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Pragmatic accelerated transcranial magnetic stimulation for posttraumatic stress disorder

Dear Editor:

Accelerated Transcranial Magnetic Stimulation (TMS) is a novel adaptation of TMS designed for faster symptomatic relief compared to standard TMS [1]. Traditional TMS involves one session per day over 6 weeks, while accelerated TMS condenses multiple sessions into a single day. One of the first uses of accelerated TMS described in 2010 [2] provided a high dose of TMS over three days with improvements occurring rapidly; a more recent example is the SAINT protocol for MDD, which combines high dose TMS with proprietary functional targeting to yield robust outcomes [3]. Thus, extant work suggests that accelerated TMS is safe, effective, and offers greater scheduling flexibility.

Within this context, TMS holds promise for posttraumatic stress disorder (PTSD); while recent randomized controlled trials have provided mixed evidence (e.g., [4–6]), large-scale effectiveness data strongly supports the use of standard TMS for those who have PTSD comorbid with MDD [7]. This study examined the first cohort of patients to receive off-label accelerated TMS with the Veterans Affairs (VA) Clinical TMS program, hypothesizing that accelerated TMS would be efficacious for PTSD symptom improvement. We also explored depression outcomes in Veterans without comorbid PTSD to provide an additional estimate of efficaciousness, and report on 3-month durability in a subset of individuals for whom data was available.

The VA Palo Alto Healthcare System Mental Illness Research Education and Clinical Center serves as the coordinating site for the VA Clinical TMS Program, and the VA Palo Alto/Stanford Institutional Review Board approved associated procedures with data gathered via VA REDCap [7]. The off label accelerated protocol was initially reported in [8], developed during the COVID-19 pandemic. The protocol was chosen based on existing literature and pragmatic considerations, namely completion within a single hospital shift and individualized scalp-based targeting via modified Beam/F3([9]; this approach is a validated, measurement-based method for locating the left dorsolateral prefrontal cortex (DLPFC) by using scalp landmarks). Thus, protocol used was left DLPFC targeting at 100 % of motor threshold, intermittent theta burst stimulation (iTBS) of 1800 pulses five times a day with a 50-min intersession interval, for five business days; total number of iTBS pulses was 45,000. Consistent with the VA program procedures, clinicians using this off-label protocol documented the rationale for use in the medical record.

The PTSD checklist for DSM-5 (PCL-5) measured change in PTSD symptoms, and the 9-item Patient Health Questionnaire (PHQ-9) evaluated depressive symptoms. Paired t-tests were used to examine changes over time, and effect sizes generated in Cohen's d (95 % confidence interval; CI). Patients were operationally defined as having PTSD if they had a pretreatment PCL-5 score of $\geq$33. PTSD clinical response was operationally defined as a decrease of at least 10, and remission operationally defined as reaching a posttreatment score of <33 (following definitions in [8]). Data was analyzed using SPSS v29 (Armonk, NY).

A total of n = 123 Veterans with PTSD across 15 sites received the accelerated TMS protocol that includes the nineteen previously reported [8]; 96 (78 %) completed the five-day protocol and had complete data. Demographics were consistent with Veteran samples; average age (standard deviation; SD) was 48 (12.6) years, majority (72 %) white, 13.8 % Hispanic, and 20 % female.

Accelerated TMS significantly improved PTSD symptoms; PCL-5 scores were reduced from 53.04 (12.3) to 31.05 (19.1) after treatment ($p < .001$, Cohen's d = 1.4 (95 % CI:1.1–1.7)). A total of 74 patients (77.1 %) achieved a clinical response with accelerated TMS, and PTSD remission occurred in 59 (61.5 %) (Fig. 1A). Depression symptoms also significantly improved with accelerated TMS, from 18.44 (4.2) to 10.2 (6.3)($p < .001$, Cohen's d = 1.2 (95 % CI:1.0–1.6). In this group, MDD response and remission rates were 43.6 % and 21.3 %, respectively (Fig. 1B). Follow up data was available for a modest percentage of completers (n = 23; 24 %) at the time of writing and was indicative of symptom stability (PTSD and depressive symptom scores were 32.35 (17.0) and 12.7 (4.9), respectively).

