Abstract

Conventional transcranial magnetic stimulation (TMS) regimens require weeks of clinic visits. Here we describe a TMS regimen enabling delivery of an entire therapeutic course in a single day. This retrospective case series reports outcomes for an optimized, neuroplasticity-enhanced depression (ONE-D) treatment regimen delivering 600-pulse iTBS (120 % MT) targeting left DLPFC via scalp heuristic, every 30 min for 20 sessions in 9.5 h, enhancing neuroplasticity via single-dose d-cycloserine (125 mg) and lisdexamfetamine (20 mg), 1 h pre-treatment. 32 TMS-eligible adults (13 prior TMS responders) with unipolar depression underwent the ONE-D regimen, with assessments on day-of-treatment and weeks 1–6, 12, and 26 post-treatment (HDRS-17, BDI-II, PHQ-9, and GAD-7). Every patient completed the regimen successfully, with no serious adverse events (mean scalp discomfort, 5.8 ± 2.1/10). Response was not immediate but followed an exponential-decay trajectory over the 6-week followup. On HDRS-17, scores improved from mean 22.6 ±SD5.3–5.5 ± 4.2 at week 6, 5.3 ± 5.7 at week 12, and 6.1 ± 5.6 at week 26 ($P < 0.001$). On BDI-II, scores improved from 37.5 ±SD9.0–7.6 ± 7.8 at week 6, 7.9 ± 8.4 at week 12, and 9.9 ± 12.1 at week 26. On PHQ-9, scores improved from 18.4 ± 3.5–4.6 ± 4.2 at week 6, 4.7 ± 5.1 at week 12, and 5.6 ± 6.8 at week 26. On GAD-7, scores improved from 14.3 ± 5.2–2.7 ± 2.9 at week 6, 3.7 ± 3.7 at week 12, and 4.0 ± 4.7 at week 26. Response / remission rates (including all 32 patients under intention-to-treat; cross-sectional, not aggregated) were 87.5 % and 71.2 % (HDRS-17), 90.6 % and 68.8 % (BDI-II), 87.5 % and 56.3 % (PHQ-9), 90.6 % and 75.0 % (GAD-7) at week 6, 84.4 % and 71.2 % (HDRS-17), 81.3 % and 65.6 % (BDI-II), 78.1 % and 59.4 % (PHQ-9), 78.1 % and 68.8 % (GAD-7) at week 12. At week 26, 16/32(50 %) showed sustained remission on HDRS-17 and BDI-II; relapse/retreatment had occurred in 25 % on HDRS-17 and 28.1 % on BDI-II. This unblinded case series suggests delivery of an effective TMS course in one day may be feasible, safe, and well-tolerated. With pharmacological augmentation, despite non-personalized, scalp-based targeting, the response and remission rates appeared robust and sustained in representative clinical populations. Follow-up studies may allow further acceleration of the regimen and generalization to other TMS indications. Ampa Health, Kind Health, and Neurostim TMS Centers provided in-kind support for this series.

Keywords

Accelerated · Plasticity · DLPFC · D-cycloserine · Depression

Introduction

Transcranial magnetic stimulation (TMS) is an increasingly widespread intervention for treatment-resistant depression (TRD) (Blumberger et al., 2018; Cole et al., 2022; George et al., 2010; Levkovitz et al., 2015; O'Reardon et al., 2007), showing superiority to pharmacotherapy in this indication (Papakostas et al., 2024). However, conventional once-daily treatment schedules (George et al., 2010; O'Reardon et al., 2007) pose a significant barrier to access, especially for those who live far from a treatment center, or those with mobility issues (Blumberger et al., 2022). Accelerated treatment regimens can reduce the number of visits required by delivering multiple sessions per day. Various studies have delivered 2–10 sessions per day (Baeken et al., 2014; Blumberger et al., 2021; Chen et al.,

2021; Cole et al., 2020; Holtzheimer et al., 2010; McGirr et al., 2015; Miron et al., 2021), and two FDA-cleared protocols now complete an entire course in 5–6 days, by delivering 5–10 sessions per day (Cole et al., 2022; U.S. Food and Drug Administration, 2025).

Note, however, that the very first report of accelerated TMS (Holtzheimer et al., 2010) used an even more abbreviated course of only 1.5 days, delivering 15 hourly sessions and achieving a 43 % response and 29 % remission rate, with sustained effects out to 6 weeks post-treatment. Remarkably, for 15 years since this intriguing report, no replication has been attempted.

A single-day TMS treatment regimen, if safe and effective, could improve access for patients in remote areas, or those with mobility issues, or those with limited time available. To facilitate the delivery of an entire course of TMS in a single day, a number of evidence-based optimizations could be drawn from existing literature. First, a 3 min intermittent theta-burst stimulation (iTBS) session of 600 pulses allows for brief sessions (Blumberger et al., 2018). Second, a 30-min intersession interval (Ramos et al., 2025) would allow 20 sessions in < 10 h. Third, a 20-session course of TMS could potentially achieve higher remission rates if augmented with D-cycloserine: recent reports using such a regimen over 10–20 days suggest a higherremission rate in major depressive disorder (MDD) (Cole et al., 2022; DeMayo et al., 2025)) and greater YBOCS reductions in obsessive-compulsive disorder (OCD) (McGirr et al., 2025). Finally, preclinical (Enomoto et al., 2015)and clinical (Wilke et al., 2022)TMS studies also support dopaminergic (L-DOPA but not pramipexole, suggesting a D1- rather than D2-dependent mechanism) (Enomoto et al., 2015) and/or psychostimulant (Wilke et al., 2022) augmentation to enhance plasticity and therapeutic effect. Psychostimulants may augment plasticity via dopamine, norepinephrine, BDNF and/or ERK signalling mechanisms, among others (e.g. Golden & Russo, 2012). Combining these optimizations into a single regimen could potentially allow strong therapeutic effects for even a single-day TMS intervention.

