The Anxiolytic and Antidepressant Effects of Transcranial Magnetic Stimulation in Patients With Anxious Depression

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ABSTRACT

Objective: To determine the extent that treatment with transcranial magnetic stimulation (TMS) in diverse clinical settings has anxiolytic and antidepressant effects in patients with major depressive disorder (MDD) and moderate-to-severe anxiety symptoms and to contrast anxious and nonanxious depression subgroups in antidepressant effects.

Methods: Within the NeuroStar Advanced Therapy System Clinical Outcomes Registry, 1,820 patients were identified with a diagnosis of MDD (using *ICD-9*, *ICD-10*, or *DSM-IV*) who completed the Patient Health Questionnaire-9 (PHQ-9) and Global Anxiety Disoder-7 scale (GAD-7) at baseline and following at least 1 TMS treatment between May 2016 and January 2021. Anxious depression was defined as a baseline GAD-7 score of 10 or greater (n = 1,514) and nonanxious depression by GAD-7 scores below this threshold (n = 306). Intent-to-treat and Completer samples were defined for patients treated with any TMS protocol and for the subgroup treated only with high-frequency left dorsolateral prefrontal cortex stimulation.

Results: Patients with anxious depression showed clinically meaningful anxiolytic and antidepressant effects, averaging approximately 50% or greater reductions in both GAD-7 and PHQ-9 scores following TMS in all samples. The anxious and nonanxious depression groups had equivalent absolute improvement in PHQ-9 scores (*P* values ≥ .29). However, the anxious group had higher scores both at baseline and following TMS resulting in significantly lower categorical rates of response (*P* values < .02) and remission (*P* values < .001) in depressive symptoms. Among those with anxious depression, the change in anxiety and depression symptoms strongly covaried ($r_{1512} = 0.75$, $P < .001$).

Conclusions: Routine TMS delivered in diverse clinical settings results in marked anxiolytic and antidepressant effects in patients with anxious depression. The extent of improvement in anxiety and depression symptoms strongly covaries.

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Anxiety and depression commonly co-occur.[1,2] Anxious depression has been variously defined as the presentation of major depressive disorder (MDD) with a comorbid anxiety disorder, MDD with clinically significant anxiety symptoms, or MDD with the anxious distress specifier, as introduced in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*).[3] Regardless of definition, the prevalence of anxious depression is high.[4,5] National[6,7] and multinational[8] epidemiologic studies have estimated that approximately 50%–80% of individuals with a lifetime history of MDD also have a history of anxiety disorder. Some studies suggest that the majority of outpatients with MDD present with comorbid generalized anxiety disorder (GAD).[9,10] Similarly, the *DSM-5* specifier *anxious distress* applies to approximately 50%–75% of patients diagnosed with MDD.[11] The temporal pattern of an anxiety disorder preceding the onset of MDD is considerably more common than the reverse.[7,8]

Compared to MDD without significant anxiety symptoms (ie, low anxiety or nonanxious depression), anxious depression is associated with greater depression symptom severity, suicidality, chronicity, and functional impairment.[7,9,12] Multiple pharmacologic studies have documented poorer MDD treatment outcome in anxious compared to nonanxious depression.[5,12–16] For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[5] 53.2% of patients treated with citalopram in Level 1 presented with anxious depression. Remission in this group was less likely and occurred after a longer delay compared to patients with nonanxious depression. Side effect frequency, intensity, and burden and the frequency of serious adverse effects were greater in the anxious depression group. Level 2 treatment outcomes were also significantly poorer in the anxious depression group, both for pharmacologic augmentation and for switching strategies.[5]

The efficacy of transcranial magnetic stimulation (TMS) in treatment-resistant depression (TRD) is well established and based on randomized sham-controlled trials,[17–19] meta-analyses,[20–22] and studies of real-world outcomes across diverse clinical settings.[23,24] Several randomized controlled trials have reported that active TMS in patients with MDD results in larger reductions of anxiety symptoms than sham or

Clinical Points

- Anxious depression is common and is associated with diminished response to antidepressant medications, increased suicidality, and increased chronicity.
- Highly anxious depressed patients treated with transcranial magnetic stimulation (TMS) began with higher Patient Health Questionnaire-9 (PHQ-9) scores but showed strong antidepressant responses, obtaining decreases in PHQ-9 scores comparable to those of non-anxious patients.
- TMS improves both depression and anxiety, and the effects strongly covary.

other comparison conditions.[17–19,25] A variety of open-label, naturalistic studies[26–31] have also documented substantial reductions of anxiety symptoms in MDD patients treated with TMS. It has been reported that, independent of the presence of MDD, the TMS protocols used in MDD exert substantial therapeutic effects in GAD and posttraumatic stress disorder (PTSD).[32] Thus, it could be that TMS, when configured for the treatment of MDD, exerts clinically meaningful anxiolytic effects in individuals with treatment-resistant anxious depression. However, traditional outcome metrics, specifically rates of response and remission of anxiety symptoms, have not been reported in a large sample of patients with anxious depression treated with TMS. Furthermore, it has been recently suggested that different anatomic TMS targets may be optimal to treat the "dysphoric" and "anxiosomatic" symptoms of MDD, with the former symptoms more responsive to dorsolateral prefrontal cortex (DLPFC) targeting and the later symptoms more responsive to dorsomedial prefrontal cortex targeting.[33] This perspective predicts that, especially when using a focal TMS coil, the relative change in dysphoric versus anxiosomatic symptoms varies with coil positioning.

