# Impact of Comorbid PTSD on Outcome of Repetitive Transcranial Magnetic Stimulation (TMS) for Veterans With Depression

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## ABSTRACT

***Objective:*** A recent randomized controlled trial of repetitive transcranial magnetic stimulation (TMS) for major depressive disorder (MDD) in veterans raised the question of whether comorbid posttraumatic stress disorder (PTSD) negatively impacted the outcome of TMS in veterans. To address this, a quality database was analyzed to compare outcomes of MDD treated with TMS in veterans with and without comorbid PTSD.

***Methods:*** The clinical outcomes of all consecutive veterans with MDD treated with TMS at the James A. Haley Veterans' Hospital as outpatients from October 2013 through September 2018 were included. Patients were initially evaluated by an experienced psychiatrist, and the diagnosis of MDD was made by clinical evaluation per *DSM-IV-TR*/*DSM-5* criteria. At the start of treatment, after every 5 treatments, and at the end of treatment, patients were assessed with self-report and clinician-rated scales of depression. All data were abstracted from an existing quality database.

***Results:*** Among the 118 patients treated with TMS for depression, 55 (47%) had comorbid PTSD and 63 (53%) had no comorbid PTSD. Response and remission rates by score on the Montgomery-Asberg Depression Rating Scale were similar between patients with PTSD (52.5% and 40.9%, respectively) and without PTSD (53.8% and 35.6%, respectively). No seizures or persistent adverse effects were observed or reported in either group.

***Conclusions:*** Comorbid PTSD did not impact the outcome of TMS for depression in this sample of veterans. Future studies should include formal ratings of PTSD to determine if the severity of PTSD affects the outcome.

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Major depressive disorder (MDD) is a significant cause of morbidity and mortality.[1–4] While treatments including medications and psychotherapy are available, there are limitations in tolerability, efficacy, and feasibility.[5,6] Transcranial magnetic stimulation (TMS) is an evidence-based, noninvasive treatment for MDD with demonstrated antidepressant effect.[7–10] When MDD is comorbid with posttraumatic stress disorder (PTSD), there is an interactive effect that worsens the symptoms of both illnesses.[11] Steiner et al[12] reported that patients with comorbid MDD and PTSD were less likely to achieve remission of MDD when treated with citalopram monotherapy compared to patients with MDD without comorbid PTSD. Comorbid MDD and PTSD have also been studied as it relates to treatment with TMS. In a 2018 open-label study, Carpenter et al[13] reported that patients with comorbid MDD and PTSD experienced significant improvement in symptoms of both illnesses when treated with 5-Hz TMS. There was, however, no comparison group with only MDD. In 2018, Yesavage et al[14] conducted a double-blind, randomized, sham-controlled clinical trial comparing TMS to sham for treatment-resistant MDD in the Department of Veterans Affairs (VA). They reported no difference between TMS and sham treatment. In a post hoc analysis of the data, they compared the outcomes of participants with and without comorbid PTSD. The rates of remission were much higher for participants with MDD without PTSD (48.8%) compared to those with comorbid PTSD (32.5%) in the active group. Additionally, the difference between the rates of remission for active versus the sham group was much greater for those without comorbid PTSD than for participants with comorbid PTSD. Yesavage et al proposed a potential moderating effect of PTSD comorbidity on TMS treatment.

In addition to comorbid PTSD as a potential predictor of outcome with TMS for depression, other predictors of response to TMS are an important topic of current investigation.[15] Patient demographics such as age and sex have been proposed as predictors of response.[15,16] Several prior studies[15–17] have reported that advanced age is a negative predictor of response to TMS. In many of these studies, TMS treatment parameters are substantially different from those used in current clinical practice. Pallanti et al[15] reported that the antidepressant effect of TMS negatively correlated with age during use of a treatment protocol in which patients received fewer total treatments (15 over 3 weeks) at lower intensity (110%) and with dramatically fewer pulses per session (420) than what

**Clinical Points**

- Predictors of response for transcranial magnetic stimulation (TMS) are an area of current research, and a recent publication proposed that posttraumatic stress disorder (PTSD) would negatively influence TMS outcomes in the treatment of depression.
- In a veteran clinic population, patients with PTSD had levels of major depressive disorder response and remission with TMS comparable to those of patients without PTSD. Older patients and patients with lower baseline anxiety tended to have better outcomes.

