Real-world effectiveness of a single-day regimen for transcranial magnetic stimulation using Optimized, Neuroplastogen-Enhanced techniques in Depression (ONE-D)

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Real-world effectiveness of a single-day regimen for transcranial magnetic stimulation using Optimized, Neuroplastogen-Enhanced techniques in Depression (ONE-D)

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Abstract

Background: Conventional transcranial magnetic stimulation (TMS) regimens are logistically burdensome, requiring days or weeks of clinic visits. Here we describe a TMS regimen enabling delivery of an entire therapeutic course in a single day.

Methods: This retrospective case series reports outcomes for an optimized, neuroplastogen-enhanced depression (ONE-D) treatment regimen delivering 600-pulse iTBS (120% MT) targeting left DLPFC via scalp heuristic, every 30 minutes for 20 sessions in 9.5 hours, enhancing neuroplasticity via single-dose d-cycloserine (125 mg) and lisdexamfetamine (20 mg), off-label, given 1 hour pre-treatment. 32 TMS-eligible adults with medication-resistant unipolar depression underwent the ONE-D regimen, with assessments on day-of-treatment then weekly x 6 weeks (HDRS-17, BDI-II, PHQ-9, and GAD-7).

Results: 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: mean weekly scores of 22.6±5.3(baseline), 13.5±6.4, 10.6±6.4, 7.9±4.9, 6.6±4.9, 6.3±4.8, 5.5±4.2 (HDRS-17), 37.5±9.0(baseline), 23.8±12.2, 17.1±11.1, 14.1±11.2, 11.0±8.7, 9.5±8.2, 7.6±7.8 (BDI-II,) 18.4±3.5(baseline), 11.4±5.1, 9.4±5.7, 6.9±5.2, 6.0±3.9, 5.3±4.0, 4.6±4.2 (PHQ-9), 14.3±5.2(baseline), 8.7±4.5, 6.4±5.0, 4.3±4.0, 3.8±3.6, 3.3±3.3, 3.1±2.7 (GAD-7). Response / remission rates (cross-sectional, not aggregated) were 90.3% and 74.2% (HDRS-17), 93.5% and 71.0% (BDI-II), 90.3% and 58.1% (PHQ-9), 93.3% and 76.7% (GAD-7) at week 6, and 92.6% and 77.8% (HDRS-17), 92.3% and 73.1% (BDI-II), 86.4% and 65.4% (PHQ-9), 91.7% and 80.0% (GAD-7) at week 12.

Conclusion: Delivery of an effective TMS course in one day appears feasible, safe, and well-tolerated. With neuroplastogen-enhancement, 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.

Introduction

Over the last two decades, transcranial magnetic stimulation (TMS) has entered increasingly widespread use as an intervention for treatment-resistant depression (TRD)[1–5], with recent evidence of superiority to pharmacotherapy in this indication[6]. TMS also enjoys a steadily growing evidence base for efficacy in other hard-to-treat psychiatric disorders, ranging from anxiety disorders[7] to post-traumatic stress disorder[8], obsessive-compulsive disorder[9,10], borderline personality disorder[7,11–13], and eating disorders[14–16], as well neurological disorders ranging from tinnitus[17] to Parkinson's disease[18] and Alzheimer's disease[19,20]. However, a significant barrier to access is the requirement for dozens of sessions of treatment in most indications. On conventional once-daily treatment schedules[1,2], the large number of clinic visits is prohibitive for many patients. This is particularly true for those who live far from a treatment center, or those with mobility issues, as is commonly encountered among older patients with depression[21], or those with Alzheimer's dementia or Parkinson's disease. In this context, there has been much recent interest in delivering TMS on accelerated treatment regimens, which reduce the number of visits required by delivering multiple sessions per day. Various studies have delivered 2-10 sessions per day[22–28], and particular enthusiasm has arisen for the therapeutic potential of TMS regimens that complete an entire course in 5 days, by delivering 8-10 sessions per day[5,29].