There is general consensus in the pharmacologic literature that the likelihoods of antidepressant response and remission are reduced in patients with anxious depression,[5,12–15] although there are some reports with null results.[34,35] In contrast, the sparse TMS literature is inconsistent. While a retrospective analysis[25] suggested that high baseline anxiety in MDD patients is associated with marked post-TMS reductions in depression symptoms and low anxiety with minimal change, other studies[29,31,36] found that patients with and without anxious depression did not differ in degree of in depressive symptom improvement. Of note, the presence of a comorbid anxiety disorder, but not the severity of anxiety symptoms, has also been associated with poorer antidepressant response to TMS.[36–38]

The NeuroStar Advanced Therapy System Clinical Outcomes Registry documents clinical outcomes with routine administration of TMS in largely private practice settings across the US. It constitutes the largest outcomes registry for any treatment of MDD. Findings from this registry have been reported regarding the overall antidepressant efficacy of TMS and demographic and treatment parameter efficacy correlates.[24,39,40] The Patient Health Questionnaire-9 (PHQ-9)[41] was completed at all registry sites, and a subset of sites also asked patients to complete the Generalized Anxiety Disorder-7 scale (GAD-7).[42] The availability of serial scores on both instruments allowed for characterization of the severity of depression and anxiety symptoms at baseline and tracking TMS therapeutic outcomes in both domains.

This study addressed the following questions: (1) Do providers administer different TMS protocols to patients with anxious and nonanxious depression? (2) Does treatment with TMS for MDD have clinically significant anxiolytic effects in patients with anxious depression, as defined by high baseline GAD-7 score? (3) Are patients with anxious depression less likely to have a clinically significant antidepressant response, and does the extent of depression symptom improvement and rates of antidepressant response and remission differ in patients with anxious versus nonanxious depression at baseline? (4) To what extent does improvement in depression symptoms covary with improvement in anxiety symptoms?

METHODS

Clinical Outcomes Registry

This study involved retrospective analysis of data collected prospectively in the NeuroStar Advanced Therapy System Clinical Outcomes Registry. In particular, the classification of participants at baseline as presenting with anxious or nonanxious depression and the determination as to when the acute TMS treatment course ended were based on retrospective application of decision rules. As described previously,[24,39,40] site selection for inclusion in this registry required that clinical facilities treated a minimum of 24 patients the year before joining the registry, used TrakStar Cloud software for recording deidentified patient characteristics and treatment parameters, and had a secure link for electronic data transfer. In addition, sites used the PHQ-9[41] and/or the Clinical Global Impressions–Severity of Illness scale (CGI-S)[43] to assess the severity of depressive symptoms by self-report and clinician rating, respectively. Once a site joined the registry, all patients treated at the site were included in the database. The registry was developed and maintained by Neuronetics Inc (Malvern, Pennsylvania), the manufacturer of the NeuroStar TMS system. The registry was compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Patient data were deidentified prior to electronic transfer. Collection and analysis of clinical data in this way does not require local Institutional Review Board approval or informed consent.

Data entry in the registry started on May 5, 2016, and this report concerns all data collected until January 22, 2021. Site personnel entered patient demographic information (date of birth, gender), site identifier, primary diagnosis and diagnoses of comorbid psychiatric conditions (using *ICD-9*, *ICD-10*, or *DSM-IV*), and the PHQ-9 and GAD-7 scores. TMS parameters were captured passively at each session and included session date, treatment location of stimulation (ie, left DLPFC, right DLPFC, or both), motor threshold (MT), number of pulses per treatment location or

session, treatment level (% device output relative to motor threshold), pulse frequency (eg, 10 Hz vs 1 Hz), duration of pulse trains, intertrain interval (ITI), and the number of treatment sessions during the acute phase treatment course. The acute phase treatment period was defined as starting with the patient's first recorded TMS treatment and continuing until there was a period of at least 7 days without any treatment.[24,39,40] There was no documentation in the registry database of DLPFC targeting method (eg, 5.5 cm rule, Beam F3, neuronavigation). While theNeuroStar system provided default coordinates for a target 5.5 cm anterior to the MT location, modifications (such as coil rotation) were often made to address patient discomfort, and other targeting methods could be used.

Sample Definitions

The registry collected data on 11,738 patients treated at 110 US sites (mean [SD] per site = 106.7 [111.6] patients) (see Table 1) during the specified time period. These registry participants were unique individuals who received at least 1 TMS treatment. The sites were almost exclusively either private practice practitioners or private practice TMS centers.

