93.3)       | 18 (100)        | 13 (92.9)         |               |
| Other                | 1 (6.7)         | 0 (0)           | 1 (7.1)           |               |
| Clinical indicators  |                 |                 |                   |               |
| Depression history, $n$ (%) |            |                 |                   | .328          |
| MDD single episode   | 0 (0.0)         | 1 (5.6)         | 1 (7.1)           |               |
| MDD recurrent        | 14 (93.3)       | 13 (72.2)       | 11 (78.6)         |               |
| Dysthymia            | 0 (0.0)         | 1 (5.6)         | 1 (7.1)           |               |
| Bipolar disorder     | 1 (6.7)         | 3 (16.7)        | 1 (7.1)           |               |
| Secondary diagnoses, $n$ (%) |            |                 |                   | .987          |
| None                 | 2 (13.3)        | 1 (5.6)         | 2 (14.3)          |               |
| Any anxiety disorder | 12 (80.0)       | 17 (94.4)       | 11 (78.6)         |               |
| Another depressive disorder | 1 (6.7) | 0 (0.0) | 1 (7.1) |               |
| Treatment number, $M$ ($SD$) | 22.9 (14.0) | 22.2 (9.3) | 24.4 (9.7) | .635          |
| BDI-II score, $M$ ($SD$) | 27.7 (15.0) | 26.0 (10.9) | 27.8 (10.8) | .949          |
| Final                | 15.8 (15.7)     | 9.7 (10.7)      | 15.0 (10.2)       | .160          |

Note: BDI-II = Beck Depression Inventory–II; rTMS = repetitive transcranial magnetic stimulation; MDD = Major Depressive Disorder. $^a$p values shown indicate between-group contrasts.
Discussion

This is the first retrospective and descriptive chart analysis of the progress of patients undergoing different high-frequency rTMS to the left DLPFC for depression. Specifically, the present study sought to examine the data of patients who underwent rTMS with stimulation at 10 Hz and 20 Hz to determine any between-group or within-group differences, as well as review progress in a group of patients who received both 10 and 20 Hz during their protocol. BDI-II scores completed by patients at the beginning and end of rTMS using the LOCF indicated treatment effectiveness. Analyses revealed the effectiveness of rTMS regardless of the form of high-frequency treatment patients received (10 Hz: \( p = .004 \), 20 Hz: \( p < .001 \), 10/20 Hz: \( p = .001 \)). These results did not change when eliminating patients with none to minimal depression at the start of treatment, as classified by BDI-II scores \( \leq 13 \) (10 Hz: \( p = .01 \), 20 Hz: \( p < .001 \)). There were no patients eliminated in the 10/20 Hz group based on these criteria. There was also no significant difference found in progress between groups (\( p = .385 \)). The average number of treatments completed using the LOCF was 22.9 for the 10 Hz group, 22.2 for the 20 Hz group, and 24.4 for the 10/20 Hz group, with no significant difference found in the number of treatments completed (\( p = .635 \)).

Categorical indicators of remission and response rates also revealed the majority of patients had depression that fell into remission after receiving rTMS, regardless of the level of frequency treatment they received (10 Hz: 66.7%, \( n = 10 \); 20 Hz: 77.8%, \( n = 14 \)). Furthermore, patients’ response rates revealed 6.7% (\( n = 1 \)) of those in the 10 Hz group and 5.6% (\( n = 1 \)) of patients in the 20 Hz group responded to treatment. In regards to partial response rates, 13.3% (\( n = 2 \)) in the 10 Hz group and 5.6% (\( n = 1 \)) of patients in the 20 Hz group partially responded.

A unique group of patients (\( n = 14 \)) received both 10 and 20 Hz rTMS. Overall, BDI-II scores revealed 57.1% (\( n = 8 \)) had depression that went into remission by the end of treatment. There were no patients in this group whose depression would be categorized as responding; however, 21.4% (\( n = 3 \)) had depression that partially responded to rTMS.

As patients in this particular group had switched parameters, it became important to look at the progress of their depression just prior to the switch. Within this group, there were 12 patients who began their treatment with parameters set at 10 Hz who then switched to 20 Hz, and 2 patients who first received 20 Hz rTMS who then switched to 10 Hz. Of those in the 10 to 20 Hz group, the average treatment number prior to the switch was 14.3. BDI-II scores for this subset revealed that 41.7% (\( n = 5 \)) of patients had depression that
went into remission prior to the switch in treatment parameters, while 8.3% \((n = 1)\) responded and 33.3% \((n = 4)\) partially responded. In addition, 16.7% \((n = 2)\) had no response prior to the switch.