is now typical practice.[18] Fregni et al[17] also reported age as a negative predictor of response using treatment protocols with similar differences from current practice parameters. The observation that age was a negative predictor of outcome in the older TMS literature is very likely attributable to differences in atrophy for motor and prefrontal cortices (ie, distance to prefrontal cortex is greater than distance to motor cortex).[19,20] This difference in distance is significant, as the dose of treatment over the prefrontal cortex is determined by the dose of TMS over the motor cortex required to move the fingers. Importantly, the negative impact of increased age on the outcome of TMS for MDD can be ameliorated by adjusting treatment parameters (ie, using 120% motor threshold).[21]

Clinical characteristics such as the severity of depressive symptoms and the duration of depressive episode have been shown to predict response to TMS.[15] Comorbid anxiety has been shown to negatively affect outcomes in MDD treated with medication[22,23]; evidence with TMS, however, has been mixed. In 2009, Lisanby et al[24] investigated clinical predictors of outcome using data from a randomized, sham-controlled trial of TMS for depression that was followed by an open extension treatment phase. A comorbid anxiety disorder was reported as negatively predicting TMS outcomes in the open-label extension phase but not the controlled portion of this trial. More recently, Clarke et al[25] assessed the influence of anxiety on outcomes of patients treated with TMS in their clinic and found that anxiety did not affect outcomes in their patients.

The use of different medications during TMS treatment has also been investigated as a predictor of response.[15] Antiepileptic drugs (AEDs) are a class of medications with various mechanisms used to treat seizure disorders. Since some AEDs have shown benefit in mood disorders,[26] patients undergoing treatment with TMS would quite likely be prescribed AEDs. All AEDs, regardless of mechanism of action, modulate neuronal excitability.[27] The effects of this modulation can be seen with changes in TMS-evoked electroencephalography potentials[28] and changes in the resting motor threshold.[29] Some clinicians have expressed concern that use of AEDs during treatment with TMS may negatively impact outcomes, though to date there have been no systematic studies evaluating this hypothesis. Specifically for lamotrigine, however, there are prior studies[30,31] with TMS and functional MRI that point toward a unique interaction that may indicate improved outcomes.

TMS is a part of routine clinical practice and is available within the VA. After the VA released an evidence brief on TMS[32] that identified the need for more data regarding the use of TMS in typical VA populations, we developed and examined a quality database of patients treated at our TMS clinic at the James A. Haley Veterans' Administration Hospital and Clinics.[33] We have continued to expand our database as more patients are treated. The primary goal of this study was to identify possible prognostic factors associated with treatment response for patients undergoing TMS. We assessed whether, similar to the findings of Yesavage et al,[14] patients with comorbid MDD and PTSD would have significantly different outcomes compared to patients with MDD but no PTSD. We anticipated that, as in patients with MDD treated with medication, comorbid anxiety would predict a lower likelihood of response or remission compared to absence of comorbid anxiety. We also examined whether the use of concomitant neuropsychiatric medications while undergoing TMS would have an effect on patients' outcomes or tolerability of treatments.

## METHODS

Primary mental health providers referred patients to the James A. Haley TMS Clinic for treatment-resistant MDD. Referral sources included the James A. Haley Hospital as well as other VA facilities throughout the Veterans Integrated Service Networks. Patients were given a diagnosis of MDD per *DSM-IV-TR*/*DSM-5* criteria and were evaluated by a credentialed TMS provider for the appropriateness of TMS. Patients with active substance use disorders were deemed not appropriate for TMS and were referred for treatment of their substance use. Patients who were deemed appropriate candidates for TMS and interested in undergoing TMS were scheduled for a motor threshold assessment and treatment. Patients were treated using the NeuroStar (Neuronetics; Malvern, Pennsylvania) or Magstim Rapid2 (Magstim Inc; Eden Prairie, Minnesota). Patients filled out rating scales at the beginning of treatment, after every 5 subsequent treatments, and at the conclusion of treatment to monitor their clinical progress. Patients self-rated their depressive symptoms with the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR)[34,35]; anxiety symptoms with the Generalized Anxiety Disorder 7-item scale (GAD-7)[36]; side effects with the Frequency, Intensity, and Burden of Side Effects Rating (FIBSR)[37]; and overall level of functioning with the Work and Social Adjustment Scale (WSAS).[38] In addition, beginning in April 2015, experienced psychiatric nurses administered the Montgomery-Asberg Depression Rating Scale (MADRS)[39] during the treatment on the same days that the self-rating scales were completed (see Van Trees et al[40] for a more detailed description of the treatment method).