The intent-to-treat (ITT) sample was defined by inclusion and exclusion criteria summarized in Table 1. Due to the COVID-19 pandemic, the TMS course was interrupted in 164 patients, who were excluded. Other exclusions included age less than 18 years, no MDD diagnosis, or a primary diagnosis other than MDD. To ensure that the treatment objective was management of an acute episode of MDD, patients with comorbid psychiatric diagnoses other than anxiety disorders were also excluded (eg, schizophrenia, bipolar disorder, autism, attention-deficit/hyperactivity disorder). Most critically, patients were excluded who did not have PHQ-9 and GAD-7 assessments within 14 days prior to the first TMS session (n = 7,831) or who did not have at least one PHQ-9 and GAD-7 assessment after starting TMS (n = 164). Finally, individuals were excluded whose baseline PHQ-9 score was less than 10, indicating insufficient severity of baseline depressive symptoms (n = 60). The ITT sample comprised 1,820 patients treated at 43 sites. The lack of GAD-7 data was the predominant reason for exclusion, as the completion of this scale was at the discretion of the sites.

A subset of the ITT sample comprised the "Completer" sample (Table 1). To ensure a minimally adequate course of TMS,[44] individuals were excluded if classified as PHQ-9 nonresponders and had ended TMS after fewer than 20 sessions. Patients were also excluded if PHQ-9 and GAD-7 assessments were not conducted near the end of acute phase treatment, ie, within ± 4 days of the final session. Thus, to be included in the ITT sample, patients had to receive at least one TMS treatment and complete the PHQ-9 and GAD-7 assessments at baseline and at any point after the start of TMS. In contrast, Completers (n = 1,429, 42 sites) received at least 20 TMS sessions before classification as PHQ-9 nonresponders and had PHQ-9 and GAD-7 assessments within 4 days of the final TMS session and within 4 days of each other.

Table 1. Inclusion/Exclusion Criteria for the Intent-To-Treat (ITT) and Completer Samples, and the Classification of Treatment Protocols

Inclusion/Exclusion Criteria for Study Samples
Registry Sample (N = 11,738; 110 sites)
• Unique individuals with ≥ 1 TMS treatment before January 22, 2021
Intent-to-Treat (ITT) Sample (N = 1,820; 43 sites)
Exclusions:
• COVID-19 treatment interruption (n = 164)
• No MDD diagnosis or primary diagnosis other than MDD (n = 1,259)
• Comorbid psychiatric diagnosis (non-MDD diagnosis other than anxiety disorder) (n = 334)
• Age < 18 y or invalid (n = 93)
• Not male or female (n = 13)
• No PHQ-9 and GAD-7 within 14 days before first TMS session (n = 7,831)
• No PHQ-9 and GAD-7 after starting TMS (n = 164)
• Baseline score on PHQ-9 < 10 (n = 60)
Completer Sample (n = 1,429; 42 sites)
Exclusions:
• < 20 treatments and classified as nonresponder on PHQ-9 (n = 122)
• PHQ-9 and GAD-7 not completed within 4 days of last TMS session (n = 267)
• PHQ-9 and GAD-7 assessment not completed within 4 days of each other (n = 2)
Criteria for TMS Protocol Classification
High Frequency, Left Unilateral (HF LUL) Treatment Group (ITT n = 625, 28 sites; Completer n = 471, 28 sites)
• Only 1 treatment protocol per session
• All treatments at 10 Hz to left dorsolateral prefrontal cortex (DLPFC)
• Mean treatment level ≥ 100% of motor threshold
• Mean number of pulses/session ≥ 2,000
Sequential Bilateral (SBL) Treatment Group (ITT n = 101, 19 sites; Completer n = 68, 15 sites)
• Left DLPFC 10 Hz stimulation and right DLPFC 1 Hz stimulation delivered sequentially in the same session, in either order, during at least 90% of sessions
• Mean treatment level of the LUL and RUL magnetic pulses ≥ 100% of the left and right motor threshold values, respectively.
• Mean number of pulses/session ≥ 2,000
Switching from LUL to SBL Treatment Group (ITT n = 518, 22 sites; Completer n = 451, 19 sites)
• LUL treatment for first ≥ 5 sessions and then at least 1 session with SBL TMS
Other Protocols (ITT n = 576, 36 sites; Completer n = 439, 31 sites)
• Not classified in one of the aforementioned treatment protocol groups

Abbreviations: GAD-7 = Global Anxiety Disorder-7 scale, MDD = major depressive disorder, PHQ-9 = Patient Health Questionnaire-9, TMS = transcranial magnetic stimulation.

The ITT and Completer samples were subdivided into 4 TMS protocol groups (see Table 1 for the criteria used to define each protocol): (1) patients treated with high frequency (HF; 10 Hz) left DLPFC (unilateral) stimulation throughout their treatment course (HF-LUL group), (2) patients treated with sequential bilateral (SBL) TMS in at least 90% of sessions (SBL group), (3) patients who initiated treatment with HF-LUL TMS for at least 5 sessions and then switched to SBL TMS (Switch group), and (4) patients whose treatments were not otherwise classified (Other group).

