OPEN

Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in Active-Duty Service Members Improves Depressive Symptoms

Alexandra E. Roach, PhD, Christopher Hines, MD,†‡ Jane Stafford, PhD,* and Scott Mooney, PhD‡§*

Objectives: Current research on the efficacy of repetitive transcranial magnetic stimulation (rTMS) over left dorsolateral prefrontal cortex as a noninvasive therapy for treatment-resistant depression is largely settled science. However, little is known about its efficacy with active-duty service members (ADSMs) with major depressive disorder. In a retrospective chart review, we examined depressive symptom ratings in ADSMs seeking treatment at the US Army Outpatient Behavioral Health Service Clinic at Eisenhower Army Medical Center, Fort Gordon, Ga.

Methods: We reviewed 121 consecutive outpatient charts, which yielded 61 ADSMs who completed a minimum of 20 rTMS sessions for refractory depression, and for whom both pretreatment and posttreatment depressive symptom ratings were available. Pre– and post–Patient Health Questionnaire 9 (PHQ-9) scores were subjected to a paired *t* test, and Reliable Change Indices were calculated to determine both reliable and clinical significance.

Results: Average (SD) pretreatment and posttreatment PHQ-9 scores were 15.8 (6.2) and 12.6 (7.6), respectively. Statistically significant reduction in post–PHQ-9 was demonstrated ($P < 0.001$), with 69% of patients lowering their ratings and 31% demonstrating reliable change (improvement >5.64). Additionally, 20% demonstrated a reliable change that placed them in the nondysfunctional range (post–PHQ-9 <9.6), demonstrating clinical significance.

Conclusions: These data confirm a course of standard rTMS to ADSMs with major depression is promising in reducing depressive symptoms. Given that success and completion rates from this clinic are similar to those reported in civilian populations (80%), rTMS may be an adequate additional treatment or augmentation strategy for refractory depression in ADSMs.

Key Words: TMS, active-duty service members, noninvasive brain stimulation, transcranial magnetic stimulation, treatment-resistant depression

(*J ECT* 2020;36: 279–284)

According to the National Institute of Mental Health's 2016 National Survey on Drug Use and Health,[1] major depressive disorder (MDD) affects 6.7% (16.2 million) of the US adult population. Prevalence is greater in the military,[2] with approximately 12.5% of active-duty service members (ADSMs) meeting formal criteria for MDD. Many ADSMs have other medical and psychiatric comorbidities such as substance use disorders,[3,4] mild traumatic brain injury,[5–7] anxiety disorders,[8] and/or posttraumatic stress disorder (PTSD).[8–11] In a meta-analysis examining MDD and PTSD, Rytwinski et al[9] found significantly higher incidence of MDD/PTSD comorbidity among military personnel when compared with civilians. Complicating matters is the perceived stigma of seeking mental health treatment within the military.[12] For these reasons, continuing to explore new treatment options for ADSMs with MDD in the military setting is of paramount importance to military mental health care.

Currently, the most common form of pharmacotherapy treatments for MDD includes a regimen of 1 or more antidepressant medications that act on specific neurotransmitters involved in mood regulation.[13,14] Although this has proven to be beneficial for behavioral health patients suffering from MDD, approximately one-third of such patients are prescribed antidepressants without clear benefit to their depressive symptoms and are otherwise considered to have variously termed treatment-resistant, treatment-refractory, or pharmacoresistant depression.[15,16] The term treatment-resistant depression (TRD) is commonly used and is broadly defined as "the occurrence of an insufficient clinical response following adequate antidepressant therapy (in terms of dosage, duration, and compliance) among patients diagnosed with major depression."[17] There have also been attempts to stage TRD severity, but they have not been empirically validated.[17,18] It has been reported that ADSMs seek alternative, nonpharmacological remedies for their behavioral health challenges at higher rates than civilian populations.[19] This is most often related to fear of "official" mental health treatment being detrimental to career progression. Additionally, ADSMs may seek alternative therapies to avoid common or perceived adverse effects associated with antidepressants or risk any perceived compromise in their physical or cognitive abilities.[12]

Historically, treatment-resistant MDD has been treated with alternative interventions such as electroconvulsive therapy (ECT) in addition to psychotherapy[20,21] and, more recently, repetitive transcranial magnetic stimulation (rTMS).[22–30] While ECT has shown to be effective in reducing depressive symptoms in severe depression,[21,30] aspects of it, including the use of anesthesia requiring additional medical personnel and the posttreatment recovery time due to both the seizure induction and the medication, render ECT a less optimal therapy for active military personnel.[31] Transcranial magnetic stimulation received US Food and Drug Administration (FDA) approval for TRD in 2008 and is a noninvasive option for treating depression that is a viable alternative to medications and ECT with few adverse effects, minimal personnel required to administer treatment, and little to no recovery time.[23,32]