As part of the quality monitoring process to ensure our clinic conformed to expected norms, a database

of information, including the characteristics and outcomes of patients, was maintained that included all patients treated in our TMS clinic. All data acquired were only for the clinical management of the patient. The database was determined by the James A. Haley Research and Development program to be part of a clinical quality evaluation project. The analysis of that database was reviewed by the University of South Florida Institutional Review Board and was deemed to meet criteria as exempt as well as being approved by the James A. Haley Research and Development program committee. Thus, all the regulatory requirements were attained. The database included all patients in the TMS clinic who initiated at least 1 TMS session starting on or after October 1, 2013. Patients without TMS treatments after the initial consultation in the TMS clinic and those who did not complete their TMS treatment by September 30, 2018, were not included in this report.

Patient information entered into the database was deidentified. The quality database recorded demographic information, psychiatric diagnoses, patient clinical characteristics, treatment parameters, and clinical instrument scores (ie, QIDS-SR, GAD-7, FIBSR, WSAS, and MADRS scores). These data were gathered from reviewing patients' medical charts in the Computerized Patient Record System; specifically, the notes documenting their initial evaluation at the TMS clinic and their subsequent daily TMS treatments were reviewed. Demographics, diagnoses, and clinical characteristics reflect those at the beginning of treatment. Clinical characteristics included psychotropic medications that patients were prescribed. The psychotropic medications recorded in the database were selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine), atypical antidepressants (mirtazapine, trazodone, nefazodone, vilazodone, bupropion, vortioxetine), antiepileptic drugs (valproic acid, carbamazepine, oxcarbazepine, lamotrigine, topiramate, levetiracetam, tiagabine), lithium, stimulants (amphetamine/methylphenidate-class psychostimulants, modafinil/armodafinil), dopamine agonists (ropinirole, pramipexole, cabergoline, bromocriptine), atypical antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, lurasidone, iloperidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, sertindole, ziprasidone), tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, lorazepam), non-benzodiazepine γ-aminobutyric acid modulators (eszopiclone, zaleplon, zolpidem, zopiclone), monoamine oxidase inhibitors (isocarboxazid, phenelzine, selegiline, tranylcypromine), and atypical anxiolytics (buspirone, hydroxyzine, diphenhydramine). As treatment parameters are titrated at the beginning of a course of treatment, these values were obtained using data from the end of treatment. Clinical instrument scale scores were gathered from the TMS daily treatment notes. Treatment side effects were

**Table 1. Demographics and Clinical Characteristics[a]**

| Variable | With Data, n | Value |
|---|---|---|
| Age, median (range), y | 118 | 55.5 (24–71) |
| Sex | | |
| Male | 118 | 100 (84.7) |
| Female | 118 | 18 (15.3) |
| Race | | |
| White | 113 | 93 (78.8) |
| African American | 113 | 13 (11.0) |
| Pacific Islander | 113 | 3 (2.5) |
| Other/unknown[b] | 113 | 9 (7.6) |
| No. of psychiatric medications, median (range) | 118 | 3 (0–8) |
| SSRIs[c] | 118 | 41 (34.7) |
| SNRIs[d] | 118 | 46 (39.0) |
| Atypical antidepressants[e] | 118 | 52 (44.1) |
| Antiepileptic drugs[f] | 118 | 8 (6.8) |
| Lamotrigine | 118 | 11 (9.3) |
| Stimulants[g] | 118 | 1 (0.8) |
| Dopamine agonists[h] | 118 | 5 (4.2) |
| Atypical antipsychotics[i] | 118 | 30 (25.4) |
| TCAs[j] | 118 | 1 (0.8) |
| Benzodiazepines[k] | 118 | 30 (25.4) |
| Non-benzodiazepine GABA modulators[l] | 118 | 22 (18.6) |
| Lithium | 118 | 6 (5.1) |
| MAOIs[m] | 118 | 2 (1.7) |
| Atypical anxiolytics[n] | 118 | 18 (15.3) |
| Gabapentin/pregabalin | 118 | 35 (29.7) |
| Prior ECT | 117 | 6 (5.1) |
| Prior TMS | 118 | 16 (13.6) |
| No. of prior psychiatric diagnoses, median (range) | 118 | 3 (1–4) |
| PTSD | 118 | 55 (46.6) |
| MDD | 118 | 109 (92.4) |
| Baseline score, median (range) | | |
| QIDS-SR | 115 | 18 (6–27) |
| GAD-7 | 115 | 16 (2–21) |
| WSAS | 114 | 32 (15–40) |
| MADRS | 83 | 33 (8–48) |