Clinical outcomes in MDD patients (i.e., without PTSD) were available in 50 patients, of which 42 (84 %) completed treatment. Accelerated TMS reduced PHQ-9 scores from 15 (5.37) to 5.6 (5.10) ($p < .001$, Cohen's d = 1.69 (95 % CI:1.2–2.1). MDD response and remission rates were 69 % and 45.2 %, respectively, which were statistically higher ($p < .05$) than the PTSD group. Follow-up PHQ-9 scores were available in 10 (23.8 %) patients and suggested symptom stability (PHQ-9 score = 6.8 (5.7) (Fig. 1C).

Conclusions

This pragmatic accelerated TMS protocol yielded a robust completion rate alongside statistically significant and clinically meaningful reductions in PTSD symptoms. Notably, this accelerated protocol achieved in 5 days what traditionally takes 6 weeks, representing a major advance in treatment efficiency; the magnitude of symptom reduction (~20 points) and PTSD response and remission rates are at least comparable to standard TMS [7]. While depressive symptom improvement was meaningful (8–10 points), clinical response and remission rates for depression were more modest in those with comorbid PTSD and MDD; in the group without PTSD, outcomes were improved overall with an average posttreatment score nearing remission. Key differences between this protocol and SAINT are half the cumulative exposure and scalp-based targeting. Results from this piece support the observation that higher cumulative exposure to TMS over time is a key consideration to more rapidly improve outcomes [1]. Recent work demonstrated high

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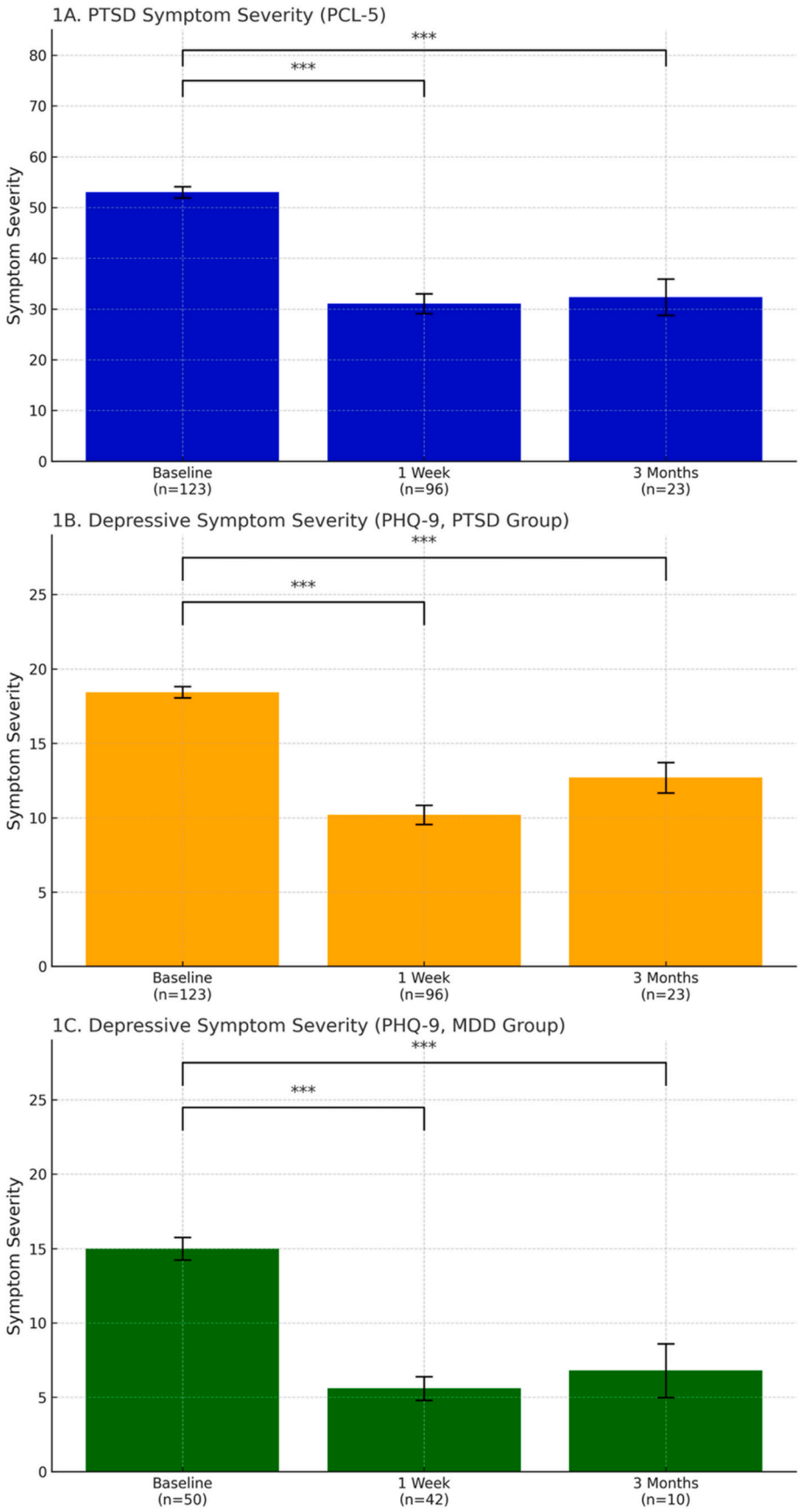