High baseline anxiety or "anxious depression" was defined by a baseline GAD-7 score ≥ 10, with nonanxious depression defined by a GAD-7 score < 10. The GAD-7 was originally developed as a screen to detect GAD in primary care settings.[42] It has strong psychometric properties, including excellent internal consistency and a unidimensional factor

Table 2. Demographic and Clinical Characteristics of High and Low Anxiety Groups[a,b]

Characteristic	Total Intent-to-Treat (ITT) Sample			HF-LUL–Only ITT Sample		
	High GAD-7 Score (n = 1,514)	Low GAD-7 Score (n = 306)	*P*	High GAD-7 Score (n = 490)	Low GAD-7 Score (n = 135)	*P*
Age, y	46.7 ± 16.2	50.7 ± 17.9	< .001	47.3 ± 16.7	52.7 ± 17.3	< .001
Female, %	63.9	58.5	.072	67.8	60.7	.127
Baseline GAD-7 score	16.4 ± 3.3	6.0 ± 2.5	< .001	16.0 ± 3.3	5.6 ± 2.5	< .001
Baseline PHQ-9 score	20.9 ± 3.7	18.2 ± 3.8	< .001	20.2 ± 3.8	17.6 ± 4.0	< .001
Baseline CGI-S score	6.0 ± 0.7	5.8 ± 0.7	.007	5.7 ± 0.7	5.7 ± 0.7	.596
n	703	157	…	186	58	…
	Total Completer Sample			HF-LUL–Only Completer Sample		
	High GAD-7 Score (n = 1,163)	Low GAD-7 Score (n = 266)	*P*	High GAD-7 Score (n = 355)	Low GAD-7 Score (n = 116)	*P*
Age, y	46.8 ± 16.3	50.9 ± 17.3	< .001	47.7 ± 16.7	52.7 ± 16.0	.005
Female, %	62.5	57.9	.162	67.3	60.3	.170
Baseline GAD-7 score	16.3 ± 3.3	6.1 ± 2.5	< .001	15.9 ± 3.3	5.6 ± 2.5	< .001
Baseline PHQ-9 score	20.9 ± 3.7	18.2 ± 3.8	< .001	20.1 ± 3.8	17.7 ± 4.0	< .001
Baseline CGI-S score	6.0 ± 0.7	5.8 ± 0.6	.003	5.7 ± 0.7	5.7 ± 0.7	.507
n	591	143	…	141	51	…

[a]Values are expressed as the mean ± SD unless otherwise indicated.
[b]*P* values derive from *t* test or χ^2 comparisons of the low and high GAD-7 groups.
Abbreviations: CGI-S = Clinical Global Impressions–Severity of Illness scale; GAD-7 = Generalized Anxiety Disorder-7; HF-LUL = high frequency, left unilateral TMS; PHQ-9 = Patient Health Questionnaire-9; TMS = transcranial magnetic stimulation.

structure,[45,46] and is widely used to assess the severity of anxiety symptoms across populations and settings.[47–50] Cut-offs ranging from a GAD-7 score of 8 to 10 have been recommended to identify individuals with clinically significant anxiety symptoms and likely to meet diagnostic criteria for an anxiety disorder.[45,51,52] Response was defined for both the GAD-7 and the PHQ-9 as a reduction of at least 50% in final score relative to pre-TMS baseline. Remission was defined as a final score less than 5 on both the GAD-7 and the PHQ-9, corresponding to the traditional cutoffs demarking minimal or no anxiety or depressive symptoms on the respective scales.[41,42,53]

Statistical Analyses

The primary analyses were conducted in the total ITT sample and then repeated for confirmation in the total Completer sample and the ITT and Completer subsamples treated only with HF-LUL TMS. The anxious depression and nonanxious depression groups were compared in demographic and treatment parameters using *t* tests and χ^2 analyses on continuous and categorical measures, respectively.

In the ITT sample, the final GAD-7 and PHQ-9 scores were the last observations obtained after baseline (last observation carried forward [LOCF]), while in the Completer sample, the final scores were obtained at the end of acute (EOA) treatment. Anxiolytic effects were defined as the change in GAD-7 scores from baseline to final observation and in terms of rates of anxiety symptom response and remission. Within the anxious and nonanxious depression groups, effect sizes (*d*) were calculated for the change in GAD-7 and PHQ-9 scores.[54] The anxious depression and nonanxious depression groups were compared in antidepressant effects by conducting *t* tests on the change in PHQ-9 scores and χ^2 tests on PHQ-9 response and remission rates. To confirm the findings of these bivariate analyses, analyses of covariance (ANCOVAs) and logistic regressions were conducted on the continuous change in PHQ-9 scores and the categorical outcomes, respectively. These models included as terms anxious/nonanxious depression group, baseline PHQ-9 score, age, gender, MT level, treatment level, pulse frequency, pulse train duration, interval between pulses trains (ITI), number of delivered pulses per session, and total number of treatment sessions in the acute course. In addition, to estimate the extent of covariation between anxiolytic and antidepressant effects, Pearson product-moment correlations were computed in each sample between the absolute changes in GAD-7 and PHQ-9 scores.

