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Posttraumatic Stress Disorder Symptom Severity Does Not Predict Depression Improvement, but May Impact Clinical Response and Remission

To the Editor: With great interest, we read the recent article by Hernandez and colleagues¹ examining whether a diagnosis of comorbid posttraumatic stress disorder (PTSD) was associated with poorer treatment outcomes of veterans receiving transcranial magnetic stimulation (TMS) for major depressive disorder (MDD). This question is of high clinical relevance, as PTSD and depression are highly comorbid in this patient population, and the interaction between these disorders worsens symptom severity,² which can complicate treatment. As such, it is possible that the severity of PTSD symptoms also has ramifications for the effectiveness of treatment. Therefore, we sought to examine the effects tested by Hernandez et al¹ in our Veterans Affairs (VA) neuromodulation clinic while also considering the effects that PTSD symptom severity can have on TMS treatment for depression.

To this end, we conducted a chart review of 57 patients with MDD and comorbid PTSD; this cohort was treated naturalistically between 2012 and 2020 (ie, before the coronavirus disease 2019 [COVID-19] pandemic). As a part of clinical care, patients completed self-reports to evaluate PTSD symptom severity using the PTSD Checklist for *DSM-5* (PCL-5)³ and MDD symptom severity using the Patient Health Questionnaire-9 (PHQ-9).⁴ Only patients with both baseline and endpoint scores on both rating scales were included in this analysis.

We examined effects of PTSD diagnosis (defined as meeting threshold-level symptoms of PTSD; ie, PCL-5 score > 33) or symptom severity (as determined by PCL-5 score) on the primary outcomes investigated by Hernandez and colleagues.¹ First, we conducted repeated-measures analyses of variance to examine whether PTSD symptom severity or diagnosis at baseline predicted improvement in depressive symptoms from pre- to post-TMS treatment. In general, patients with worse PTSD symptoms at baseline (PCL total score: $F_{1,54} = 35.59$, $P = .000$, $\eta_p^2 = 0.40$; threshold: ($F_{1,54} = 10.93$, $P = .002$, $\eta_p^2 = 0.17$) exhibited more severe depressive symptoms. However, similar to the findings of Hernandez et al,¹ neither PTSD diagnosis ($F_{1,54} = 0.19$, $P = .67$, $\eta_p^2 = 0.00$) nor symptom severity ($F_{1,54} = 0.18$, $P = .67$, $\eta_p^2 = 0.00$) differentiated the degree of improvement in depressive symptoms with TMS.

Next, we extended the findings of Hernandez et al¹ by conducting logistic regression to examine the extent to which PTSD diagnosis or symptom severity predicted MDD categorical response (ie, at least 50% reduction in PHQ-9 score) and remission (ie, PHQ-9 score < 5), while controlling for baseline depressive symptom severity. Regarding response, both diagnosis ($B = -1.45$; $SE = 0.66$; $OR = 0.24$; 95% CI, 0.06–0.86; $P = .029$) and symptom severity ($B = 0.06$; $SE = 0.02$; $OR = 0.95$; 95% CI, 0.91–0.99; $P = .026$) scores predicted poorer outcomes. For remission, only PTSD diagnosis ($B = -1.61$; $SE = 0.76$; $OR = 0.20$; 95% CI, 0.05–0.90; $P = .035$), but not PTSD severity ($B = -0.05$; $SE = 0.27$; $OR = 0.96$; 95% CI, 0.91–1.01; $P = .088$), predicted poorer outcomes.

In summary, we partially replicated the findings of Hernandez et al, as our results suggest that a categorical diagnosis of PTSD was not predictive of depressive symptom improvement. This finding indicates TMS can be an effective treatment for patients with comorbid PTSD and depression, regardless of the severity of symptom presentation. Yet, when we examined categorical

outcomes in depression, a more complicated picture emerged. Having sufficient symptom severity to reach threshold for diagnosis (our operational definition of PTSD diagnosis) predicted reduced chance of clinical response and remission, which is a finding reminiscent of that reported in prior randomized controlled trials of TMS for depression.⁵ These results underscore the importance of understanding baseline symptom severity to predict how patients may respond to TMS and provide realistic expectations to those seeking treatment.