For 2 decades, rTMS of the left dorsolateral prefrontal cortex has successfully been used therapeutically to reduce depressive symptoms in individuals diagnosed with MDD,[25,33] as well as those with MDD whose symptoms remain antidepressant-resistant.[22,23,27,34,35] Given that rTMS has been shown to be a well-tolerated and effective treatment for TRD in civilian populations,[27,36] it could become an attractive alternative within the

From the *Department of Psychology, University of South Carolina Aiken, Aiken, SC; †Outpatient Behavioral Health Service, Eisenhower Army Medical Center, Fort Gordon; ‡Department of Psychiatry and Health Behavior, Medical College of Georgia at Augusta University, Augusta; and §Neuroscience & Rehabilitation Center, Eisenhower Army Medical Center, Fort Gordon, GA.

Received for publication September 24, 2019; accepted January 22, 2020.

Reprints: Alexandra E. Roach, PhD, University of South Carolina Aiken, 471 University Pkwy, Aiken, SC 29801 (e-mail: alexandraro@usca.edu).

The authors have no conflicts of interest or financial disclosures to report.

DOI: 10.1097/YCT.0000000000000680

military health care system. However, there are scant peer-reviewed publications presenting TMS use with ADSMs (rTMS or other TMS protocols). A 2018 article by Yesavage et al[37] reported on a randomized controlled trial (RCT) comparing active rTMS treatment to sham treatment in 164 military veterans and found no significant difference between the active and sham treatment arms. These results vary significantly from the positive findings in multiple civilian population-based RCTs. The study had high placebo response and was postulated by the authors to be due to the daily interaction with clinicians and rigorous monitoring; however, the results may point to a less effective response in the unique military population. A 2012 study from Carpenter et al[38] used a naturalistic study design to look at rTMS in patients receiving usual clinical care in multiple practice locations (similar to our own clinical site) and did find significant and durable positive effects when using TMS adjunctively to standard care. Here, we attempt to fill this incongruence in the literature with results from an inpatient/outpatient treatment service employing rTMS for MDD in a specific population, ADSMs.

Currently, the Outpatient Behavioral Health Service (OBHS) at Fort Gordon's Dwight D. Eisenhower Army Medical Center, Fort Gordon, Ga, uses rTMS therapy for ADSMs with treatment-resistant MDD. Active-duty service members seeking therapy for depression come into the clinic for treatment evaluation, and if rTMS is the appropriate treatment option for them, they are initiated into the clinical protocol. The clinic is a standard behavioral health treatment program with a typical military clinical population. This article reports on the use of rTMS in ADSMs and provides promising evidence of the effectiveness of rTMS in a real-world military population.

MATERIALS AND METHODS

Patient Population

This was a retrospective study of 121 consecutive ADSMs from the OBHS at Dwight D. Eisenhower Army Medical Center. The data were drawn from an ongoing database collected for quality management review. The data were generated and collected between 2014 and 2017. Since 2014, the OBHS has used rTMS therapy to treat ADSMs with treatment-resistant MDD. Active-duty service members were referred by clinical providers to the TMS intervention suite if they were determined to have refractory depression spectrum diagnosis and had inadequate response to other therapeutic options. Active-duty service members were excluded from the rTMS treatment protocol if they did not meet FDA guidelines for TMS, which includes having nonremovable conductive or ferromagnetic metal hardware near the head (eg, cochlear implant or bullet fragment) or a history of seizures.[39] During this time frame, more than 120 soldiers were treated, and 97 received 20 to 40 individual daily rTMS sessions for 4 to 6 weeks (ie, "completers") using a standard FDA-approved TMS protocol for MDD.