Descriptive statistics are reported as mean ± SD for continuous variables and frequency counts and percentages for categorical variables. For each patient, treatment parameters were averaged over all treatment sessions in their acute course. Significance values are 2-tailed with an α of .05. All *P* values reported are without multiplicity adjustment. Analyses were conducted using SAS v9.4 (SAS Institute Inc; Cary, North Carolina).

RESULTS

Sample Characteristics

Table 2 presents demographic and clinical characteristics for the nonanxious and anxious depression groups in the total ITT and Completer samples and for the subsets treated

Table 3. TMS Protocols, Number of Sessions, and Treatment Parameters for High and Low Anxiety Groups[a,b]

Variable	Total Intent-to-Treat (ITT) Sample			HF-LUL–Only ITT Sample		
	High GAD-7 Score (n = 1,514)	Low GAD-7 Score (n = 306)	*P*	High GAD-7 Score (n = 490)	Low GAD-7 Score (n = 135)	*P*
TMS Protocol, %						
HF-LUL	32.4	44.1	< .001	100	100	…
SBL	5.8	4.2	.267	…	…	…
Switch from HF-LUL to SBL	29.0	25.8	.258	…	…	…
Other protocol	32.8	25.8	.016	…	…	…
TMS Sessions						
No. of sessions in acute course	31.4 ± 8.8	32.9 ± 8.3	.008	30.6 ± 9.2	32.1 ± 8.7	.097
Acute course						
Acute course duration, d	51.7 ± 17.6	54.6 ± 17.8	.010	50.1 ± 18.6	52.1 ± 16.9	.127
No. of treatments per session	1.4 ± 0.5	1.3 ± 0.4	.004	1.0 ± 0.0	1.0 ± 0.0	…
TMS Parameters						
MT, standardized unit	1.04 ± 0.22	1.02 ± 0.21	.089	1.03 ± 0.22	1.01 ± 0.21	.322
Treatment level (% MT)	112.8 ± 7.4	114.2 ± 7.0	.003	115.2 ± 4.2	116.1 ± 3.7	.024
Pulse frequency per session	7.2 ± 2.5	7.8 ± 2.4	< .001	10.0 ± 0.0	10.0 ± 0.0	…
Duration of pulse trains, s	3.5 ± 3.4	3.4 ± 1.2	.787	4.0 ± 0.0	4.0 ± 0.0	…
ITI, s	9.5 ± 5.5	10.6 ± 6.2	< .001	13.7 ± 5.6	14.4 ± 6.4	.235
No. of pulses per session	3,524.4 ± 634.9	3,401.4 ± 563.5	.002	3,062.9 ± 190.2	3,077.2 ± 235.0	.465
	Total Completer Sample			HF-LUL–Only Completer Sample		
	High GAD-7 Score (n = 1,163)	Low GAD-7 Score (n = 266)	*P*	High GAD-7 Score (n = 355)	Low GAD-7 Score (n = 116)	*P*
TMS Protocol, %						
HF-LUL	30.5	43.6	< .001	100	100	…
SBL	5.0	3.8	.396	…	…	…
Switch from HF-LUL to SBL	32.8	25.9	.031	…	…	…
Other protocol	31.6	26.7	.114	…	…	…
TMS Sessions						
No. of sessions in acute course	33.7 ± 6.0	34.1 ± 6.9	.339	33.4 ± 6.4	33.4 ± 7.3	.992
Acute course						
Acute course duration, d	55.4 ± 14.2	56.9 ± 16.2	.144	54.3 ± 15.5	54.3 ± 15.4	.964
No. of treatments per session	1.4 ± 0.4	1.3 ± 0.4	.003	1.0 ± 0.0	1.0 ± 0.0	…
TMS Parameters						
MT, standardized unit	1.04 ± 0.22	1.02 ± 0.21	.192	1.03 ± 0.22	1.03 ± 0.21	.722
Treatment level (% MT)	113.8 ± 6.8	114.5 ± 6.8	.110	116.1 ± 3.4	116.3 ± 3.7	.721
Pulse frequency per session	7.1 ± 2.5	7.8 ± 2.4	< .001	10.0 ± 0.0	10.0 ± 0.0	…
Duration of pulse trains, s	3.4 ± 3.8	3.4 ± 1.1	.854	4.0 ± 0.0	4.0 ± 0.0	…
ITI, s	9.3 ± 5.4	10.5 ± 6.0	.003	13.7 ± 5.6	14.0 ± 6.2	.697
No. of pulses per session	3,547.5 ± 620.0	3,417.1 ± 575.7	.002	3,074.2 ± 214.8	3,086.9 ± 251.5	.595