[a]Values are shown as n (%) unless otherwise noted. For race, percentages are calculated from the whole sample (n = 118).
[b]Hispanic n = 2, mixed n = 1, Native American n = 1, missing = 5.
[c]Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.
[d]Desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine.
[e]Mirtazapine, bupropion, trazodone, nefazodone, vilazodone, vortioxetine.
[f]Antiepileptic drugs other than lamotrigine (valproic acid, carbamazepine, oxcarbazepine, topiramate, levetiracetam, tiagabine).
[g]Amphetamine and methylphenidate-class psychostimulants; modafinil, armodafinil.
[h]Bromocriptine, cabergoline, pramipexole, ropinirole.
[i]Aripiprazole, asenapine, brexpiprazole, cariprazine, lurasidone, iloperidone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, sertindole, ziprasidone.
[j]Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine.
[k]Alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, lorazepam.
[l]Eszopiclone, zaleplon, zolpidem, zopiclone.
[m]Isocarboxazid, phenelzine, selegiline, tranylcypromine.
[n]Hydroxyzine, diphenhydramine, buspirone.
Abbreviations: ECT = electroconvulsive therapy, GABA = γ-aminobutyric acid, GAD-7 = Generalized Anxiety Disorder 7-item scale, MADRS = Montgomery-Asberg Depression Rating Scale, MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, PTSD = posttraumatic stress disorder, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TMS = transcranial magnetic stimulation, WSAS = Work and Social Adjustment Scale.

**Table 2. Demographic and Clinical Characteristics of Patients by PTSD Status[a]**

| Variable | Patients Without PTSD (n = 63) | Patients With PTSD (n = 55) | *P* Value |
|---|---|---|---|
| Age, median (range), y | 54 (24–70) | 56 (30–71) | .271 |
| Sex | | | .76 |
| Male | 57 (90.5) | 43 (78.2) | |
| Female | 6 (9.5) | 12 (21.8) | |
| Race | | | .565 |
| White | 49 (77.8) | 44 (80.0) | |
| African American | 6 (9.5) | 7 (12.7) | |
| Other/unknown | 8 (12.7) | 4 (7.2) | |
| No. of psychiatric medications, median (range) | 3 (0–5) | 3 (0–8) | .516 |
| SSRIs | 19 (30.2) | 22 (40) | .333 |
| SNRIs | 25 (39.7) | 21 (38.2) | 1.000 |
| Atypical antidepressants | 28 (44.4) | 24 (43.6) | 1.000 |
| Antiepileptic drugs | 5 (7.9) | 3 (5.5) | .722 |
| Lamotrigine | 4 (6.3) | 7 (12.7) | .343 |
| Stimulants | 0 | 1 (1.8) | .466 |
| Dopamine agonist | 4 (6.3) | 1 (1.8) | .370 |
| Atypical antipsychotics | 12 (19.0) | 18 (32.7) | .096 |
| TCAs | 1 (1.6) | 0 | 1.000 |
| Benzodiazepines | 16 (25.4) | 14 (25.5) | 1.000 |
| Non-benzodiazepine GABA modulators | 11 (17.5) | 11 (20.0) | .814 |
| Lithium | 4 (6.3) | 2 (3.6) | .684 |
| MAOIs | 2 (3.2) | 0 | .498 |
| Atypical anxiolytics | 12 (19.0) | 6 (10.9) | .306 |
| Gabapentin/pregabalin | 16 (25.4) | 19 (34.5) | .316 |
| Prior ECT | 4 (6.3) | 2 (3.6) | .684 |
| Prior TMS | 7 (11.1) | 9 (16.4) | .428 |
| No. of prior psychiatric diagnoses, median (range) | 3 (1–4) | 4 (2–4) | < .001 |
| MDD | 58 (92.1) | 51 (92.7) | 1.000 |
| Baseline score, median (range) | | | |
| QIDS-SR | 17 (6–27) | 18 (9–25) | .305 |
| GAD-7 | 14 (2–21) | 16 (4–21) | .036 |
| WSAS | 31 (15–40) | 34 (19–40) | .036 |
| MADRS | 32 (8–45) | 34 (22–48) | .267 |

[a]Values are shown as n (%) unless otherwise noted.