Active-duty service members who underwent a standard course of rTMS for the treatment of MDD between January 2014 and April 2017 were referenced for possible inclusion in the present analysis. During this time frame, the OBHS provided care for 134 consecutive cases, 13 of which were patients returning for follow-up booster sessions, leaving 121 unique patients. For those who received booster rTMS sessions, only data from their first round of treatment were included in the analyses. Ninety-seven of the 121 service members completed at least 20 sessions of rTMS (the remaining 24 patients either had not yet received 20 sessions, or they discontinued treatment during the time frame), and of the 97 completers, 61 had both pretreatment and posttreatment Patient Health Questionnaire 9 (PHQ-9) scores. The PHQ-9 was used to measure clinical improvement with respect to depressive symptoms. As shown in Table 1, independent t tests and Pearson χ^2 analyses demonstrated no statistical differences across age, gender, ethnicity, educational attainment, branch of service, or medical history between patients who were included in the study (n = 61) and those excluded from study (n = 60). Table 1 provides additional military characteristics including the number of deployments and time in military service, all not significantly different between included and excluded patients. The only measure for which there was a significance between groups was the number of daily TMS sessions, $t_{115} = -4.43$, $P < 0.001$, which was due to the inclusionary criteria of a minimum of 20 sessions. Classifications for categorical data including ethnicity and branch of service were determined from standard Army intake demographic questionnaires, and participants voluntarily self-reported this information. Table 2 presents similar findings on baseline levels of PHQ-9, that is, no significant difference between included and excluded patients. The 60 patients not included in the analysis were excluded solely on the basis of missing PHQ-9 data or noncompletion of treatment at the time of chart review.

Measures

Our measure is drawn from a standard battery of self-report questionnaires administered electronically (via Behavioral Health Data Platform) to nearly every service member receiving care within Department of Defense–affiliated behavioral health clinics within and outside the continental United States.

Patient Health Questionnaire 9

The PHQ-9[40–42] was utilized to measure depression severity; its 9 items assess symptom severity over the previous 2-week period, with total scores ranging from 0 to 27, with lower scores indicating less symptom severity. This measure was chosen by the Department of Defense to function as the primary depression screening and response tool because it has been widely studied and validated and has been found to have good internal consistency (Cronbach α of 0.89).[40] The baseline measure for PHQ-9 (pre–PHQ-9) was recorded prior to the start of rTMS treatment, and the posttreatment PHQ-9 (post–PHQ-9) was recorded after a full round of at least 20 rTMS sessions.

Procedures

The NeuroStar TMS Therapy System (Neuronetics, Inc, Malvern, Pa) was utilized. A standard course of rTMS involves patients, including the present patient sample, receiving pulsed magnetic current at 120% motor threshold at 10 Hz with 4 seconds of pulses followed by 10- to 26-second rest repeating for a total of 3000 pulses per session. Typically, treatments occur 5 days a week for 4 to 6 weeks, for a recommended total of 90,000 pulses. Thirty rTMS sessions are preferred, but 20 completed sessions are the minimum for a complete, FDA-approved, standard course. All patients included in this study completed a standard course of rTMS that consisted of at least 20 sessions.

Data Analysis

Effect of rTMS on Treatment Outcome (PHQ-9) and Clinical Significance Test

To test whether depressive symptoms changed significantly over the course of treatment, a paired t test was performed on the pre–PHQ-9 and post–PHQ-9 scores. We used Jacobson and Truax's[43] Reliable Change Index to test for a reliable change and clinical significance. A reliable change in symptom severity

TABLE 1. Demographic Characteristics, Military Branch, and Self-reported Medical History of ADSMs With Means (SD) or Frequencies (%) for Included and Excluded Patients