[a]Values are expressed as the mean ± SD unless otherwise indicated.
[b]*P* values derive from *t* test or χ^2 comparisons of the low and high GAD-7 score groups.
Abbreviations: GAD-7 = Generalized Anxiety Disorder-7; HF-LUL = high frequency, left unilateral TMS; ITI = intertrain interval; MT = motor threshold; PHQ-9 = Patient Health Questionnaire-9; SBL = sequential bilateral; TMS = transcranial magnetic stimulation.

only with HF-LUL TMS. More than 75% of patients had baseline GAD-7 scores of 10 or greater and were classified with anxious depression. The anxious and nonanxious depression groups did not differ in the distribution of gender. The anxious group was significantly younger than the nonanxious group by an average of approximately 5 years. In addition to the marked differences in baseline GAD-7 scores, the groups differed in baseline PHQ-9 scores. In line with reports that the severity of depressive symptoms is greater in anxious than in nonanxious depression,[12,55–57] baseline PHQ-9 scores were approximately 2.5 points higher in the anxious depression group, a notable finding since the PHQ-9 does not contain items directly assessing anxiety.

Treatment Protocols and Parameters

The anxious and nonanxious groups differed in the TMS protocols they were administered (ITT sample: $\chi^2_3 = 16.22$, $P < .001$; Completer sample: $\chi^2_3 = 16.93$, $P < .001$) (see Table 3). The exclusive use of the HF-LUL protocol was more common in the nonanxious depression group, while the anxious depression group was more likely to receive TMS protocols that were unclassified (eg, < 2,000 pulses per session, 1 Hz over right DLPFC) or protocols that involved SBL stimulation. Accordingly, outcomes for the two groups were evaluated both across all forms of TMS (total ITT and Completer samples) and when restricted to the HF-LUL protocol. The anxious and nonanxious depression groups treated with HF-LUL TMS did not differ in the duration of the TMS course or in virtually all TMS parameters. In the total sample, the nonanxious depression group received slightly more sessions over a slightly longer acute course duration. In the total sample, the difference between the anxious and nonanxious depression groups in treatment parameters reflected the fact that patients with anxiety were more likely to be started on or switched to SBL protocols than nonanxious patients.

Table 4. Clinical Outcomes on the GAD-7 and PHQ-9 for High and Low Anxiety Groups[a,b]

	Total Intent-To-Treat (ITT) Sample			HF-LUL–Only ITT Sample		
	High GAD-7 Score (n = 1,514)	Low GAD-7 Score (n = 306)	*P*	High GAD-7 Score (n = 490)	Low GAD-7 Score (n = 135)	*P*
GAD-7 Outcomes						
Baseline GAD-7 score	16.4 ± 3.3	6.0 ± 2.5	< .001	16.0 ± 3.3	5.6 ± 2.5	< .001
LOCF GAD-7 score	9.2 ± 6.0	4.4 ± 4.3	< .001	8.2 ± 5.8	3.6 ± 4.0	< .001
Difference (pretreatment – posttreatment)	7.2 ± 5.9	1.7 ± 4.4	< .001	7.7 ± 5.9	1.9 ± 4.3	< .001
Effect size (*d*) of GAD-7 score change	1.22	0.39		1.31	0.44	
Response rate, %	47.8	…		52.7	…	
Remission rate, %	26.4	…		32.9	…	
PHQ-9 Outcomes						
Baseline PHQ-9 score	20.9 ± 3.7	18.2 ± 3.8	< .001	20.2 ± 3.8	17.6 ± 4.0	< .001
LOCF PHQ-9 score	10.3 ± 7.0	7.2 ± 5.8	< .001	9.3 ± 6.6	6.5 ± 5.7	< .001
Difference (pretreatment – posttreatment)	10.5 ± 7.2	11.0 ± 6.3	.285	10.8 ± 7.0	11.1 ± 6.7	.646
Effect size (*d*) of PHQ-9 score change	1.46	1.75		1.54	1.66	
Response rate, %	55.2	71.9	< .001	57.3	73.3	< .001
Remission rate, %	24.0	39.2	< .001	27.3	45.9	< .001
	Total Completer Sample			HF-LUL–Only Completer Sample		
	High GAD-7 Score (n = 1,163)	Low GAD-7 Score (n = 266)	*P*	High GAD-7 Score (n = 355)	Low GAD-7 Score (n = 116)	*P*
GAD-7 Outcomes						
Baseline GAD-7 score	16.3 ± 3.3	6.1 ± 2.5	< .001	15.9 ± 3.3	5.6 ± 2.5	< .001
EOA GAD-7 score	8.4 ± 5.8	4.0 ± 3.9	< .001	7.3 ± 5.6	3.1 ± 3.5	< .001
Difference (pretreatment – posttreatment)	7.9 ± 5.8	2.2 ± 4.1	< .001	8.5 ± 5.8	2.6 ± 3.8	< .001
Effect size (*d*) of GAD-7 score change	1.36	0.54		1.47	0.68	
Response rate, %	54.3	…		60.6	…	
Remission rate, %	30.6	…		38.0	…	
PHQ-9 Outcomes						
Baseline PHQ-9 score	20.9 ± 3.7	18.2 ± 3.8	< .001	20.1 ± 3.8	17.7 ± 4.0	< .001
EOA PHQ-9 score	9.3 ± 6.7	6.5 ± 5.2	< .001	8.2 ± 6.2	5.7 ± 5.1	< .001
Difference (pretreatment – posttreatment)	11.6 ± 7.1	11.7 ± 6.0	.827	12.0 ± 6.9	12.0 ± 6.5	1.000
Effect size (*d*) of PHQ-9 score change	1.63	1.95		1.74	1.85	
Response rate, %	63.5	77.4	< .001	66.8	78.4	.017
Remission rate, %	28.4	42.1	< .001	33.2	50.9	< .001