We recently reported outcomes (Vaughn et al., 2025) for 5 TRD patients who underwent such a regimen, involving 20 TMS sessions in a single day, with pharmacological enhancement of plasticity using an NMDA agonist (D-cycloserine or D-serine) as well as psychostimulant augmentation (lisdexamfetamine) in some instances. Encouragingly, each of these patients achieved remission from major depression, as well as improvement in comorbid generalized anxiety and/or OCD symptoms, where present. However, these 5 patients had some heterogeneity in the precise regimen of targets, stimulation patterns, and pharmacological augmentation strategy employed. A larger open-label replication, employing a consistent regimen across all cases, would therefore be helpful.

Here we present outcomes from a retrospective naturalistic case series in 32 TRD patients who all underwent a consistent single-day TMS regimen. The regimen involved a target in the left dorsolateral prefrontal cortex (DLFPC) via scalp heuristic, an brief stimulation pattern (iTBS, 600 pulses (Blumberger et al., 2018)), a 30-min interval between session onsets, and a consistent pharmacological augmentation strategy (single-dose, off-label D-cycloserine 125 mg and lisdexamfetamine 20 mg, 1 h before commencing TMS). For convenience, we refer to this regimen as an Optimized, Neuroplasticity-Enhanced regimen in Depression (ONE-D).

Retrospective case series in community settings have previously been useful in generating observations to support future formal study of off-label TMS techniques, including dorsomedial

prefrontal TMS (Bakker et al., 2015), add-on low-frequency right DLPFC-TMS (Aaronson et al., 2022), additional pulses (Sackeim et al., 2020) of high-frequency left DLPFC-TMS, shortened inter-train intervals for 10 Hz stimulation(Carpenter et al., 2021), and TMS in adolescents (Croarkin, Dojnov, et al., 2024; Croarkin, Zuckerman, et al., 2024). The present retrospective was similarly intended to illustrate single-day TMS outcomes under naturalistic conditions, as a foundation for future study under randomized controlled conditions.

Methods

Sample definition

This retrospective, naturalistic case series draws upon de-identified observational data collected at clinics participating in the OBSERVER clinical TMS registry (NCT06512324). The participating clinic groups for this sample (Kind Health Group, Encinitas, CA; NeuroStim TMS Centers, Seattle, WA) are community-based practitioners of therapeutic TMS with >9000 total courses of treatment and volumes of > 200 new patients per month. The OBSERVER registry (Advarra IRB#: Pro00075982) is a repository of data contributed anonymously by consenting TMS patients undergoing treatment for major depression and/or anxiety disorders, concerning clinical and demographic variables, treatment parameters, and outcomes on standard clinician-rated and self-rated symptom scales. The present sample includes patients who were assessed by their provider as suitable for TMS, but were unwilling or unable under the present circumstances to attend a conventional multi-visit course of treatment for logistical reasons, and who instead opted to pursue a single-day regimen of treatment, following a standard discussion of risks, benefits, and off-label treatment elements with their prescribing physician. Classification of illness as pharmacological treatment-resistant depression by formal criteria was not required of this naturalistic sample, although all patients had either failed to respond to or were not able to adhere to previous medications and/or therapy (Table 1). All of the patients reported in the present retrospective series were treated without charge, on a compassionate basis. No financial incentives were provided to either clinics or patients for involvement. The participating clinics do also provide compassionate care at no cost to some patients outside the present series, based on individual circumstances, and following other regimens at prescriber's discretion. The present review includes clinical, demographic, and outcome data from adult patients participating in the OBSERVER registry, with a primary diagnosis of unipolar major depression, who underwent a single-day treatment course that included all of the elements of the ONE-D regimen (described in detail below) between June 1 and November 30, 2024. Reporting of the clinical data was covered by Advarra IRB#: Pro00075982 as above.

	Overall
# Patients	32
Male	9 (28.1%)

	Overall
Age	41.9 ± SD12.1 years
Duration of Current Episode	18.0 ± SD19.5 months
Previous TMS	13 (40.6 %)
Previous ECT	1 (3.1 %)

Table 1
Demographic and clinical characteristics of patient sample.

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ONE-D regimen description

ONE-D regimen adherence was operationalized as including the following elements: 1) a single dose of D-cycloserine 125 mg, compounded oral disintegrating tablet, taken 50–70 min before beginning TMS; 2) a single dose of lisdexamfetamine 20 mg, taken 50–70 min before beginning TMS; 3) a course of 20 sessions of TMS treatment, delivered 30 min ± 3 min; 4) each TMS session delivered with the following parameters: intermittent theta burst stimulation (iTBS: 50 Hz triplet bursts, 5 bursts per second, 2 s on and 8 s off for 20 trains of 600 pulses, preceded by an introductory 3-train acclimatization titration), at atarget intensity of 120 % of motor threshold for contralateral upper extremity; 5) target defined at the causal-network-mapping-derived left posterior DLPFC maximum of Siddiqi et al. (2021) [MNI X-46 Y+9 Z+31] and localized using the updated BeamF3-like scalp heuristic of Mir-Moghtadaei et al. (2022), where the circumferential parameter (leftward from FPz) *X* = head circumference × 18.47 %, and the radial parameter (from Cz toward *X*) *Y* = mean of nasion-inion distance and tragus-tragus distance) × 24.8 %; 6) motor threshold determination and all baseline clinical symptom assessments obtained in-clinic at the beginning of the day of treatment. Patients from the OBSERVER registry whose treatment and assessment parameters included all 6 of these elements were included in the present retrospective case series.