	Included in TMS Efficacy Analysis (n = 61)	Excluded From TMS Efficacy Analysis (n = 60)	*P*
Demographics, mean (SD) or n (%)			
Age, y	34.8 (8.9)	32.5 (8.6)	0.150
Sex			0.169
Male	51 (83.6)	44 (73.3)	
Female	10 (16.4)	16 (26.7)	
Ethnicity			0.215
Caucasian	43 (70.5)	40 (66.7)	
African American	10 (16.4)	15 (25.0)	
Latino/Hispanic	5 (8.2)	0 (0.0)	
Asian American	1 (1.6)	1 (1.7)	
Native American	0 (0.0)	1 (1.7)	
Other	1 (1.6)	1 (1.7)	
Unknown	1 (1.6)	2 (3.3)	
Education level			0.899
GED	1 (1.6)	1 (1.7)	
High school	12 (19.7)	12 (20.0)	
Some college	7 (11.5)	6 (10.0)	
Associate's degree	10 (16.4)	8 (13.3)	
Bachelor's degree	11 (18.0)	6 (10.0)	
Master's degree	4 (6.6)	4 (6.7)	
Doctorate	4 (6.6)	1 (1.7)	
Unknown	12 (19.7)	22 (36.7)	
Military service			
Branch			0.234
Army	50 (82.0)	55 (91.7)	
Navy	6 (9.8)	2 (3.3)	
Marines	0 (0.00)	2 (3.3)	
Air Force	2 (3.3)	1 (1.7)	
Coast Guard	1 (1.6)	0 (0.0)	
Multiple branches	0 (0.0)	0 (0.0)	
Unknown	2 (3.3)	0 (0.0)	
No. deployments, mean (SD)	2.1 (2.5)	1.5 (1.3)	0.193
Years in service, mean (SD)	12.7 (7.6)	11.8 (8.2)	0.647
Medical history			
History of (yes/no/unknown)			
Cerebrovascular accident (stroke)	0/61/0	0/56/4	*
Parkinson disease	0/49/12	0/42/18	*
Dementia	0/49/12	1/42/17	0.283
Multiple sclerosis	0/49/12	0/42/18	*
Epilepsy	0/60/1	1/54/5	0.294
ADD/ADHD	10/40/11	10/29/21	0.527
Depression	61/0/0	57/0/3	0.332
PTSD	15/33/13	10/30/20	0.517
Alcohol/drug use	21/35/5	17/26/17	0.837
Residential treatment	13/48/0	12/48/0	0.859
Prescription drug history (yes/no/unknown)			
Anxiolytics	25/26/10	22/13/25	0.205
Antidepressants	55/2/4	48/2/10	0.894
Mood stabilizers	5/37/19	6/27/27	0.446
Neuroleptics	4/38/19	5/27/28	0.426
No. daily TMS sessions	28.98 (4.8)	21.95 (11.4)	<0.001
No. days between first and last session	45.43 (14.2)	41.21 (44.6)	0.484

Continued next page

Continuous variables were subjected to between-subjects *t* tests, and categorical data were subjected to Pearson χ^2 analysis. *P* values listed are for tests of significance assuming an α of 0.05 (2-tailed).

*No statistic computed for dichotomous variables with only 1 value endorsed.

ADD/ADHD, attention-deficit disorder/attention-deficit/hyperactivity disorder.

is denoted when the difference between pre–PHQ-9 and post–PHQ-9 is greater than a 5.64-point ($S_{DIFF} \times 1.96$) reduction (ie, greater than what would be expected because of normal variability of an individual on this measure given its internal consistency). Normative values for calculation of the Reliable Change Index were taken from Kroenke et al,[40] who reported a mean of 3.3 (SD, 3.8) for a sample of 474 participants, and dysfunctional values came from our patient pretreatment PHQ-9 scores (Table 2). This gave us a cutoff for subthreshold depression of 9.6 on the post–PHQ-9, meaning that those whose posttreatment PHQ-9 scores were less than 9.6 ([normative mean + pretest "dysfunctional" mean]/2) were considered to no longer be dysfunctional. To assess whether the presence of comorbidity influenced the treatment outcome, we ran a linear regression on the difference score (post–PHQ-9 − prePHQ-9), with comorbidity as a 4-level factor (no comorbidity, PTSD only, substance abuse only, or both PTSD and substance abuse). To assess whether prior history of antidepressant, anxiolytic, mood stabilizers, or neuroleptic medication use influenced the treatment outcome, we ran a linear regression on the difference score, with these 4 dichotomous variables as predictors. All statistical analyses were conducted using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).[44]

RESULTS

Demographic Characteristics

Further characterization of the 61 patients included in this study reveals that the average age was 34.8 (SD, 8.9). Eighty-four percent were male, 71% were white, 16% were African American, 8% were Latino/Hispanic, and 59% had participated in some college. Eighty-two percent were Army, 10% were Navy, and 3% were Air Force. Seventy-nine percent were considered senior noncommissioned officers (ie, advanced to rank E-5+) or commissioned officers. Average time in service was 12.7 (SD, 7.6) years, and the average number of deployments was 2.1 (2.5). Medically, none of the patients had a self-reported preexisting history of cerebrovascular accident or stroke, Parkinson disease, dementia, multiple sclerosis, or epilepsy, whereas 17 (28%) endorsed having had at least 1 concussion. Common psychiatric comorbidities included PTSD (25%) and substance abuse (34%), with as many as 21% having undergone residential treatment for addiction/dual diagnosis. From a psychotherapeutic medical management perspective, 41%, 90%, and 8% of study participants had undergone a trial of anxiolytic, antidepressant, or mood stabilizer, respectively.

