

Repetitive transcranial magnetic stimulation for treatment of major depressive disorder with comorbid generalized anxiety disorder

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BACKGROUND: Repetitive transcranial magnetic stimulation (rTMS) has shown promising results in treating individuals with behavioral disorders such as major depressive disorder (MDD), posttraumatic stress disorder, obsessive-compulsive disorder, and social anxiety disorder. A number of applications of rTMS to different regions of the left and right prefrontal cortex have been used to treat these disorders, but no study of treatment for MDD with generalized anxiety disorder (GAD) has been conducted with application of rTMS to both the left and right prefrontal cortex. We hypothesized that applying low-frequency rTMS to the right dorsolateral prefrontal cortex (DLPFC) before applying it to the left DLPFC for the treatment of depression would be anxiolytic in patients with MDD with GAD.

METHODS: Thirteen adult patients with comorbid MDD and GAD received treatment with rTMS in an outpatient setting. The number of treatments ranged from 24 to 36 over 5 to 6 weeks. Response was defined as a $\geq 50\%$ reduction in symptoms from baseline, and remission was defined as a score of < 5 for anxiety symptoms on the 7-item Generalized Anxiety Disorder (GAD-7) scale and < 8 for depressive symptoms on the 21-item Hamilton Rating Scale for Depression (HAM-D-21).

RESULTS: At the end of the treatment period, for the GAD-7 scale, 11 out of 13 (84.6%) patients' anxiety symptoms were in remission, achieving a score of < 5 on the GAD-7, and 10 out of 13 patients (76.9%) achieved a HAM-D-21 score of < 8 for depressive symptoms.

CONCLUSIONS: In this small pilot study of 13 patients with comorbid MDD and GAD, significant improvement in anxiety symptoms along with depressive symptoms was achieved in a majority of patients after bilateral rTMS application.

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INTRODUCTION

Depression (major depressive disorder [MDD] and dysthymia), as shown in a study conducted in 2010, is a leading cause of global burden of disease of years lived with disability.¹ Often, depression is accompanied by generalized anxiety disorder (GAD). Worldwide, from 1990 to 2010, GAD ranked as the 21st most common cause of sequelae leading to disability, accounting for >272 million cases of disability worldwide.² As the population continues to grow, it is apparent that the volume of patients presenting with MDD with comorbid GAD also will continue to increase.

Studies have shown success in treating unipolar depression with the application of repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) daily for 20 days.^{3,4} Paes et al⁵ applied rTMS over the right DLPFC for the treatment of GAD and for social anxiety disorder using low-frequency rTMS treatment over the right medial prefrontal cortex (mPFC), with high-frequency rTMS treatment over the left mPFC. In a study by Diefenbach and colleagues,⁶ 8 out of 32 patients who met criteria for MDD and anxiety-related symptoms were treated with rTMS to the left DLPFC over a period of 20 days. In that study, the 21-item Hamilton Rating Scale for Depression (HAM-D-21) and HAM-D subscales for anxiety were used to aid in the diagnosis of these disorders, as well as reassess these disorders in patients throughout treatment and post treatment. The study showed improvement in both depressive and anxiety symptoms in patients with refractory MDD.

In this study, both the HAM-D and GAD scales were used because they have been accepted as valid tools for screening and measuring treatment outcomes for depression and anxiety, respectively.^{7,8}

rTMS has been used to treat anxiety disorders and MDD, but a study has yet to establish a treatment for MDD with comorbid GAD on the basis of treating the right DLPFC with rTMS to address MDD, and then following up rTMS to the left DLPFC to address GAD. The goal of this study is to show the benefits of bilateral rTMS in treating anxiety symptoms that are comorbid with MDD and compare outcomes with other available rTMS studies.

The outcome and success in achieving remission in this study were measured on the basis of baseline

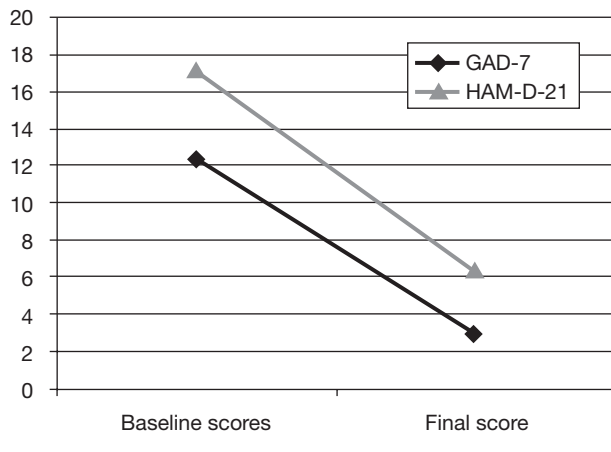
and final scoring on the 7-item Generalized Anxiety Disorder (GAD-7) scale and HAM-D-21. rTMS was used at high frequency on the left DLPFC to treat MDD, and a low frequency of 1 Hz was used over the right DLPFC to treat GAD symptoms. As Paes et al⁵ showed in the social anxiety study, use of low frequency with rTMS in this study also provided a calming effect when applied to the right prefrontal cortex. They concluded that a combination of low-frequency rTMS on the right mPFC with high-frequency rTMS on the left mPFC over 4 weeks provided beneficial outcomes for social anxiety.