TMS technique

All TMS treatments were delivered using a MagVenture R30 pulse generator (Magventure, Farum, Denmark) equipped with an Ampa L-Coil (Ampa Health, Palo Alto, California). This coil is a 15 × 20 cm figure-8 coil, containing a miniature endoscope videocamera at the center of the windings, to facilitate and document on-target coil position and orientation during each treatment session (Supplementary Figure S2). To ensure accuracy and consistency of target definition, patients wore pre-printed scalp caps pre-marked with a labelled target circle at the intended location in posterior left DLPFC, which was localized via *X* and *Y* proportions of the three cardinal scalp measurements, using

the BeamF3-like heuristic of Mir-Moghtadaei et al. (2022) above (Supplementary Figure S1). Please note that this apparatus was not yet FDA-cleared at the time of data collection, but was among the equipment explicitly included under the protocol of Advarra IRB# Pro00075982 as above. Patients received 3 min sessions of iTBS, initiated every 30 min according to the parameters above, and were free to move about the clinic and pursue other activities between sessions, with no specific curriculum or program of therapy provided other than the TMS itself. Likewise, upon completing the day of treatment, patients returned home, with no further interaction with clinic staff and no further program of therapy provided, other than weekly virtual clinical assessments as detailed below.

Clinical assessments

The OBSERVER registry includes a set of clinical assessments comprising the 17-item Hamilton Depression Rating Scale(HDRS-17) (Hamilton, 1960), Beck Depression Inventory-II(BDI-II) (Beck et al., 2011), Patient Health Questionnaire-9(PHQ-9) (Kroenke et al., 2001), and General Anxiety Disorder-7 Scale (GAD-7) (Spitzer et al., 2006). Follow-up assessments were completed remotely without the patients returning to clinic; clinician-rated HRDS-17 assessments were performed via videoconference.

All patients in the present series successfully contributed at least one set of clinical assessments on the day of treatment (prior to TMS) and on at least 1 occasion in the 6 weeks following treatment. 12 week and 26 week follow-up assessments, if available, were also included in the retrospective analysis. For categorical outcomes, response was defined at ≥ 50 % improvement for each scale and remission was defined at HDRS-17 < 8, BDI-II< 10, PHQ-9 < 5 and GAD-7 < 5. The clinician-rated assessments (HDRS-17) in the present series were all performed by the same individual (author BM), an experienced psychiatric nurse practitioner, trained in the administration of a standardized form of the HDRS-17, the GRiD-HAMD (Williams et al., 2008).

Analytical approach

For the purposes of this analysis, the primary outcome measure was defined as the remission rate on the HDRS-17 at 6 weeks post-treatment; this interval is specified to accommodate the brevity of the one-day intervention, as well as previous reports of delayed response to accelerated TMS regimens in some individuals in some previous studies (Cole et al., 2022; Duprat et al., 2016). Remission rates on the BDI-II, PHQ-9, and GAD-7 were adopted as secondary outcome measures. Response rates on the 4 available clinical outcome measures at 6 weeks were adopted as supplementary outcome measures. Durability of response at 12 and 26-week follow up visits were also adopted as supplementary outcome measures. Note that all response and remission rates throughout the Abstract, Results, and Supplementary material are calculated out of the original 32-patient sample, under an intention-to-treat framework.

Comparisons among subgroups were performed using the two-sample *t*-test for continuous variables or Fisher's Exact Test for categorical variables. Linear regression was used to assess the significance of correlations between HDRS-17 improvement and the following continuous predictor variables: baseline symptom severity, episode duration length in months, and number of previous medication trials. As 13 patients were previous TMS responders, which may confer a higher likelihood of response,

outcomes for this subgroup were also plotted and analysed separately with comparisons to the TMS-naive group (Table 3, Figure S4).

	Overall
# Patients	32
Side Effect(s) Reported During Treatment	25 (78.1 %)
Headache	12 (48.0 %)
Scalp Pain	6 (24.0 %)
Jaw Pain	2 (8.0 %)
Neck Tension	2 (8.0 %)
Transient Tinnitus	1 (4.0 %)

Table 2
Side effects and adverse events.

Note: 5 patients reported 2 side effects during treatment and 2 patients reported 3 side effects during treatment each; 1 patient reported 3 side effects 1 week after treatment.

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Outcome Measure	TMS Naive	TMS Previous	P Value
HDRS–17			
N	18	13	
Mean Score ± SD	5.7 ± 5.0	5.2 ± 3.0	$t_{29} = 0.34$; $p = 0.735$
% Improvement	73.7 %	78.1 %	$t_{29} = -1.0$; $p = 0.329$

Outcome Measure	TMS Naive	TMS Previous	P Value
Responders	15/19 (78.9 %)	13/13 (100 %)	$p = 0.128$

Table 3
Comparison of outcomes for TMS-naive vs previous TMS responder patients at 6 weeks.