TABLE 2. Total Score on the PHQ-9* With Means (SD) for Included and Excluded Patients

Metric	Included in TMS Efficacy Analysis (n = 61)	Excluded From TMS Efficacy Analysis (Pre, n = 20; Post, n = 15)	*P*
PHQ-9			
First session (pre)	15.8 (6.2)	15.3 (5.2)	0.720
Last session (post)	12.6 (7.6)	11.7 (7.0)	0.655

*PHQ-9, the primary variable of interest, a measure of depressive symptom severity. This scale ranges from 0 to 27, with lower scores indicating less symptom severity and higher scores indicating greater symptom severity. *P* values listed are for tests of significance assuming an α of 0.05 (2-tailed).

Some ADSMs were included after a failed trial of therapy secondary to either refusal or inability to undergo a trial of medication. Average number of rTMS sessions completed across a trial of treatment was 29.0 (SD, 4.8), and the average duration of rTMS treatment, start to finish, for study participants was 45.4 (SD, 14.2) days. See Table 1 for complete demographic characteristics and medical histories.

Study Objective: Examining Clinical Effectiveness of rTMS in a Military Setting

Overall, posttreatment PHQ-9 scores decreased compared with pretreatment scores. Average pretreatment baseline PHQ-9 score was 15.8 (SD, 6.2), whereas average posttreatment scores decreased to 12.6 (SD, 7.6). A paired *t* test revealed that the average 3.16-point decrease in depressive symptom ratings was significant, $t_{60} = 3.796$, $P < 0.001$, with a medium effect size (Cohen $d = 0.46$). See Figure 1 for a scatterplot of pretest and posttest scores.

Reliable Change and Clinical Significance

Forty-two patients (69%) showed an improvement (reduction) in PHQ-9 scores. Nineteen patients (31%) demonstrated a reliable change (ie, >5.65-point reduction), with 12 of those 19 individuals (20%) falling in the nondysfunctional range after a standard rTMS treatment, with posttreatment PHQ-9 scores less than 9.56 (our clinical cutoff,[40] see above for explanation). See Figure 1 for a scatterplot of pre–PHQ-9 and post–PHQ-9 scores with the reliable change bands displayed. Scores that fall beyond the right diagonal band on the scatterplot indicate a reliable improvement. Scores that additionally fall below the normative cutoff of 9.6 represent patients who had both a reliable and clinically significant change.

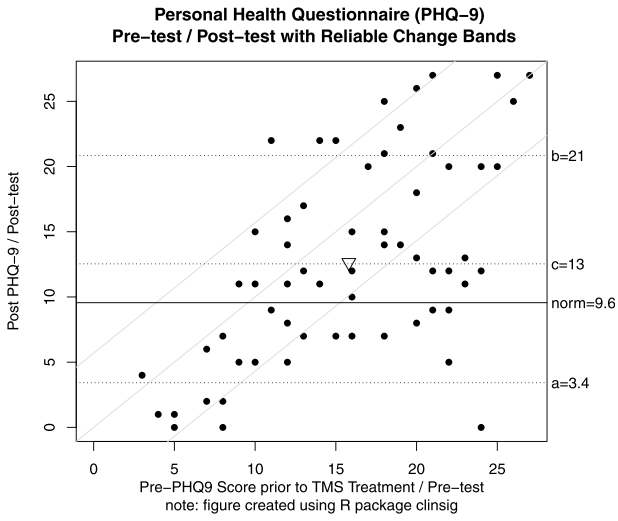

FIGURE 1. Scatterplot of pre–PHQ-9 and post–PHQ-9 scores with reliable change bands.

Influence of Comorbidities and Prescription Medication

Among those patients included in the main efficacy analysis, roughly half (n = 31) had comorbidity with PTSD only (n = 10) or substance abuse only (n = 16) or both (n = 5). Results of the linear regression assessing the influence of comorbidity (ie, none, PTSD, substance abuse, or both) on treatment outcome (ie, the difference between pre– and post–PHQ-9) revealed that there was no difference as a result of comorbidity (all *P*'s > 0.47). Importantly, this indicates there was no reported difference in improvement in depressive symptoms whether the patient had no comorbidity or had MDD plus PTSD, substance abuse, or both. See Figure 2 for a graph showing mean difference scores by comorbidity, with error bars representing the SEM. The number of daily rTMS sessions between patients with and without comorbidity differed significantly $t_{59} = 2.72$, $P = 0.009$. On average, those with comorbidities received fewer individual sessions (27.4 [SD, 5]) than those with only MDD (30.6 [SD, 4]). Linear regression was used to test if prescription drug history (antidepressants, anxiolytics, mood stabilizers, or neuroleptics) predicted patient PHQ-9 difference scores. The result of the regression indicates the 4 predictors explained 21.5% of the variance ($R^2 = 0.22$, $F_{2.4,35} = 2.4$, $P = 0.07$). Additionally, we found that mood stabilizers significantly predicted difference scores ($\beta = 0.38$, $P = 0.015$), which is consistent with the findings of a small 2010 study by Harel et al,[45] which found rTMS improved bipolar depressive symptoms.