Abbreviations: ECT = electroconvulsive therapy, GABA = γ-aminobutyric acid, GAD-7 = Generalized Anxiety Disorder 7-item scale, MADRS = Montgomery-Asberg Depression Rating Scale, MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, PTSD = posttraumatic stress disorder, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TMS = transcranial magnetic stimulation, WSAS = Work and Social Adjustment Scale.

included in the database only if they were significant enough to impact treatment or to cause termination of treatment.

The demographic characteristics of the patients and tolerability of the TMS treatments were evaluated in all patients who started treatment. Response was defined as ≥ 50% change in QIDS-SR and MADRS scores from baseline to last treatment. Remission was defined as a score ≤ 5 on the QIDS-SR and ≤ 10 on MADRS at the time of last treatment. Thus, response measures required at least two measures and remission required only one.

Differences in baseline characteristics between patients with and without PTSD were evaluated using $\chi^2$ test for the categorical variables and the Wilcoxon rank sum test for continuous variables. Response and remission rates for patients with and without PTSD were compared using $\chi^2$ analysis. Subgroup analysis determined rates of response and remission for patients who received the minimum effective treatment course, which was defined as at least 20 treatments. Association of demographic characteristics with response and remission rates was calculated using univariable logistic regression. Association between baseline GAD-7 score and likelihood of response and remission was calculated using the Wald test. The effect of medications on response and remission rates was analyzed by $\chi^2$ test. For instances when event rates were less than 5, we used the Fisher exact test. Categorical data are reported as number and percentage with event, and continuous data are reported as median and range. Analyses were performed using IBM SPSS Statistics version 25 (Armonk, New York: IBM Corp; 2017).

## RESULTS

A total of 118 veterans received TMS at the James A. Haley Veterans' Hospital from October 2013 through September 2018. Demographics and clinical characteristics of the sample are listed in Table 1. Of the 118 patients treated in the TMS clinic, all were included in the analysis. Baseline QIDS-SR data were available for 115 of these patients. MADRS data were available for 83 patients as it was not administered until fiscal year 2015.

For all patients treated in the TMS clinic, the rates of response and remission as measured by the QIDS-SR were

**Table 3. Response Rates, Remission Rates, Baseline and Last Observation Scores, and Change From Baseline for Patients With MDD by PTSD Status**

| Variable | N | Overall | MDD Without PTSD | MDD With PTSD | *P* Value (PTSD vs no PTSD) |
|---|---|---|---|---|---|
| QIDS-SR | | | | | |
| Response, n/total n (%) | 108 | 39/108 (36.1) | 20/58 (34.5) | 19/50 (38.0) | .704 |
| Remission, n/total n (%) | 110 | 23/110 (20.9) | 12/58 (20.7) | 11/52 (21.2) | .952 |
| Baseline score, mean (SD) | 108 | 17.77 (3.825) | 17.29 (3.830) | 18.32 (3.782) | .305 |
| Last observation, mean (SD) | 108 | 11.30 (5.997) | 10.72 (5.770) | 11.96 (6.243) | .258 |
| Change from baseline score, mean difference (95% CI) | 108 | 6.472 (5.398 to 7.547) | 6.569 (5.064 to 8.073) | 6.360 (4.773 to 7.947) | .732 |
| *P* value (baseline vs last observation) | | < .001 | < .001 | < .001 | |
| MADRS | | | | | |
| Response, n/total n (%) | 79 | 42/79 (53.2) | 21/39 (53.8) | 21/40 (52.5) | .905 |
| Remission, n/total n (%) | 89 | 34/89 (38.2) | 16/45 (35.6) | 18/44 (40.9) | .603 |
| Baseline score, mean (SD) | 79 | 32.97 (7.122) | 31.64 (7.912) | 34.28 (6.076) | .267 |
| Last observation, mean (SD) | 79 | 16.76 (12.072) | 16.18 (12.392) | 17.33 (11.881) | .706 |
| Change from baseline score, mean difference (95% CI) | 79 | 16.215 (13.608 to 18.822) | 15.462 (11.607 to 19.316) | 16.950 (13.276 to 20.624) | .670 |
| *P* value (baseline vs last observation) | | < .001 | < .001 | < .001 | |

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder PTSD = posttraumatic stress disorder, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report.