HDRS-17 = 17-item Hamilton Depression Rating Scale; BDI-II = Beck Depression Inventory-Second Edition; PHQ-9 = 9-item Patient Health Questionnaire; GAD-7 = Generalized Anxiety Disorder 7-item; SD = standard deviation; SE= standard error.

Unpaired 2-sample *t*-tests are employed for continuous variables and Fisher's Exact test for categorical variables in all comparisons above.

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Results

Clinical and demographic characteristics

Clinical and demographic characteristics of the series are presented in Table 1. The series included 32 patients (ages 22–62 yrs, 9 male and 23 female) with unipolar major depression and a current episode duration of 18.0 ±SD19.5 months (range, 2–60), with a mean 1.19 ±SD 1.12 failed antidepressant medication trials by ATHF-SH criteria. 19/32 were TMS-naive; the remainder had previously received conventional once-daily TMS (N = 11), or 8x-daily treatment for 5 days (N = 2). Comorbid diagnoses included generalized anxiety disorder (N = 21) and panic disorder (N = 1) (Supplementary Table S2), but none had comorbid active substance use, bipolar illness, or psychotic illness. All patients in the series had been on a stable medication regimen for a minimum of 4 weeks at the time of treatment. None of the patients in the present series were taking benzodiazepine medications at > 2 mg lorazepam equivalent per day.

Safety, tolerability, and adverse effects

All 32 patients completed the full set of 20 sessions in a single day, on the intended schedule, without any treatment-limiting adverse effects. The most common adverse effect was scalp discomfort during sessions, rated at 5.8/10 ±SD2.0/10 on a numerical rating scale (0 =no discomfort, 10 = maximum tolerable discomfort). 9/32 patients received an NSAID medication on the day of treatment to assist with tolerability. 7 patients were unable to reach the intended stimulation intensity level of 120 % MT: two reached a maximum of 90 %, four reached a maximum of 100 %, and one reached a maximum of 110 % MT. The mean treatment intensity was 36.7 %±SD7.0 % maximum stimulator output (range, 24–55 %). 12/32 patients reported transient headache/jaw pain on the treatment day, and 7/32 reported some transient headache or jaw pain in the week following treatment. There were no seizures,

emergent episodes of mania/hypomania, or any other serious adverse events during treatment or in the 6 weeks after treatment. Follow-up assessments were successfully obtained for 31/32 patients at week 6, 30/32 patients at week 12 and 25/32 patients at week 26.

Treatment outcomes

The trajectories of response to the ONE-D regimen on the HDRS-17, BDI-II, PHQ-9, and GAD-7 over the 12 weeks following treatment are presented in Fig. 1A-D. Response followed a delayed, exponential-decay-like trajectory, with improvements reaching a plateau around weeks 4–6 post-treatment in most cases. From baseline to week 6, scores improved on HDRS-17 from 22.6 ±SD5.3–5.5 ±SD4.2 (Cohen's *d*, 3.58), on BDI-II from 37.5 ±SD9.0–7.6 ±SD7.8 (Cohen's *d*, 3.73), on PHQ-9 from 18.4 ±SD3.5–4.6 ±SD4.2 (Cohen's *d*, 3.36), and on GAD-7 from 14.3 ±SD5.2–2.7 ±SD2.9 (Cohen's *d*, 3.71) (if excluding six patients with baseline GAD-7 <10, improvement was from 16.2 ±SD3.2–3.1 ±SD3.1, Cohen's *d*, 4.04). The values for all scales for all timepoints are presented in Table S1 in the Supplementary Material.

