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Accelerated transcranial magnetic stimulation: A pilot study of safety and efficacy using a pragmatic protocol

Dear Editor:

Transcranial magnetic stimulation (TMS) is an effective FDA-approved treatment for treatment-resistant major depressive disorder (MDD) [1,2]. The most common TMS protocol in the US involves once daily treatment for 36 sessions over a period of 8–10 weeks [3]. Accelerated protocols that shorten the treatment course while preserving effectiveness could have substantial advantages.

The development of the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol supports this possibility. In an open-label study [4] and a randomized sham-controlled trial [5], Cole and colleagues obtained high remission rates with only a 5-day acute treatment period. The SAINT protocol, cleared by the FDA, includes several innovations intended to accelerate antidepressant effects [6], including administration of 50 sessions, spaced hourly. At each session, intermittent Theta Burst Stimulation (iTBS) is administered with three times the number of pulses (1800 pulses/session) than used in the original once daily iTBS (600 pulses) protocol that received FDA clearance [7]. The TMS coil is positioned over an individualized target in the left dorsolateral prefrontal cortex (DLPFC) based on structural and resting-state functional MRI scans that identify the area most anti-correlated with subgenual anterior cingulate cortex [8]. Neuronavigation technology maintains coil positioning over the personalized MRI-defined target.

Combining these multiple innovations in a novel intervention was justified by their experimental use in patients with severe, highly treatment-resistant MDD [4,5]. However, these features have limited evidentiary support and constrain adoption since most major US insurance carriers currently authorize a course of 36 sessions [3,9]. The neuroimaging demands involving specific fMRI protocols, the logistics related to image transfer and storage, access to a functional-connectivity processing pipeline with quality control and troubleshooting, as well as the stereotaxic neuronavigation procedures require specialized expertise and add substantial costs. Radiology providers may not offer or process the specific fMRI protocols. Further, the necessity of the intensive dosing (high pulse counts and treatment session) is also untested.

To test the safety and efficacy of a pragmatic accelerated iTBS protocol that addresses the real-world limitations of SAINT, we conducted a prospective, open-label, pilot study of 21 outpatients with treatment-resistant MDD treated with 36 sessions over 5 days, 600 iTBS pulses per session, and coil placement based on scalp anatomic landmarks using the Beam F3 method [10]. The trial was conducted between November 23, 2022 and July 28, 2023 at a mental health clinic in Minnetonka, MN. The study was approved by the WCG Institutional Review Board (Protocol #20225985); clinicaltrials. gov: NCT06113575. Participants provided written informed consent prior to study procedures.

Eligibility criteria were age 22–70 years, with a primary diagnosis of MDD, defined by DSM-5 criteria. Participants had documented failure to benefit from at least one pharmacological treatment at adequate dose and duration in the current episode and had a minimum score of at least 20 on the Montgomery Åsberg Depression Rating Scale (MADRS) at both screening and baseline visits. Exclusion criteria included history of bipolar disorder, autism, obsessive-compulsive disorder, any psychotic or delusional disorder, active substance use disorder other than nicotine, or treatment with TMS in the past 6 months. Participants maintained a stable antidepressant regimen throughout the study. The baseline visit occurred 3 days before the first iTBS session. The accelerated protocol was administered over 5 consecutive days (Monday through Friday) with clinical evaluations performed at the end of each day. Participants returned for assessment 4 weeks later.

A NeuroStar System (version 3.6) delivered TMS. Resting motor threshold (MT) was quantified at the first treatment using an iterative algorithm. Stimulation intensity relative to MT (treatment level) was progressively increased over the TMS course to the maximum level comfortably tolerated. For retention in efficacy analyses, participants were required to reach a treatment level of at least 90 % MT by the end of the accelerated course, and, for safety purposes, treatment level was kept below 120 % MT throughout. Due to discomfort, one participant did not reach the 90 % MT threshold and was excluded from the modified intent-to-treat (mITT) sample but retained in the safety sample. The remaining 20 participants were treated at 63.25 % $\pm$ 7.30 (Mean $\pm$ SD) and 103.5 % $\pm$ 12.15 at the start and end of the accelerated protocol, with an average of 93.98 % $\pm$ 16.19 during the accelerated course.

Participants received 36 iTBS sessions, in the sequence of 6, 8, 8, 8, 6 sessions/day. There was no dropout. Each session began 60 min after the start of the previous session and consisted of 20 cycles of 10 bursts of 3 pulses at 50 Hz every 200 ms (5 Hz) delivered in 2 s trains with an 8 s intertrain interval (600 pulses/session). Participants received 21,600 pulses during the accelerated course.