**Table 4. Demographics as Predictors of Outcomes**

| Outcome | Odds Ratio | 95% CI | *P* Value |
|---|---|---|---|
| MADRS response | | | |
| Age | 1.054 | 1.014 to 1.096 | .008 |
| Sex | 1.650 | 0.442 to 6.160 | .456 |
| Race (white vs other) | 1.104 | 0.399 to 3.057 | .849 |
| MADRS remission | | | |
| Age | 1.074 | 1.029 to 1.120 | .001 |
| Sex | 2.117 | 0.646 to 6.941 | .216 |
| Race (white vs other) | 0.901 | 0.332 to 2.445 | .838 |
| QIDS-SR response | | | |
| Age | 1.043 | 1.006 to 1.081 | .022 |
| Sex | 2.286 | 0.759 to 6.882 | .142 |
| Race (white vs other) | 2.071 | 0.801 to 5.354 | .133 |
| QIDS-SR remission | | | |
| Age | 1.041 | 0.997 to 1.0870 | .071 |
| Sex | 3.059 | 0.960 to 9.744 | .059 |
| Race (white vs other) | 1.353 | 0.466 to 3.927 | .578 |

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report.

36.1% (39/108) and 20.9% (23/110), respectively. The rates of response and remission as measured by the MADRS were 53.2% (42/79) and 38.2% (34/89), respectively. A subgroup analysis was performed including only patients who received a minimum adequate treatment of TMS that was defined as 20 treatments. Ninety-seven (82%) were treated for a minimum of 20 treatments. Those receiving a minimum number of TMS treatments demonstrated response in 39 (41%) of 95 patients with QIDS-SR data and 42 (60%) of 70 with MADRS data available. The number achieving remission was 23 (24%) of 97 for the QIDS-SR and 33 (42%) of 78 using the MADRS.

Separating the sample into groups based on the presence of comorbid PTSD, demographic and clinical characteristics were similar between those groups with some differences (see Table 2). Baseline GAD-7 and WSAS scores, as well as the number of psychiatric diagnoses, were all higher in the group of patients with PTSD. Rates of response and remission of depressive symptoms as measured by the QIDS-SR and MADRS were similar for patients with PTSD and patients without PTSD (see Table 3). There was a significant improvement in QIDS-SR score between baseline and last treatment (mean difference = 6.472; 95% CI, 5.398 to 7.547). There was also a significant difference between MADRS score at baseline and last treatment (mean difference = 16.215; 95% CI, 13.608 to 18.822).

Anxiety levels reduced the chance of response. For this sample, the median baseline GAD-7 score was 16 (range, 2–21). For each point value of increase in the baseline GAD-7 score, the odds of achieving MADRS response and remission were 21.9% lower (odds ratio [OR] = 0.881; 95% CI, 0.796 to 0.976; $P = .015$) and 9.0% lower (OR = 0.910; 95% CI, 0.829 to 0.999; $P = .047$), respectively. For each point value of increase in the baseline GAD-7 score, the odds of achieving QIDS-SR response and remission were 8.0% lower (OR = 0.920; 95% CI, 0.844 to 1.002; $P = .056$) and 5.2% lower (OR = 0.948; 95% CI, 0.860 to 1.045; $P = .284$), respectively.

The predictors of outcome based on demographic information provided intriguing results. While sex and race did not correlate with response or remission, there was a positive correlation between age and rate of response and rate of remission (see Table 4). This finding is counter to prior reports that identified increasing age as a negative predictor of clinical outcome.