DISCUSSION

In this analysis of data from a retrospective chart review of consecutive ADSM patients treated with rTMS in a military treatment facility, we were able to demonstrate that rTMS is an efficacious nonpharmacological treatment option for active military with refractory (treatment-resistant) depression. We had a slightly less robust effect size (Cohen $d = 0.46$ on the paired *t* test of pre–/post–PHQ-9)

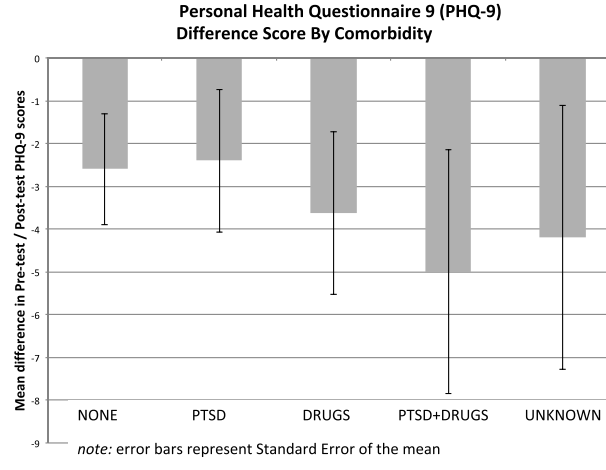

FIGURE 2. Personal Health Questionnaire 9 difference score by comorbidity.

than the only other reported data on the effects of rTMS on ADSMs found by Lande and Pierce,[46] whose report on 34 ADSMs also yielded significant improvements (Cohen $d = 0.63$ on the paired t test of Zung's[47] Self-rating Depression Scale pre/post scores). Our results are consistent with the existing literature demonstrating effectiveness of rTMS for depression and unique in that this is the largest sample size of ADSMs undergoing rTMS for depression reported to date. Importantly, there was no difference in the success of rTMS among those with comorbidities of PTSD or substance abuse. This indicates that rTMS is not selectively successful in this unique sample.

Our findings differ significantly from the study of Yesavage et al[37] and are more in line with the findings of Carpenter et al[38] and Lande and Pierce.[46] Our patients were significantly younger (34.8 vs 55.2 years) than those in the sample of Yesavage et al,[37] which may speak to retained plasticity and less entrenched disease in the younger brain. In addition, a greater percentage of our patients were employed (100% vs 23.8%), which may attenuate the placebo response to clinical contact and being evaluated daily. Our positive results were less robust, but in line with the findings of the naturalistic trial of Carpenter et al[38] and Lande and Pierce's[46] retrospective review of ADSMs receiving rTMS treatment.

Study Limitations

This study has many limitations. Given that the OBHS at Dwight D. Eisenhower Army Medical Center is a naturalistic, nonrandomized, treatment-as-usual clinical setting, there was no control group and sham treatment, and the study was not double-blind. Additionally, the protocol does not allow for follow-up to determine long-term response and remission rates. We chose to include in our percentage of patients who achieved reliably and clinically significant change in PHQ-9 those whose pre–PHQ-9 score was not high enough to reach dysfunctional levels of depression at baseline (ie, pretreatment PHQ-9 scores were not >9.56 to begin with for 2 patients). Had we included only those whose initial PHQ-9 was greater than 9.56, our reliable change would have been 27% compared with our reported 31%. We chose to include these individuals because the PHQ-9 is a self-report measure and because active military personnel may have underreported on this measure for myriad reasons, including fear of altering their career, stigma, and perception of peers and leadership.[48,49]

CONCLUSIONS

In this study, we were able to demonstrate that rTMS for treatment of refractory depression is an adequate treatment or augmentation option for ADSMs with MDD. The mean response was significant but less robust than those seen with ECT and may not be sufficient for the more severely depressed ADSMs. Although ADSMs are typically more transient due to frequent moves by both provider and ADSM, and they have higher operational work demands than civilian employees that may make them less likely to complete treatment, only 24 of 121 (20%) did not complete an adequate number of rTMS sessions in the present study. Some of the more recent patients were simply in the middle of their first standard course, whereas others terminated completely. This completion rate demonstrates that rTMS can be applied to a military population with comparable success to civilian populations. A second frequently voiced concern regarding rTMS in ADSMs is that commanders would have concerns about ADSMs' time away from duty; we have not had commander concerns regarding mission decrement due to ADSMs receiving this treatment and in fact have found commanders to be quite supportive and appreciative of improved soldier functioning. Repetitive TMS appears to be a functional alternative treatment for active service members stationed on or near base (ie, none of the patients included were deployed).