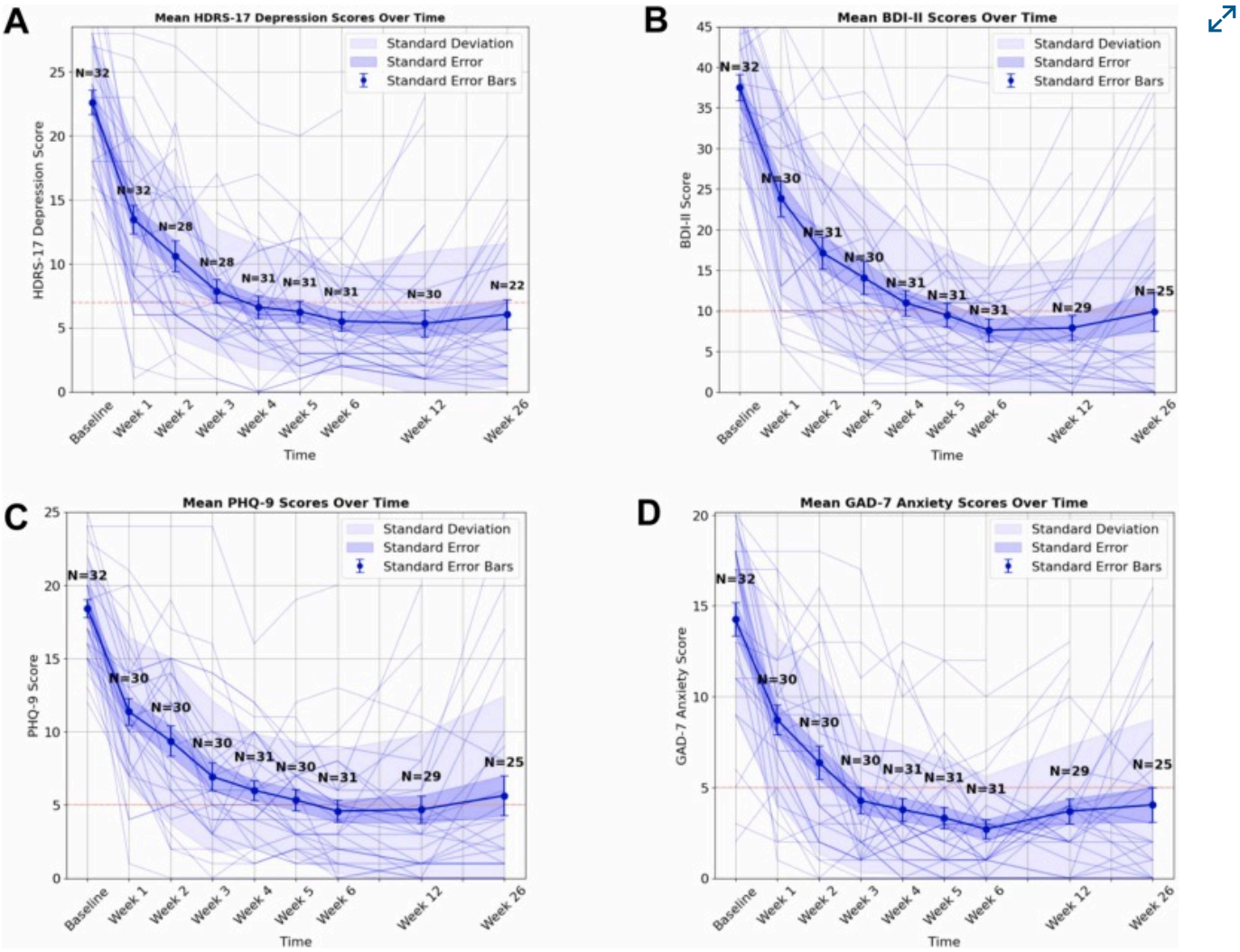

Fig. 1 **Trajectories of improvement following delivery of the ONE-D regimen on the HDRS-17 (A), BDI-II (B), PHQ-9 (C), and GAD-7 (D) symptom scales. Individual thin blue lines indicate trajectories for each individual patient; thick blue line indicates the mean, and shading indicates standard deviation and standard error of the mean. Remission cutoffs are indicated with dotted horizontal red lines.**

Note that relatively few patients reach remission in the week after treatment, but that improvement continues steadily over the 6 weeks of follow-up and appears to be largely maintained at 12 and 26 weeks for most patients on most scales.

When plotted in terms of percent improvement from baseline (Supplementary Figure S3), the trajectory of improvement across all 4 scales was very similar, and again followed an exponential-decay-like curve reaching a plateau over 4–6 weeks, with the maximal improvement at 75.1 %±SD17.2 % for HDRS-17, 79.2 %±SD19.0 % for BDI-II, 75.9 %±SD19.2 % for PHQ-9, and 79.2 %±SD21.1 % for GAD-7 (if excluding six patients with baseline GAD-7 <10, percentage improvement was 79.9 % +/- SD 20.4 %).

In terms of categorical outcomes, at week 6, on the HDRS-17, 28/32(87.5 %) of patients met response and 23/32(71.9 %) met remission criteria. On BDI-II, 29/32(90.1 %) of patients met response and 22/32(68.8 %) met remission criteria. On the PHQ-9, 28/32(87.5 %) of patients met response and 18/32(56.3 %) met remission criteria. On the GAD-7, 29/32(90.6 %) of patients met response and 24/32(75.0 %) met remission criteria; if excluding six patients with baseline GAD-7 < 10, 23/26 (88.5 %) were responders and 18/26 (69.2 %) were remitters. These proportions are based *only* on the score at week 6, without aggregating patients who met response or remission criteria at earlier timepoints or carrying forward previous observations. Notably, the proportion of responders and remitters was initially much lower at week 1, but increased by diminishing increments over the 6 weeks post-treatment on each scale (Fig. 2A-D).