In regards to the two patients who switched from 20 to 10 Hz, there was no benefit obtained by these patients prior to the switch after receiving an average of seven treatments. However, their depression went into remission by the end of their entire protocol. It is important to note that in all cases, patients switched to a different frequency stimulation after consultation with their psychiatrist. It was unknown at the time which treatment would be more beneficial to patients. As can be seen in the current study, those in the 20 Hz treatment group had the highest rate of remission and the lowest rate of nonresponse of all three groups, even though the between-group differences in treatment were not significant. In addition, this group had the lowest overall ending BDI-II mean score.

In terms of nonresponders, 7 out of 47 (14.9%) patients failed to receive any benefit from rTMS. This included 2 patients from the 10 Hz group, 2 patients from the 20 Hz group, and 3 patients from the 10/20 Hz group. Possible explanations for why they did not experience any improvement in depressive symptoms may be the presence of significant comorbid Anxiety Disorders. As the treatment of Anxiety Disorders typically involves rTMS to the right DLPFC (Alonso et al., 2001), addressing anxiety symptoms that often mimic or accompany symptoms of depression is difficult when treatment is only delivered to the left side. In fact, it is currently debated in the literature whether it is important to use low-frequency treatment to the right DLPFC in conjunction with high-frequency rTMS to the left DLPFC so there is an inhibitory effect on the brain as well. There are also mixed results in studies as to the most effective treatment for patients with Anxiety Disorders. Specifically, a summary of published articles in which patients with different Anxiety Disorders received rTMS revealed a lack of clinical sham-controlled trials for these disorders (Pallanti & Bernardi, 2009). In addition, although most studies demonstrate treatment efficacy, some speak to temporary and small effects (Pallanti & Bernardi, 2009).

There were eight patients excluded from further analysis due to a lack of sufficient data to determine treatment progress, as well as an additional seven patients who completed less than 10 rTMS treatments. Reasons for discontinuation included concerns about cost, protocol violation, and patient request (due to circumstances such as moving or vacation).

Most studies examined rTMS efficacy through studying the effects on patients in randomized, controlled, laboratory trials. Patients typically cannot be on medications or make changes to psychotherapy while receiving rTMS and can only have a particular subset of diagnoses. Although this is important and necessary when examining treatment efficacy, this limits external validity. Because the current study was a retrospective chart review of progress, the patients included in these analyses took their regular psychotropic medication and possibly attended psychotherapy while receiving treatment. This is important given taking medications and comorbidity are not exclusionary criteria for undergoing rTMS in a real-world setting. Furthermore, studies found receiving rTMS treatment while taking an antidepressant can accelerate the effects of the drug (Rumi et al., 2005). Thus, the strength of this article lies in its increased applicability to practitioners.

The present study’s limitations include patients may be in therapy and/or take medication while receiving rTMS. Thus, even though there were no changes to either while receiving treatment, it still becomes difficult to determine the degree to which rTMS was solely responsible for alleviating depressive symptoms. To that note, however, it is important to recognize that the best manner to treat depression is a combination of treatments. Accordingly, once a method has been proven efficacious, the most important factor is the patient’s overall progress.

Another limitation of the present review lies in the measurement of effectiveness. Discrepancies may exist between the patients’ and psychiatrist’s viewpoint of progress and the focus of this article was on the patients’ perspectives. Using another measure completed by a clinician may yield different results than did those when progress was assessed using the BDI-II. Furthermore, mean BDI-II baseline scores of all groups indicated levels of depression in the moderate range at the start of treatment, which may not be severe enough to observe a decrease in symptomatology. There also were no significant between-group differences in progress, which supports replicating the study on a larger scale as well. Both within-group and between-group differences cannot be found if there is insufficient power due to a small study sample and limited severity of depression.

Nevertheless, the present study adds to the existing literature in demonstrating the overall effectiveness of rTMS for depression when treatment applied in a psychiatric setting. This article also further clarifies a trend in progress when patients receive rTMS in an outpatient psychiatric setting.

Authors’ Note

Dr. DeBlasio discloses previously lecturing for Neuronetics. Dr. Tendler was also a lecturer for Mylan, Neuronetics, and Reckitt Benckiser.

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