The MADRS, Quick Inventory of Depressive Symptoms: Self-Report (QIDS-SR), Patient Health Questionnaire (PHQ-9), and Generalized Anxiety Disorder-7 (GAD-7) were completed at baseline, immediately following the last accelerated treatment (end-of-acute, EOA), and 4-weeks later. Response was defined as $\geq$ 50 % reduction from baseline on each scale. Remission was defined by a score on the MADRS $\leq$9, $\leq$5 on the QIDS-SR, and $\leq$4 on the PHQ-9 and GAD-7. Suicidality was assessed with the MADRS suicide item. After each of the 5 days of treatment, the QIDS-SR, PHQ-9, and GAD-7 were completed.

The primary outcome was change in MADRS scores 4 weeks following the 5-day accelerated course relative to baseline. Secondary outcomes included change in total scores and response and remission

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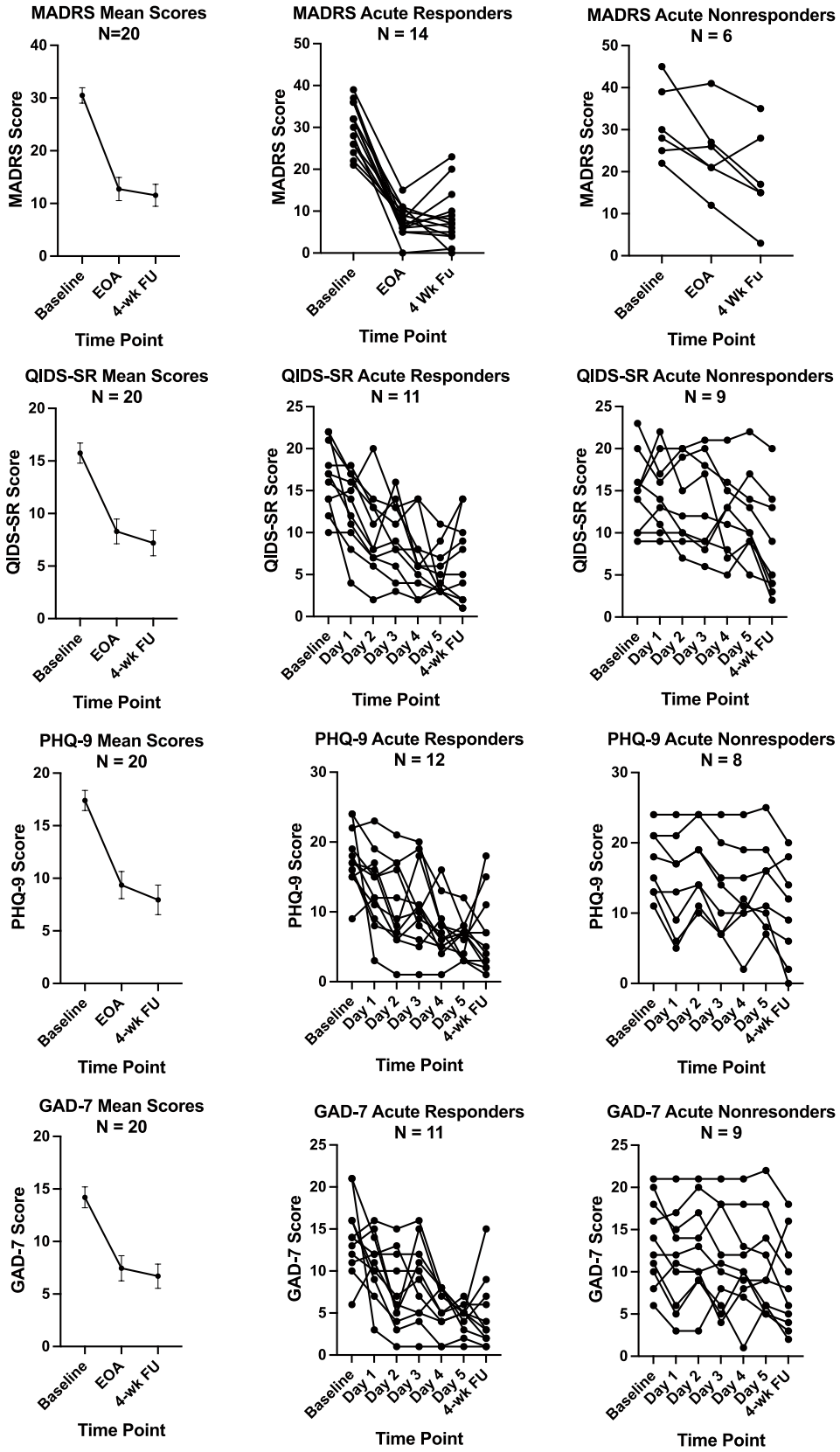