No medication or class of medications that were analyzed consistently demonstrated a significant worsening of outcome (see Table 5 for medications with number of participants sufficient for analysis). Lamotrigine was recorded separately from other antiepileptic medications due to its unique impact on TMS as measured by interleaved TMS/functional magnetic resonance imaging (fMRI). Of the 110 patients included in the analysis, 11 were taking lamotrigine. Due to the asymmetrical size of these groups, testing for significance was not performed. Rates of response and remission as measured by the MADRS were

**Table 5. Medication Effect on Response and Remission Rates**

| Outcome | Without Drug, n (%)[a] | With Drug, n (%)[a] | *P* Value |
|---|---|---|---|
| Benzodiazepines | | | |
| MADRS response | 30 (52.6) | 12 (54.5) | .640 |
| MADRS remission | 26 (39.4) | 8 (34.8) | .361 |
| QIDS response | 28 (35.0) | 11 (39.3) | .684 |
| QIDS remission | 19 (23.5) | 4 (13.8) | .425 |
| Atypical anxiolytics | | | |
| MADRS response | 37 (54.4) | 5 (45.5) | .581 |
| MADRS remission | 31 (40.3) | 3 (25.0) | .360 |
| QIDS response | 33 (35.9) | 6 (37.5) | .900 |
| QIDS remission | 22 (23.4) | 1 (6.3) | .119 |
| Gabapentin | | | |
| MADRS response | 32 (54.5) | 10 (50.0) | .743 |
| MADRS remission | 25 (38.5) | 9 (37.5) | .934 |
| QIDS response | 26 (33.3) | 13 (43.3) | .333 |
| QIDS remission | 15 (18.8) | 8 (26.7) | .363 |
| Atypical antidepressants | | | |
| MADRS response | 25 (55.6) | 17 (50.0) | .591 |
| MADRS remission | 23 (44.2) | 11 (29.7) | .295 |
| QIDS response | 28 (45.2) | 11 (23.9) | .023 |
| QIDS remission | 13 (20.6) | 10 (21.3) | .935 |
| SSRIs | | | |
| MADRS response | 34 (63.0) | 8 (32.0) | .010 |
| MADRS remission | 28 (45.2) | 6 (22.2) | .041 |
| QIDS response | 29 (41.4) | 10 (26.3) | .118 |
| QIDS remission | 18 (25.0) | 5 (13.2) | .146 |
| SNRIs | | | |
| MADRS response | 19 (43.2) | 23 (65.7) | .046 |
| MADRS remission | 14 (28.0) | 20 (51.3) | .025 |
| QIDS response | 21 (31.8) | 18 (42.9) | .244 |
| QIDS remission | 10 (14.9) | 13 (30.2) | .054 |
| Atypical antipsychotics | | | |
| MADRS response | 34 (56.7) | 8 (42.1) | .268 |
| MADRS remission | 28 (40.6) | 6 (30.0) | .391 |
| QIDS response | 31 (38.3) | 8 (29.6) | .418 |
| QIDS remission | 22 (26.5) | 1 (3.7) | .013 |

[a]Number of patients used to calculate percentages varied due to available data.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

87.5% and 44.4%, respectively, for those taking lamotrigine compared to rates for those not taking lamotrigine, which were 49.3% and 37.5%, respectively. Rates of response and remission as measured by the QIDS-SR were 75.0% and 20.0%, respectively, for those taking lamotrigine compared to rates for those not taking lamotrigine, which were 33.0% and 21.0%, respectively.

## DISCUSSION

The findings from our study demonstrate TMS to be an effective treatment option for veterans with MDD. Response and remission rates as measured by validated patient-rated (QIDS-SR, 36.1% and 20.9%, respectively) and clinician-rated (MADRS, 53.2% and 38.2%, respectively) scales were robust given that the population treated was very treatment-resistant and had multiple comorbidities. These rates were similar to those described elsewhere in the literature.[41–43] TMS treatments were generally very well tolerated, and no patients developed persistent side effects or seizures during treatment.

The results of our analysis do not support the proposed moderating of effect of PTSD on MDD outcomes in treatment with TMS. Patients with comorbid PTSD responded equally well to TMS as those without PTSD by both patient-rated and clinician-rated scales. In our database, demographics and clinical characteristics were similar overall for patients with and without comorbid PTSD, but with some differences. Patients with PTSD had a greater number of psychiatric diagnoses than those without PTSD, as would be expected by such a grouping. Baseline GAD-7 and WSAS scores were higher in those with PTSD than those without, reflecting higher levels of anxiety and dysfunction, but patients with PTSD responded equally well. There are several possibilities for this difference in findings between our study and the outcomes reported by Yesavage et al.[13] A factor that is not accounted for in our comparison is the severity of PTSD symptoms. The severity of PTSD symptoms was not routinely measured in our TMS clinic. If there was a significant difference in the degree of symptom burden from PTSD between our sample and the sample analyzed by Yesavage et al, it may account for the different findings. In addition, the study by Yesavage and colleagues was a randomized controlled trial versus standard clinical care. Our experienced TMS treatment nurses were not limited in their interactions with patients, which may account for the lack of impact that PTSD had on outcomes in our sample.