METHODS

Patients whose data were used in this study were treated in an outpatient setting at Midtown Psychiatry and TMS Center in Houston, Texas, USA, with the use of a Neuronetics NeuroStar TMS Therapy system. Patients were either self-referred or referred by their treating physician specifically for TMS treatment of refractory depression. Patients completed the self-reported scales (GAD-7, HAM-D-21, the 9-item Patient Health Questionnaire, and the Quick Inventory of Depressive Symptomatology) during their initial evaluation to confirm the diagnosis of MDD and comorbid GAD based on DSM-IV criteria. Patients provided routine consent for receiving rTMS treatment while continuing their previous medication regimen.

Thirteen adult patients (8 women and 5 men; mean age, 42.46 years), with comorbid MDD and GAD received right-sided rTMS at low frequency (1000 stimuli at 1-Hz frequency), followed by treatment with left-sided DLPFC high-frequency (10 Hz). GAD-7 and HAM-D-21 were administered at the beginning and throughout the rTMS treatments. The number of treatments ranged from 24 to 36 per patients over 5 to 6 weeks. Response was defined as a ≥50% reduction in symptoms from baseline, and remission was defined as a GAD-7 score of <5 for anxiety symptoms and a HAM-D-21 score of <8 for depressive symptoms. Measurements were taken to show the differences in baseline scores and final scores for both the GAD-7 and HAM-D-21 scales. These differences were calculated for each individual patient as well as summed and averaged to show the overall change as a group for the 13 patients.

FIGURE 1
Mean change in rating scale scores



GAD-7: Generalized Anxiety Disorder scale, 7-item; HAM-D-21: Hamilton Rating Scale for Depression, 21-item.

RESULTS

At the end of the treatment period, 11 of the 13 patients (84.6%) achieved a score of <5 on the GAD-7 and 10 of the 13 patients (76.9%) achieved a HAM-D-21 score of <8 (TABLE). The black line in FIGURE 1 represents the mean change from baseline score to final score for all 13 patients on the GAD-7 scale, and the gray line represents the mean change from baseline score to final score for all 13 patients on the HAM-D-21 scale. Eleven of the 13 patients showed a change of ≥ 5 points on both the HAM-D-21 and GAD-7 scales. Nine patients also showed an improvement of $\geq 50\%$ from baseline score to final score on the HAM-D-21 scale, and 11 patients showed an improvement of $\geq 50\%$ from baseline score to final score on the GAD-7 scale (TABLE and FIGURE 2). In conducting a paired t test comparing baseline to final scores for HAM-D-21 and GAD-7, a markedly significant difference was found for both the GAD-7 ($t = 5.59$, $P < .0005$) and the HAM-D-21 ($t = 6.20$, $P < .0005$) scores (TABLE). Overall, the study findings suggested a decrease of 65% and 75% in depression and anxiety, respectively, from the baseline scores to the final scores (FIGURE 1).

In a study by Diefenbach and colleagues,⁶ 8 patients with MDD and anxiety-related symptoms were treated with rTMS to the left DLPFC at 10 Hz. Treatment took place over a period of 20 days with a mean of 31 treatments. All patients were taking an antidepressant during the treatment. Each patient's level of depression was mea-

sured using the HAM-D-21, which was also used to measure anxiety, using the anxiety/somatization factors on the scale.⁶ The study showed decreases of 35% and 32% in depression and anxiety, respectively, from baseline scores to final scores.

DISCUSSION

This study showed great response to rTMS for both MDD and GAD. Using a GAD-7 scale in addition to the HAM-D-21 scale allowed for more specific measurement of the anxiety portion of this comorbid disorder. The remission rates for depression and anxiety in this study were comparable with the Diefenbach et al study,⁶ with remission in both symptoms by 62% and 75%, respectively. The percentage decrease in mean scale scores from baseline to final score in Diefenbach et al⁶ (35% reduction in depression and 32% reduction in anxiety) in comparison to this study (a decrease of 65% and 75% in depression and anxiety, respectively) may suggest the importance of treating the DLPFC on the right before treating the left DLPFC in treating MDD with comorbid GAD. Additionally, treatment to the right prefrontal cortex may have an additive effect in treating depression. Fitzgerald et al⁹ applied rTMS to the left prefrontal cortex and low-frequency rTMS to the right prefrontal cortex also found a synergistic effect in treating depression.