This study contributes significantly to the field of noninvasive brain stimulation by demonstrating that rTMS is an effective alternative to or augmentation of the usual standard-of-care treatment for depressive symptoms in the military. Additionally, this study provides successful replication of rTMS efficacy in both general terms and its specific use within a military population.

This retrospective review should be followed up with an RCT in ADSMs. Future studies may compare rTMS to other types of noninvasive electrical brain stimulation, such as neuronavigation-guided rTMS, intermittent theta burst TMS, or high-definition transcranial direct current stimulation, to determine which is most efficacious, least disruptive, portable, and cost-effective. Currently, rTMS is not widely available to service members as it is used only at select treatment facilities. With the ongoing concern for ADSM suicide[50,51] (321 in 2018[52]), the limited treatment options available, and the high percentage of ADSMs whose depression is treatment-resistant, the authors believe rTMS shows promise as an effective therapy for military personnel.

REFERENCES

1. National Institute of Mental Health's 2016 National Survey on Drug Use and Health. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf. Accessed July 1, 2018.
2. Gadermann AM, Engel C, Naifeh JA, et al. Prevalence of *DSM-IV* major depression among US military personnel: meta-analysis and simulation. *Mil Med*. 2012;177:47–59.
3. Bray RM, Hourani LL. Substance use trends among active duty military personnel: findings from the United States Department of Defense Health Related Behavior Surveys, 1980–2005. *Addiction*. 2007;102:1092–1101.
4. Bray RM, Pemberton MR, Lane ME, et al. Substance use and mental health trends among U.S. military active duty personnel: key findings from the 2008 DoD health behavior survey. *Mil Med*. 2010;175:390–399.
5. Donnell AJ, Kim MS, Silva MA, et al. Incidence of postconcussion symptoms in psychiatric diagnostic groups, mild traumatic brain injury, and comorbid conditions. *Clin Neuropsychol*. 2012;26:1092–1101.
6. Isaac L, Main KL, Soman S, et al. The impact of depression on veterans with PTSD and traumatic brain injury: a diffusion tensor imaging study. *Biol Psychol*. 2015;105:20–28.
7. Matthews SC, Strigo IA, Simmons AN, et al. A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion. *Neuroimage*. 2011;54(suppl 1):S69–S75.
8. Contractor AA, Elhai JD, Fine TH, et al. Latent profile analyses of posttraumatic stress disorder, depression and generalized anxiety disorder symptoms in trauma-exposed soldiers. *J Psychiatr Res*. 2015;68:19–26.
9. Rytwinski NK, Scur MD, Feeny NC, et al. The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. *J Trauma Stress*. 2013;26:299–309.
10. Ragen BJ, Roach AE, Chollack C. Chronic stress, regulation of emotion and functional activity of the brain. In: Fink G, ed. *Stress Concepts and Cognition, Emotion and Behavior*. London: Academic Press; 2016: 241–249.
11. Walter KH, Glassman LH, Michael Hunt W, et al. Evaluation of an integrated treatment for active duty service members with comorbid posttraumatic stress disorder and major depressive disorder: study protocol for a randomized controlled trial. *Contemp Clin Trials*. 2018;64:152–160.
12. Greene-Shortridge TM, Britt TW, Castro CA. The stigma of mental health problems in the military. *Mil Med*. 2007;172:157–161.
13. Kemp AH, Gordon E, Rush AJ, et al. Improving the prediction of treatment response in depression: integration of clinical, cognitive,

psychophysiological, neuroimaging, and genetic measures. *CNS Spectr*. 2008;13:1066–1086; quiz 1087–8.