Taken together, both our data and those from Hernandez et al¹ suggest that veterans with comorbid depression and PTSD can be effectively treated with TMS, and clinicians should consider PTSD symptom severity at the start of TMS treatment. While these findings require replication in larger and prospective studies, this work and the report from Hernandez et al contribute to the ever-growing effectiveness literature supporting the use of TMS for MDD and commonly comorbid conditions including PTSD^{6–8} and suicidality.⁹ The primary limitations of this work are those inherent to chart reviews of naturalistic patient care; we were not powered to evaluate whether medication or other treatment influenced these findings, although, as a requirement at our clinic, prior treatments must be stable for at least 6 weeks. We also did not perform structured clinical interviews, but relied on patient self-reported outcomes. These caveats aside, the results presented by Hernandez et al and the research mentioned in this letter highlight the importance of improving our understanding of TMS outcomes to improve clinical care.

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Veterans With Comorbid Depression and PTSD Can Be Effectively Treated With TMS

To the Editor: We were heartened to learn that Brigido and colleagues have largely replicated our findings published in *The Journal of Clinical Psychiatry* that comorbid posttraumatic stress disorder (PTSD) is not a negative predictor for the treatment of depression with transcranial magnetic stimulation (TMS).¹ These findings are unique since, for many treatments of depression, comorbid PTSD is a strong negative predictor of outcome.

In addition to being a unique sample of patients being treated at another institution, the sample and analysis by Brigido et al differed from our own in a few other notable respects: (1) our sample consisted of 115 patients, whereas theirs included 57 patients; (2) we utilized the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR) and Montgomery-Asberg Depression Rating Scale (MADRS), whereas they utilized the Patient Health Questionnaire-9 (PHQ-9) for assessment of depressive symptoms; and (3) we determined presence or absence of current PTSD based on a detailed interview by an experienced psychiatrist versus their use of a cutoff score on the PTSD Checklist for DSM-5 (PCL-5). Also, as mentioned in the Discussion section of our article, we did not have a measure of severity of PTSD as was available in the analysis by Brigido et al. Despite these differences, Brigido et al found that neither the presence of PTSD diagnosis nor the severity of PTSD symptoms predicted the degree of improvement in depressive symptoms. Accounting for PTSD symptom severity with the PCL-5 is an important addition to the analysis of the relationship between MDD, PTSD, and TMS.

Conversely, their logistic regression provided some results that conflicted with ours when the presence and severity of PTSD were modeled with the categorical response or remission of MDD based on PHQ-9 score. In apparent contradiction to their first analysis, this logistic regression showed that both PTSD diagnosis by cutoff score and severity of PTSD symptoms predicted poorer response to TMS for depressive symptoms. In this model, PTSD diagnosis but not PTSD severity predicted lower odds of achieving remission. Our results previously demonstrated no difference in categorical outcomes (response and remission) based on presence of PTSD diagnosis for QIDS-SR or MADRS scores. A number of possibilities exist to explain this discrepancy between the findings. Most likely among them is the nature of defined cutoff scores for response (typically 50% reduction in score) and remission (typically achieving a minimum score such as PHQ-9 score < 5, QIDS-SR score ≤ 5, or MADRS score ≤ 10). Although the values used are generally agreed upon percentages and values for consistency, they can obfuscate the true outcome due to their somewhat arbitrary definition. For example, if a patient has a 49% improvement in PHQ-9 score or a final score of 5, they would be counted as neither a responder nor a remitter despite having a meaningful change in symptoms and experiencing a minimal degree of depressive symptoms. This is especially problematic for

smaller-sample studies. We suspect that this may be playing a role in this current discrepancy in findings.

In summary, we agree with Brigido et al that veterans with comorbid depression and PTSD can be effectively treated with TMS. The direct replication of our finding that neither the presence of PTSD diagnosis nor severity of PTSD symptoms impacts the degree of improvement in depressive symptoms when treating with TMS is an important addition to the literature. These findings need to be confirmed in adequately powered and well-designed randomized controlled trials to generate conclusive evidence. Larger-sample studies in the future can address the discrepancy based on the categorical grouping of response and remission.

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