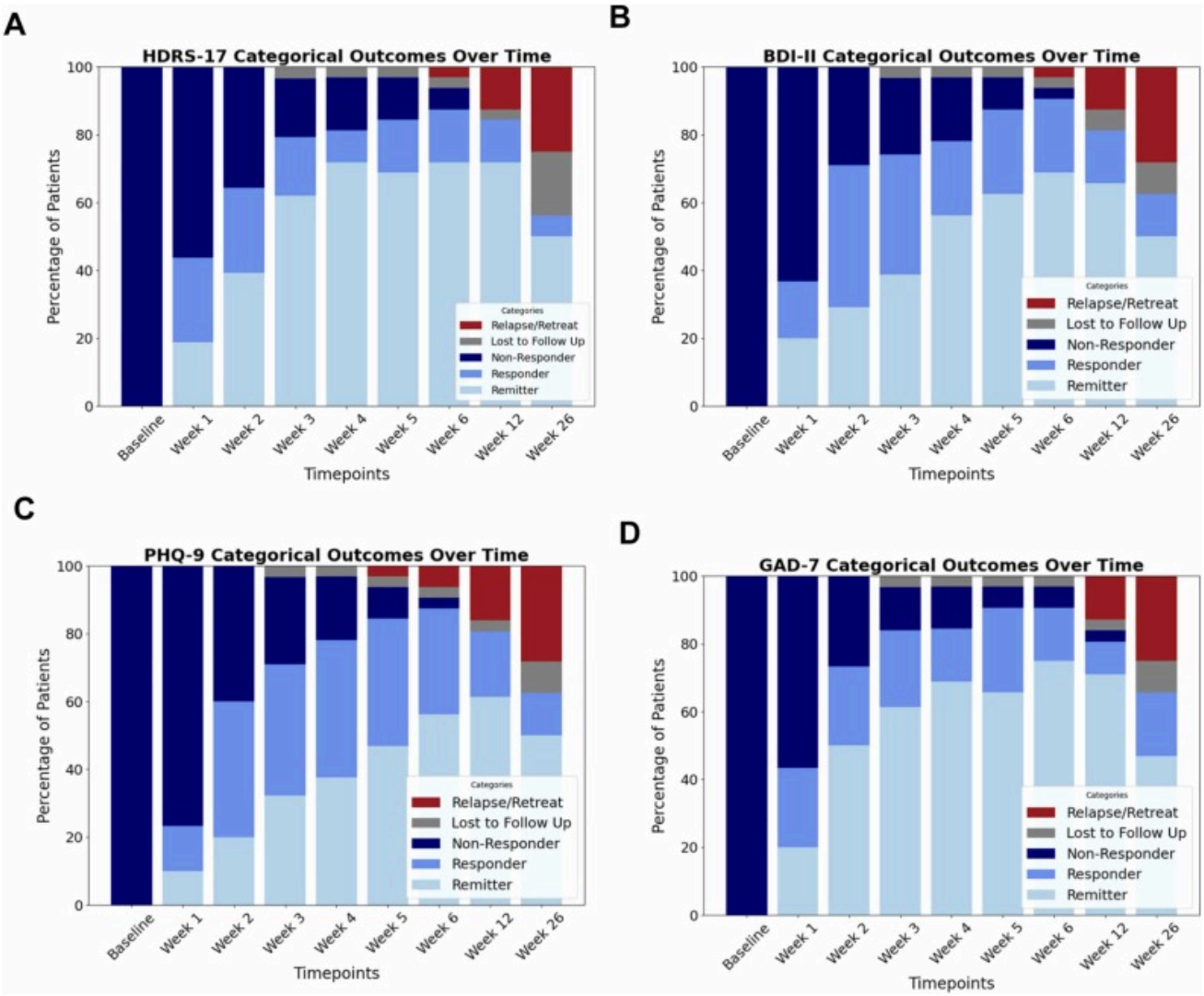

Fig. 2 **Categorical outcomes following delivery of the ONE-D regimen on the HDRS-17 (A), BDI-II (B), PHQ-9 (C), and GAD-7 (D) symptom scales. The proportion of patients meeting criteria for non-response, response, remission, lost to follow up, and relapse/retreat at each week of follow-up (cross-sectional, not aggregated) are indicated via stacked bars. Note once again that relatively few patients meet response or remission criteria immediately after treatment, but these proportions increase to a plateau that is reached by week 6 and maintained to week 12 on most scales.**

In terms of durability, at 12 weeks, considering all 32 patients, response and remission rates were 84.4 % and 71.2 % on the HDRS-17, 81.3 % and 65.6 % on the BDI-II, 78.1 % and 59.4 % on the PHQ-9, and 78.1 % and 68.8 % on the GAD-7 (73.1 % and 61.5 % if excluding six patients with baseline GAD-7 <10). Likewise, the degree of improvement appeared stable at 76.4 %±SD27.9 % for HDRS-17, 77.1 %±SD28.7 % for BDI-II, 74.5 %±SD29.2 % for PHQ-9, and 69.9 %±SD34.5 % for GAD-7 (71.3 %±SD27.0 % if excluding six patients with baseline GAD-7 <10).

Regarding longer term durability, at week 26 (±1 week), data was available for 22 patients on the HDRS-17, and for 25 patients on the BDI-II, PHQ-9, and GAD-7. Based on the entire ITT sample of 32 patients, on the HDRS-17, 16/32 (50.0 %) had sustained remission, 2/32 (6.3 %) had response but not remission, 0/32 (0.0 %) were in sustained nonresponse, 8/32 (25.0 %) either relapsed or were re-treated,

and 6/32 (18.8 %) were lost to follow-up. On the BDI-II, 16/32 (50.0 %) had sustained remission, 4/32 (12.5 %) had response but not remission, 0/32 (0.0 %) were in sustained nonresponse, 9/32 (28.1 %) either relapsed or were re-treated, and 3/32 (9.4 %) were lost to follow-up. On the PHQ-9,16/32 (50.0 %) had sustained remission, 4/32 (12.5 %) had response but not remission, 0/32 (0.0 %) were in sustained nonresponse, 9/32 (28.1 %) either relapsed or were re-treated, and 3/32 (9.4 %) were lost to follow-up. On the GAD-7, 15/32 (46.9 %) had sustained remission, 6/32 (18.8 %) had response but not remission, 0/32 (0.0 %) were in sustained nonresponse, 8/32 (25.0 %) either relapsed or were re-treated, and 3/32 (9.4 %) were lost to follow-up.