14. Ohayon MM. Epidemiology of depression and its treatment in the general population. *J Psychiatr Res*. 2007;41:207–213.
15. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;53:649–659.
16. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry*. 2007;68(S8):17–25.
17. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry*. 2007;52:46–54.
18. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997;58(suppl 13): 23–29.
19. Goertz C, Marriott BP, Finch MD, et al. Military report more complementary and alternative medicine use than civilians. *J Altern Complement Med*. 2013;19:509–517.
20. Husain MM, Rush AJ, Fink M, et al. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. *J Clin Psychiatry*. 2004;65:485–491.
21. Spaans HP, Verwijk E, Comijs HC, et al. Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study. *J Clin Psychiatry*. 2013;74:e1029–e1036.
22. George MS, Wassermann EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport*. 1995;6:1853–1856.
23. Pascual-Leone A, Rubio B, Pallardó F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet*. 1996;348:233–237.
24. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry*. 1997;154:1752–1756.
25. Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry*. 1999;56: 315–320.
26. George MS, Nahas Z, Molloy M, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biol Psychiatry*. 2000;48: 962–970.
27. Avery DH, Holtzheimer PE III, Fawaz W, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry*. 2006;59:187–194.
28. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry*. 2010;67:507–516.
29. Slotema CW, Blom JD, Hoek HW, et al. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry*. 2010;71:873–884.
30. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. *Curr Opin Psychiatry*. 2013;26:13–18.
31. Lee JH, Kung S, Rasmussen KG, et al. Effectiveness of electroconvulsive therapy in patients with major depressive disorder and comorbid borderline personality Disorder. *J ECT*. 2019;35:44–47.
32. Wajdik C, Claypoole KH, Fawaz W, et al. No change in neuropsychological functioning after receiving repetitive transcranial magnetic stimulation (TMS) treatment for major depression. *J ECT*. 2014;30:320–324.
33. Hunter AM, Minzenberg MJ, Cook IA, et al. Concomitant medication use and clinical outcome of repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder. *Brain Behav*. 2019;49:e01275.
34. Fitzgerald PB, Brown TL, Marston NA, et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2003;60:1002–1008.
35. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007; 62:1208–1216.
36. Carpenter LL, Aaronson ST, Clarke GN, et al. rTMS with a two-coil array: safety and efficacy for treatment resistant major depressive disorder. *Brain Stimul*. 2017;10:926–933.
37. Yesavage JA, Fairchild JK, Mi Z, et al. Effect of repetitive transcranial magnetic stimulation on treatment-resistant major depression in US veterans: a randomized clinical trial. *JAMA Psychiatry*. 2018;75:884–893.
38. Carpenter LL, Janicak PG, Aaronson ST, et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. *Depress Anxiety*. 2012;29:587–596.
39. Center for Devices and Radiological Health. January 2011. Guidance Documents (Medical Devices & Radiation-Emitting Products)—Guidance for Industry and FDA Staff—Class II Special Controls Guidance Document. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/class-ii-special-controls-guidance-document-repetitive-transcranial-magnetic-stimulation-rtms. Accessed July 1, 2018.
40. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613.
41. Löwe B, Kroenke K, Herzog W, et al. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). *J Affect Disord*. 2004;81:61–66.
42. McMillan D, Gilbody S, Richards D. Defining successful treatment outcome in depression using the PHQ-9: a comparison of methods. *J Affect Disord*. 2010;127:122–129.
43. Jacobson N, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991;59:12–19.
44. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2014. Available at: http://www.R-project.org/. Accessed August 1, 2019.
45. Harel EV, Zangen A, Roth Y, et al. H-coil repetitive transcranial magnetic stimulation for the treatment of bipolar depression: an add-on, safety and feasibility study. *World J Biol Psychiatry*. 2011;12:119–126.
46. Lande RG, Pierce J. Efficacy of transcranial magnetic stimulation for treatment resistant depression among active duty service members. *Gen Hosp Psychiatry*. 2017;45:99–100.
47. Zung WW. A Self-rating Depression Scale. *Arch Gen Psychiatry*. 1965;12: 63–70.
48. Visco R. Postdeployment, self-reporting of mental health problems, and barriers to care. *Perspect Psychiatr Care*. 2009;45:240–253.
49. Hoge CW, Castro CA, Messer SC, et al. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 2004;351:13–22.
50. Bullman T, Schneiderman A, Bossarte R. Suicide risk by unit component among veterans who served in Iraq or Afghanistan. *Arch Suicide Res*. 2018; 22:1–10.
51. Reimann CA, Mazuchowski EL. Suicide rates among active duty service members compared with civilian counterparts, 2005–2014. *Mil Med*. 2018; 183(suppl 1):396–402.
52. Kime P. Active-duty military suicides at record highs in 2018. Available at http://www.military.com. Updated January 30, 2019. Accessed April 19, 2019.