[a]Values are expressed as the mean ± SD unless otherwise indicated.
[b]*P* values derive from *t* test or χ^2 comparisons of the low and high GAD-7 score groups.
Abbreviations: EOA = end of acute treatment; GAD-7 = Generalized Anxiety Disorder-7; HF-LUL = high frequency, left unilateral TMS; LOCF = last observation carried forward; PHQ-9 = Patient Health Questionnaire-9; TMS = transcranial magnetic stimulation

Anxiolytic and Antidepressant Effects

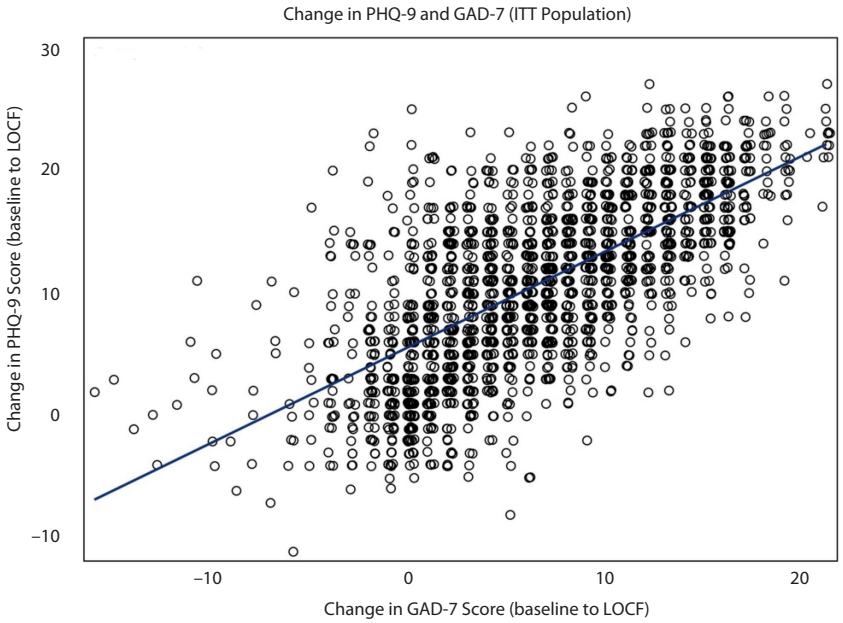
Anxiolytic and antidepressants effects were consistent across the ITT and Completer samples and patients who received any TMS protocol or only HF-LUL TMS (Table 4). GAD-7 scores decreased markedly in the anxious depression group, with the GAD-7 response rates ranging from 47.8% to 60.6% and GAD-7 remission rates ranging from 26.4% to 38.0%. GAD-7 scores also decreased significantly in the nonanxious group (all *P* values < .0001). The effects size for the decrease in GAD-7 scores ranged from 1.22 to 1.47 among the anxious depression samples and from 0.39 to 0.68 among the nonanxious depression samples.

The anxious depressed group scored approximately 2.5 points higher on the PHQ-9 than the nonanxious group both before TMS and at final observation, and the groups did not differ in the magnitude of change in PHQ-9 scores. The effect size for the change in PHQ-9 scores ranged from 1.46 to 1.74 in the anxious depression samples and from 1.66 to 1.95 in the nonanxious depression samples. Both groups showed marked antidepressant effects, with response rates in the anxious depression group ranging from 55.2% to 66.8% and remission rates ranging from 24.0% to 33.2%. Nonetheless, in each comparison, response and remission rates were significantly higher in the nonanxious depression group. Thus, despite the two groups' manifesting the same degree of change in PHQ-9 scores, the higher baseline and post-TMS scores in the anxious depression group resulted in significantly lower response and remission rates. The multivariate ANCOVA and logistic regression analyses confirmed these findings. The nonanxious group had PHQ-9 outcomes superior to those of the anxious group in all comparisons (all *P* values ≤ .002). However, the difference in post-TMS adjusted means was small (ITT sample: 10.2 vs 8.4 in anxious and nonanxious groups), and the groups also did not differ in the absolute extent of symptom improvement after multivariate adjustment.