CONCLUSIONS

In this small pilot study of 13 patients with MDD, patients achieved high remission rates in symptoms of both anxiety and depression. This exploratory analysis provides additional support for the application of low-frequency, right-sided rTMS for the anxiety symptoms frequently associated with MDD. Future studies with larger sample sizes would be ideal to further solidify the use of rTMS in treating MDD with comorbid GAD. Further studies are needed to determine whether treatment to both sides of the prefrontal cortex would continue to show significant improvement in both MDD and GAD, rather than treating only the left or right side alone for each disorder, as shown in previous studies. How much of an antidepressant effect low-frequency

TABLE
GAD-7 and HAM-D-21 numeric results at baseline and end of treatment

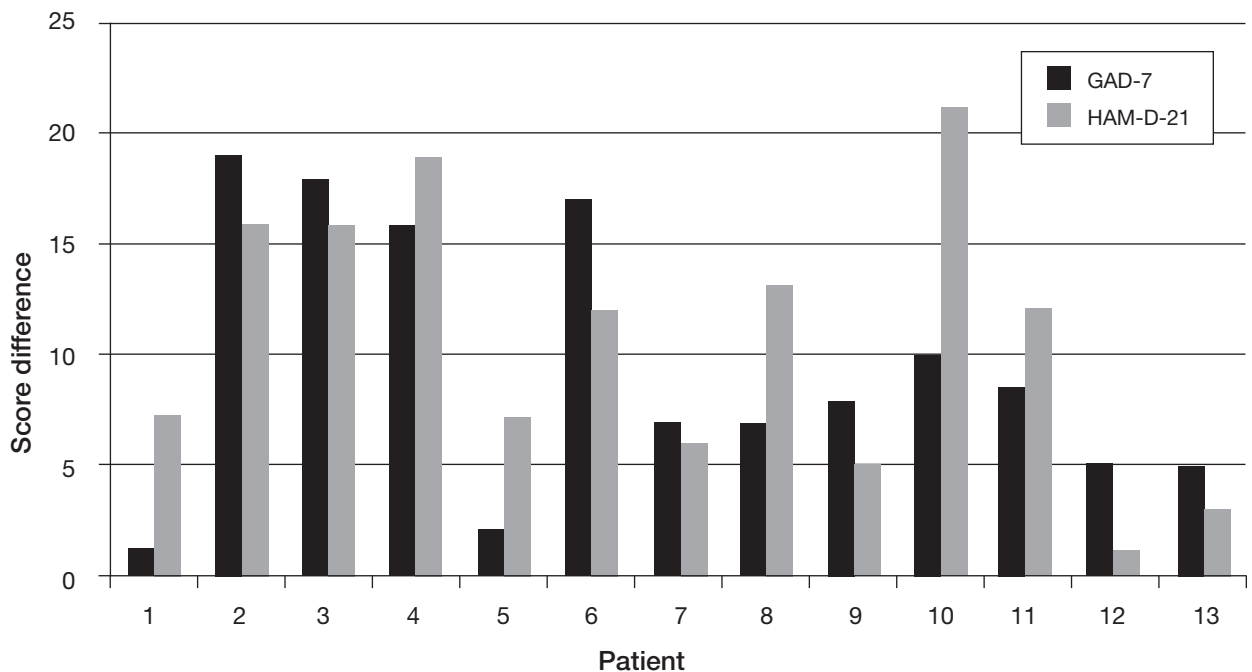
Score	Scale	Patient													Mean	
Baseline	GAD-7	7	20	19	19	13	18	7	9	8	13	12	9	7	12	
	HAM-D-21	19	20	23	22	24	19	13	20	6	25	20	9	3	17	
Final	GAD-7	6	1	1	3	11	1	0	2	0	3	4	4	2	3	
	HAM-D-21	11	4	7	3	17	7	7	7	1	4	7	8	0	6	
	GAD-7 differences	-1	-19	-18	-16	-2	-17	-7	-7	-8	-10	-8	-5	-5	Average of differences	-9.46
	HAM-D-21 differences	-8	-16	-16	-19	-7	-12	-6	-13	-5	-21	-13	-1	--	Average of differences	-10.77
	GAD-7 SD ^a	6.10	SE	1.69		<i>t</i> score	-5.59									
	HAM-D-21 SD ^b	6.27	SE	1.74		<i>t</i> score	-6.20									

^a*t* > *P* of .0005; therefore, the null of no significant decrease in baseline vs posttreatment GAD-7 scores can be rejected.

^b*t* > *P* of .0005; therefore, the null of no significant decrease in baseline vs posttreatment HAM-D-21 scores can be rejected.

GAD-7: Generalized Anxiety Disorder scale, 7-item; HAM-D-21: Hamilton Rating Scale for Depression, 21-item; SD: standard deviation.

FIGURE 2
Difference in baseline and final scores by patient



GAD-7: Generalized Anxiety Disorder scale, 7-item; HAM-D-21: Hamilton Rating Scale for Depression, 21-item.

rTMS to the right side of the prefrontal cortex contributed to the high remission of MDD should also be considered in future studies. ■

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