Fig. 1. Left Panel: Mean (±SEM) scores of all participants on the MADRS, QIDS-SR, PHQ-9, and GAD-7 at baseline, end of acute (EOA) treatment, and 4-week follow-up. Middle panel: Scores of individual participants who were classified as EOA responders on each depression and anxiety severity scale, at all timepoints (baseline, at the end of each day in the 5-day accelerated course, and at 4-week follow-up). Right panel: Scores of individual participants who were classified as EOA non-responders on each depression and anxiety severity scale, at all timepoints (baseline, at the end of each day in the 5-day accelerated course, and at 4-week follow-up).

rates immediately and at 4-week follow-up for the MADRS and self-report inventories. One-way repeated measures analyses of variance (rmANOVAs) with Huynh-Feldt correction were conducted on total scores at baseline, EOA treatment, and 4-week follow-up, followed by Bonferroni corrected paired t-tests contrasting the 3 time points. Similar one-way rmANOVAs tested the main effect of time on total scores at baseline and the end of each of the 5 treatment days for the self-report inventories. Bonferroni corrected paired t-tests contrasted adjacent time points in degree of change. The alpha level was 0.05 and all tests were two-sided.

Demographic and clinical features of the mITT sample are presented in Supplemental Tables 1 and 2 The participants had moderate-to-severe depression and anxiety symptoms at baseline, and, on average, long duration of current episode and resistance to multiple antidepressant medications.

The rmANOVA on MADRS scores indicated marked change across the three time points, $F(1.8, 34.9) = 62.01$, $P < 0.0001$, with a large reduction in scores immediately following the accelerated course, $t(19) = 7.99$, $P < 0.0001$, which was maintained at 4-week-follw-up, $t(19) = 0.80$, $P = 0.43$ (Supplemental Table 2). The effect size for the change in MADRS scores from baseline to 4-week follow-up ($d = 2.2$) was nearly 3 times the magnitude of a large effect ($d = 0.8$). At 4-week follow-up, 70 % and 55 % of the sample met MADRS response and remission criteria, respectively. The same pattern was manifested in the other depression, anxiety, and suicidality measures (Supplemental Table 2).

Each of the rmANOVAs on the self-report depression and anxiety scores obtained during the accelerated course yielded a main effect of time (all P's < 0.0001) (Fig. 1). Paired comparisons indicated that scores generally decreased after each of the 5 treatment days relative to the previous day, except for the third accelerated day (Wednesday) which did not differ from the second day (Tuesday) on any measure.

There were no serious adverse events. The only adverse events reported were physical discomfort during stimulation (N = 3, 15 %), headache (N = 5, 25 %), and fatigue (N = 2, 10 %).

This prospective, open-label trial found that a 5-day pragmatic TMS protocol was feasible, safe, and exerted marked antidepressant and anxiolytic effects that were sustained for at least 4 weeks. The protocol was limited to 36 sessions of standard iTBS treatment, with scalp landmarks determining coil positioning. The findings suggest that some of the innovations introduced with the SAINT protocol may not be necessary or may be of value in patients with especially severe treatment-resistant MDD. In our sample of outpatients seeking TMS for treatment-resistant MDD, the rates of response and remission were substantial across all measures. While the findings are preliminary and limited by the relatively small sample size and the uncontrolled, open-label, study design, they justify randomized controlled trials to confirm the acute effectiveness and durability of pragmatic forms of accelerated TMS.

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Data sharing statement

The de-identified database used in this report is available upon request to the corresponding author, Dr Sackeim.

CRediT authorship contribution statement

John G. Luehr: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Erin Fritz:** Writing – review & editing, Project administration, Data curation. **Mitchell Turner:** Writing – review & editing, Data curation. **Charles Schupp:** Writing – review & editing, Funding acquisition, Conceptualization. **Harold A. Sackeim:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis.

Declaration of competing interest

Dr. Luehr, Ms. Fritz, and Mr. Schupp and Turner report no financial relationship with commercial interests. Dr. Sackeim receives consulting fees from Cerebral Therapeutics Inc, Holmusk Inc, LivaNova PLC, MECTA Corporation, NeuroInsights Inc., Neurolief LTD, Neuronetics Inc, Parow Entheobiosciences LLC and SigmaStim LLC. He receives honoraria and royalties from Elsevier Inc and Oxford University Press. He is the inventor on non-remunerative US patents for Focal Electrically-Administered Seizure Therapy (FEAST), titration in the current domain in ECT, and the adjustment of current in ECT devices, each held by SigmaStim LLC. He is also the originator of magnetic seizure therapy (MST).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.07.009.

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