Correlation Between Anxiolytic and Antidepressant Effects

Figure 1 plots absolute change in GAD-7 scores versus change in PHQ-9 scores for the total ITT sample, $r_{1818} = 0.69$, $P < .001$. The relationship was robust in the anxious depression group ($r_{1512} = 0.75$, $P < .001$) and less robust in the nonanxious depression group ($r_{304} = 0.50$, $P < .001$), in which patients had much lower baseline GAD-7 scores. This pattern was consistent across all the samples. In the anxious

Figure 1. Change in GAD-7 Scores Plotted Against Change in PHQ-9 Scores for the Total ITT Sample (N = 1,820)[a]



[a]On each scale, positive values indicate symptomatic improvement and negative values reflect worsening.
Abbreviations: GAD-7 = Generalized Anxiety Disorder-7, ITT = intent-to-treat, LOCF = last observation carried forward, PHQ-9 = Patient Health Questionnaire-9.

depression group, change in GAD-7 and PHQ-9 scores shared approximately 60% variance.

DISCUSSION

At the outset, we posed 4 questions to be addressed in this study. The first was, "Do providers administer different TMS protocols to patients with anxious and nonanxious depression?" We found that exclusive use of the HF-LUL TMS protocol was more likely in the nonanxious depressed group, while the SBL TMS protocol was used more commonly in the anxious depressed group.

The second question was, "Does treatment with TMS for MDD have clinically significant anxiolytic effects in patients with anxious depression?" In by far the largest sample collected to date of patients with anxious depression treated with TMS, there were marked and clinically meaningful anxiolytic and antidepressant effects in self-report measures. In this group, on average, GAD-7 scores were approximately halved following TMS compared to baseline, and approximately 50% of patients were classified as anxiety symptom responders and 30% as remitters.

The third question was, "Are patients with anxious depression less likely to have a clinically significant antidepressant response?" The anxious depressed group had comparable reductions in PHQ-9 scores over the TMS course when compared to a similar nonanxious depression group treated at the same sites. Since the anxious depression group also had higher PHQ-9 scores at baseline, they were less likely to meet traditional categorical thresholds for antidepressant response and remission despite the same change in depression severity scores. In this respect, the findings are consistent with multiple reports that severity of depressive symptoms is greater in anxious depression[12,55–57] and a large pharmacologic literature that documents reduced antidepressant effects.[5,12–16] The differences between the anxious and nonanxious groups in depression efficacy measures were relatively minor compared to the magnitude of the antidepressant effects observed in both groups and the anxiolytic effects observed in the anxious depression group.

The fourth question was, "To what extent does improvement in depression symptoms covary with improvement in anxiety symptoms?" The findings also indicted that the extent of improvement in depression severity scores over the TMS course was highly correlated with the change in anxiety severity scores. Providers can generally expect that if there is improvement in one domain, there will be improvement in the other domain. This information may be useful when educating patients about the potential benefits of TMS, gauging treatment progress, and in managing concomitant pharmacotherapy during TMS.

At the mechanistic level, the strong concordance between improvement in anxiety and depression symptoms among patients treated with the HF-LUL protocol suggests that TMS delivered to the left DLPFC with a relatively focal figure-8 coil[58] modulates in a similar manner the circuitry subserving therapeutic effects in these symptom domains. Nonetheless, it is also possible that spatially disparate targets or other variation in TMS protocols may be optimal in treating different depression subtypes or symptom constellations,

especially since the correlation between anxiolytic and antidepressant effects, while robust, was imperfect. Indeed, in this study the anxious and nonanxious depression groups differed in the TMS protocols they were administered, with less utilization of HF-LUL treatment in the anxious depression group. While the method used to position the coil over the DLPFC target was not documented, the spatial coordinates of the coil position were routinely recorded, and future research may test whether coil positioning and other protocol variations are systematically associated with the magnitude of anxiolytic and/or antidepressant effects.

Although the clinical data examined in this study were prospectively collected, a limitation is the retrospective nature of the analyses, as key design considerations involved retrospective application of decision rules. The classification of participants as anxious or nonanxious was based on a threshold retrospectively applied to the baseline GAD-7 score, with a single point on this scale defining the boundary between these two groups. The determination of when the acute TMS course ended was based on a minimum gap of 7 days without receiving TMS, as opposed to prospective documentation of when the acute course was terminated.

Another limitation of this study is the fact that the GAD-7 was administered at only a minority of the registry sites and inconsistently among patients treated at individual sites. Undoubtedly, the desire to track anxiety symptoms in symptomatic patients drove use of the GAD-7, and the rates of anxious and nonanxious depression in this study may not be representative of the total registry. Nonetheless, such a selection bias enriched this sample with patients presenting with anxious depression. It is noteworthy that the antidepressant effects observed in the anxious depression group were similar in magnitude to those reported for the much larger registry sample.[24,39] The findings indicate that, in this subgroup, routine TMS in diverse clinical settings results in marked anxiolytic and antidepressant effects. Furthermore, the extents of improvement in anxiety and depression symptoms are strongly linked.

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