Assessment of clinical and demographic predictors of improvement

Regarding outcomes for male and female patients, the percent improvement from baseline to week 6 on HDRS-17 was 83.1 ±SD8.4 (M, $n = 9$) vs 72.3 ±SD18.7 (F, $n = 23$) (unpaired $t_{29} = 2.19$; $p = 0.037$). For patients with versus without anxiety disorder comorbidity, the percent improvement from baseline to week 6 on HDRS-17 was 73.9 ±SD17.5 (anxiety comorbidity, $n = 21$) vs 77.7 ±SD17.2 (no anxiety comorbidity, $n = 10$) (unpaired $t_{29} = -1.45$; $p = 0.573$). For patients with versus without previous TMS treatment, the percent improvement from baseline to week 6 on HDRS-17 was 78.4 ±SD11.3 (previous TMS, $n = 13$) vs 72.7 ±SD20.4 (no previous TMS, $n = 19$) (unpaired $t_{29} = -0.99$; $p = 0.329$); full post-treatment trajectories on all 4 measures are plotted separately for both subgroups in Figure S4.

Regarding continuous variables, the correlation between baseline symptom severity on HDRS-17 versus percent improvement on HDRS-17 from baseline to week 6 was $r = 0.010$; $p = 0.959$. The correlation between the duration of the current depressive episode in months, versus percent improvement on HDRS-17 from baseline to week 6, was $r = 0.024$; $p = 0.898$. The correlation between the number of previous failed medication trials versus percent improvement on HDRS-17 from baseline to week 6, was $r = -0.164$; $p = 0.377$.

Discussion

To our knowledge, this is the first case series reporting outcomes for a homogeneous single-day regimen of TMS in a group of TRD patients under naturalistic conditions. The results indicate that the pharmacologically augmented, 20-session ONE-D TMS regimen is feasible, safe, well-tolerated, and effective, with almost all patients showing sustained effects at 3 months and a slight majority of patients showing sustained effects even at 6 months post-treatment. It is important to acknowledge from the outset that the present report remains an unblinded case series, which cannot yet disambiguate the relative contributions of the 20 iTBS sessions, the D-cycloserine, the lisdexamfetamine, or combinations thereof to the observed clinical effect; moreover, augmentation of plasticity is assumed but not yet measured in this naturalistic setting.

One notable outcome was the relatively delayed response to treatment. Pharmacological single-day interventions for TRD, such as ketamine/esketamine (Vekhova et al., 2024) or scopolamine (Drevets & Furey, 2010; Furey & Drevets, 2006), achieve a strong therapeutic effect within hours, which then fades over the following days and weeks. The response trajectory with ONE-D was effectively the opposite, with minimal effect in the initial hours and days after treatment, but steadily increasing proportions

of patients achieving remission in the 1–6 weeks after the intervention, and the majority maintaining their response 3–6 months post-treatment (Fig. 2).

The delayed response to ONE-D is particularly striking given the complete lack of any further psychosocial or other intervention following the treatment day. Conventionally, the therapeutic effect of TMS has been attributed not only to the magnetic pulses themselves but also to nonspecific factors associated with clinic visits: behavioral activation, social interaction, therapeutic contact, structure and daily routine, as well as concomitant psychotherapy in some cases (Donse et al., 2018). Thus it is unexpected that, with such nonspecific therapeutic factors removed, the effectiveness of the ONE-D intervention remains high, yet with a delayed response trajectory reminiscent of the exponential decay curve that has recently been described for once-daily TMS regimens (Berlow et al., 2023).

The delayed response to ONE-D also contrasts with much more rapid improvement reported for interventions such as the 5-day accelerated SAINT/SNT protocol (Cole et al., 2020, 2022). Whereas the ONE-D regimen surpassed 50 % remission only by week 3, the mean time to remission originally reported under SAINT was a much more rapid 2.6 days (Cole et al., 2020). The SAINT protocol includes additional features not present in the ONE-D regimen, including more pulses and sessions, as well as fMRI-personalized targeting; these features, alone or in combination, might facilitate rapid response, albeit at the cost of scalability. Combining elements of SAINT and ONE-D might therefore be a fruitful approach to achieve both rapid and durable effect.

The response and remission rates in the present series were also much higher than would normally be expected for a once-daily20-session course of TMS, in the absence of pharmacological augmentation. However, we note that Cole et al. (Cole et al., 2022) also delivered 20 once-daily sessions of 600 pulses of iTBS to a non-personalized left DLPFC target. Pre-administering DCS for only 10 of the 20 sessions, versus placebo, was already sufficient to boost the response rate from 29 % to 74 %, and the remission rate from 18 % to 39 %. DCS augmentation of all 20 sessions, in Ramos et al. (2025), boosted the remission rate to 75 %. The present findings thus replicate the recent reports of Ramos et al., and Cole et al., in suggesting that DCS augmentation could be a simple yet highly potent strategy for improving TMS outcomes.