Fig. 1. Clinical outcomes for accelerated transcranial magnetic stimulation in patients with PTSD and comorbid MDD (1A and 1B for PTSD and MDD symptoms, respectively) and those with MDD only (1C). Error bars represent standard error of the mean. *** Represents paired t-tests significant at $p < .001$ comparing pre-treatment baseline with relevant timepoints. Abbreviations: PCL-5, PTSD Checklist for DSM-5; PHQ-9, 9-Item Patient Health Questionnaire.

precision of the modified Beam/F3 protocol with evidence that it can engage putative neural mechanism(s) underlying therapeutic TMS [10]. Limitations include those inherent to Veteran cohort studies and limited durability data. Whether patients presented for care of PTSD or MDD as their primary concern is unknown. Examination of PTSD-specific symptom domains was not performed due to concerns of statistical power. Furthermore, there was no control group, and as such controlled trials of accelerated TMS are needed, with the caveat that sham-controlled designs may raise ethical concerns when adequate treatments are clinically available. Whether this protocol would work with PTSD but without comorbid MDD also remains unknown. Limitations aside, this report describes large and robust improvements in PTSD symptoms in a short period of time using a highly scalable TMS protocol, underscoring the potential for accelerated TMS to dramatically reduce treatment duration while maintaining efficacy, potentially improving access to care.

CRediT authorship contribution statement

Noah S. Philip: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **F Andrew Kozel:** Writing – review & editing, Writing – original draft, Supervision. **Elizabeth A. Walter:** Writing – review & editing, Project administration. **Emily K. McMillan:** Writing – review & editing, Project administration. **Bo Dehm Wicklund:** Writing – review & editing, Data curation. **Zachary D. Zuschlag:** Writing – review & editing, Project administration, Methodology. **Michelle R. Madore:** Writing – review & editing, Writing – original draft, Visualization, Investigation.

Disclosures

The authors report no relevant biomedical conflicts of interest; in the last three years, NSP has received clinical trial support (through VA contracts) from Neurolief and Wave Neuro, is on the scientific advisory board of Pulvinar Neuro and is a consultant for Motif Neurotech. FAK is supported by Mina Jo Powell Endowed Chair – Neurological Sciences, has received travel and small honorarium for Clinical TMS Society meeting lectures 2021 & 2022 and as Associate Editor of *Transcranial Magnetic Stimulation*. He also reports temporary loan of equipment from Neuronetics and NIRx. EAW, EKM, ZDZ, BDW, and MRM have no disclosures.

Declaration of competing interest

The authors report no relevant biomedical conflicts of interest.

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