Anxiety negatively predicted the outcome of TMS for depression in a graded manner. Higher scores on the patient-rated anxiety scale (GAD-7) corresponded with lower rates of response or remission. This relationship was statistically significant for MADRS rates of response ($P = .015$) and remission ($P = .047$) but not QIDS-SR response ($P = .056$) and remission ($P = .284$). Future analyses on other datasets are needed to determine if this relationship holds. If this relationship holds in future analyses, an important question to address is whether other treatment parameters might ameliorate this difference, as the vast majority of patients treated in this database received left dorsolateral prefrontal 10-Hz stimulation. Specifically, a greater degree of anxiety may direct the use of right dorsolateral prefrontal 1-Hz stimulation or bilateral stimulation.

In our analysis, there was a clinically small but statistically significant positive correlation between age and both response and remission. This finding is the opposite of that from prior reports in the literature[15–17] suggesting that older age predicts worse outcomes in TMS. This difference may be due to changes in treatment parameters over time. With higher intensity of stimulation based on larger percentage of motor threshold, current TMS treatment parameters may now be effectively stimulating targeted neural networks in older patients despite the cortical atrophy seen in this population. Other factors should be investigated in future studies to better understand this relationship between age and outcome.

Eleven patients in the database were taking lamotrigine during their treatment. While the conventional wisdom of some clinicians has been to avoid the use of anticonvulsants,

including lamotrigine, in patients undergoing TMS, there have been no reports in the literature of associated negative outcomes or moderation of clinical response. Since the number of patients taking lamotrigine in the database was small, neither formal comparison nor hypothesis testing could be performed. We observe that these patients had no adverse effects while taking lamotrigine during treatment with TMS. The rates of response and remission in these patients appear similar; however, larger samples would be needed for a formal analysis. The effects of lamotrigine on cortical activity have been studied previously in 2 studies[30,31] using interleaved TMS/fMRI, which demonstrated that lamotrigine increased activity in the dorsomedial prefrontal cortex with dorsolateral stimulation. The aforementioned results are promising, but further research with a larger number of participants will be needed to adequately establish the role of lamotrigine in TMS.

This report has several limitations. Because this was a quality database of patients treated with TMS, there was no sham treatment or randomization. Thus, TMS effects cannot be separated from effects due to other aspects of treatment. In our database, the number of failed antidepressant trials was not recorded, and as such the degree of treatment resistance could not be factored into the analysis. While the presence of PTSD in patients was carefully evaluated and recorded, monitoring the severity of PTSD symptoms with validated scales was not part of the practice of this clinic. In addition, the nature of trauma was also not determined. Studies have demonstrated that there are neuroanatomical and physiologic differences in individuals who have experienced childhood trauma compared to those with trauma in adulthood.[44,45] Even among those with adult trauma, clinical manifestations may differ based on the type of traumatic event that occurred.[46] The nature of trauma and degree of PTSD symptom burden may have been confounding factors affecting this analysis. These factors could be addressed in the future by recording and categorizing nature of trauma and adding the PTSD Checklist for *DSM-5* (PCL-5) to the scales used to monitor symptoms, which is ongoing in a national VA TMS pilot program. Future databases should also record the number of failed, adequate antidepressant trials during the current episode to reflect the degree of treatment resistance.

## CONCLUSION

Analysis of this quality database supports TMS as an effective treatment for MDD in veterans with and without comorbid PTSD. Increasing age may actually be a positive predictor of clinical TMS outcome for MDD using current treatment parameters. Anxiety appears to negatively predict response to treatment, which may require adjustment of treatment parameters. The use of lamotrigine during TMS did not result in any adverse effects, though future research with a greater number of participants is necessary to further describe the potential effects of lamotrigine on TMS.

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