Several key questions await clarification in future work. The ONE-D regimen, or variants thereof, should be assessed for generalizability to other clinical settings, and other configurations of TMS equipment and accessories. A propensity-matched comparative analysis of outcomes for non-ONE-D patients from the same clinics should be conducted to address possible sources of selection bias (e.g., age, sex, episode duration or medication-resistance). 7/32 patients (21.9 %) reported headache 1 week after the ONE-D regimen. While this is lower than the 65 % of iTBS patients reporting headache in the THREE-D trial (Blumberger et al., 2018), future studies should monitor for persistent headache or other symptoms following single-day treatment regimens. It should be clarified whether there is additive benefit to using both lisdexamfetamine and DCS, or whether only one of these agents would suffice. Although lisdexamfetamine was used to obtain a longer effect from the single dose, other generic options are also available with similar extended effect, and may be worth testing. Likewise, it remains unclear whether other non-prescription NMDA agonists, such as D-serine (Kantrowitz et al., 2015; Niimi et al., 2020) and sarcosine (Huang et al., 2013; Padhan et al., 2024), might achieve similar effects to DCS. It will also be important to determine whether DCS augmentation is useful only with iTBS, or

whether it may apply also to conventionally-patterned TMS at 1 Hz (Miron et al., 2021) or 10 Hz (Brown et al., 2020; Holtzheimer et al., 2010). Finally, it is unclear whether inter-session intervals shorter than 30 min could be attempted in the presence of pharmacological augmentation (Kukushkin et al., 2024). In answering these questions, we note that a single-day treatment regimen, quite aside from any clinical advantages, may also facilitate future empirical research on parameter optimization for therapeutic TMS.

Important limitations of this retrospective case series bear acknowledgment. No placebo comparator group was present for either the pharmacological augmentation or the TMS. Neither patients nor prescribers or assessors were blinded to the nature of the intervention. Only 19/32 patients were TMS-naive; the remainder were previous TMS responders, with a higher expected remission rate. Although the overall effect was similar in both groups (78 % vs 74 % HDRS-17 improvement in previous TMS responders, versus TMS-naive), future studies should likely focus on TMS-naive patients. The posterior DLPFC target also differs from the more commonly used BeamF3 or 5-cm-rule targets in common clinical use. The use of D-cycloserine and/or lisdexamfetamine for TMS augmentation remains off-label for clinicians. Outcomes may not generalize to broader populations with more severe illness, or more acute treatment settings. Positive incentives (e.g., gratitude for free treatment, expectations of success) cannot be ruled out as a potential source of bias for patient- and clinician-reported outcomes. Finally, durability beyond 6 months, and the viability of re-treatment following relapse, remain to be characterized in more detail.

In summary, an optimized TMS intervention requiring only one day for administration appears feasible, safe, tolerable, and at least as effective as current regimens. The delayed onset of effect may be less ideal for acute settings, where rapid response is required and personalized targeting may be worthwhile. Adding personalized targeting to a single-day, plasticity-augmented regimen could potentially facilitate more rapid response alongside more durable remission in a higher proportion of patients. If replicated under randomized controlled conditions, the efficacy of a single-day, neuroplastogen-enhanced treatment regimen could markedly improve the practical accessibility of TMS under real-world conditions.

CRediT authorship contribution statement

Donald A. Vaughn: Writing – review & editing, Supervision, Resources, Conceptualization. **Brooke Marino**: Writing – review & editing, Validation, Project administration, Investigation, Data curation. **Alex Engelbertson**: Investigation, Data curation. **Alexandra Dojnov**: Writing – review & editing, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Lena Johnson**: Writing – review & editing, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Madison Stine**: Validation, Project administration, Investigation, Data curation. **Fidel Vila-Rodriguez**: Writing – review & editing, Supervision, Investigation. **Nicholas Weiss**: Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation. **Georgine Nanos**: Supervision, Resources, Investigation. **Jonathan Downar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Donald Vaughn reports a relationship with Ampa Health that includes: board membership, employment, and equity or stocks. Brooke Marino reports a relationship with Ampa Health that includes: employment. Aleksandra Dojnov reports a relationship with Ampa Health that includes: employment. Lena Johnson reports a relationship with Ampa Health that includes: employment. Jonathan Downar reports a relationship with Ampa Health that includes: board membership, employment, and equity or stocks. Alex Engelbertson reports a relationship with NeuroStim TMS Centers that includes: employment. Madison Stine reports a relationship with NeuroStim TMS Centers that includes: employment. Nicholas Weiss reports a relationship with NeuroStim TMS Centers that includes: employment. Nicholas Weiss reports a relationship with Ampa Health that includes: equity or stocks. Nicholas Weiss reports a relationship with Arc Health Partners that includes: equity or stocks. Donald Vaughn reports a relationship with Arc Health Partners that includes: equity or stocks. Fidel Vila-Rodriguez reports a relationship with Seedlings Foundation that includes: funding grants. Fidel Vila-Rodriguez reports a relationship with Canadian Institutes of Health Research that includes: funding grants. Fidel Vila-Rodriguez reports a relationship with Brain Canada Foundation that includes: funding grants. Fidel Vila-Rodriguez reports a relationship with MagVenture Inc that includes: non-financial support. Fidel Vila-Rodriguez reports a relationship with BC Schizophrenia Society that includes: non-financial support. Jonathan Downar reports a relationship with National Institutes of Health that includes: funding grants. Jonathan Downar reports a relationship with Canadian Institutes of Health Research that includes: funding grants. Jonathan Downar reports a relationship with Brain Canada Foundation that includes: funding grants. Jonathan Downar reports a relationship with Ontario Brain Institute that includes: funding grants. Jonathan Downar reports a relationship with MagVenture Inc that includes: non-financial support. Jonathan Downar reports a relationship with TMS Neuro Solutions that includes: consulting or advisory. Jonathan Downar reports a relationship with Arc Health Partners that includes: consulting or advisory and equity or stocks. Jonathan Downar has patent Neuronavigation Caps issued to Jonathan Downar, Donald Vaughn. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A Supplementary material (1)

Document (15.46 MB)

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