It is worth noting, however, that the very first report of accelerated TMS[22] used an even more abbreviated course of only 1.5 days, over which 15 hourly sessions were delivered. In an open-label case series of 14 patients with depression, this regimen achieved a respectable 43% response and 29% remission rate, comparable to that seen in subsequent large trials of once-daily treatment[4,25] and superior to pharmacotherapy outcomes in a recent large comparative trial[6]. Yet, remarkably, in the decade and a half since this initial report, no subsequent case series has followed up to replicate or refute the finding of successful TMS treatment in 1.5 days.

From a patient perspective, the question of what benefits may be obtained from a single day of treatment is of high interest, since there are many patients who have illnesses that are treatable by TMS, but who cannot overcome the logistical barriers to either 30 short daily visits or 5 long daily visits (as per the most common conventional or accelerated regimens). In particular, patients who live in remote areas, or those with mobility issues, or those with limited time available, may be interested in an estimate of the maximum response and remission rates that can be achieved by TMS in a single clinic visit.

A single-day treatment regimen for TMS could, of course, draw upon several evidence-based optimizations based on discoveries made in the preclinical and clinical literature since the original report of Holtzheimer et al., in 2010[22]. First, rather than the

37.5-minute 10 Hz sessions in common use at that time, a 3 min intermittent theta-burst stimulation (iTBS) session of 600 pulses could be substituted[4]. Second, regarding the interval between sessions, in clinical literature, accelerated TMS regimens have used intervals as short as 15 minutes[23,27,31], and preclinical work in motor cortex by Nettekoven et al. suggests that while an interval of 15 minutes between iTBS sessions may be insufficient to engender additional plasticity, an interval of 30 minutes does indeed allow for additional plasticity[30].

Of note, in an important yet somewhat neglected follow-up preclinical study by the same authors[32], more than half of the participants were described 'non-responders' to iTBS in *motor cortex*, showing no facilitation of the motor evoked potential and thus, no TMS-induced plasticity, regardless of inter-session interval. In the clinical literature, TMS non-response has often been attributed to off-target stimulation[33–35], and a variety of approaches have been developed using neuroimaging and frameless stereotaxy to ensure that stimulation is delivered at a personalized target, to improve the likelihood of response[28,36,37]. Yet the results of Nettekoven et al. [32] suggest that even when stimulation is known to be on-target (since primary motor cortex stimulation elicits visible movements of the upper extremity), it is still possible for a large proportion of individuals to show 'non-response': a lack of any *enduring* effects of TMS beyond the sessions of stimulation themselves, suggesting a failure of plasticity rather than a failure of targeting. In this context, an optimized regimen for therapeutic TMS would be advised to include techniques to enhance neuroplasticity. Such measures might increase the effect and durability of treatment, and perhaps even reduce the proportion of 'non-responders' lacking any durable effect from stimulation.

The neuroplastic effects of TMS are thought to be dependent on the well-studied mechanisms of long-term potentiation (LTP) and long-term depression (LTD) as mediated in part by glutamatergic neurotransmission at the NMDA receptor[38,39]. Preclinical evidence indicates that the NMDA partial agonist d-cycloserine (DCS) may enhance the effects of TMS on motor facilitation[40]. Likewise, an important recent clinical trial[41] indicated that pre-administration of 100 mg of DCS, ~1 hour before treatment, was able to markedly increase the response rates for a 20-session course of TMS from 29% to 74%, with remission rates increasing from 18% to 39%.

Finally, TMS-induced neuroplasticity (both facilitatory and inhibitory) has also been enhanced preclinically with the dopamine precursor L-DOPA (although, notably, *not* with the D2 agonist pramipexole)[42]. If increased dopamine at the synapse translates into enhanced neuroplasticity, one might expect that patients taking psychostimulant medications (which are thought to increase synaptic dopamine levels[43]) would show faster and stronger responses to therapeutic TMS. Indeed, this very finding was recently reported in a retrospective analysis of treatment outcomes for patients undergoing open-label TMS for depression in a large, academically based

clinic[44]. Lower doses (e.g., ~20 mg dextroamphetamine) appeared to be slightly more effective. Thus, dopaminergic augmentation of plasticity via low-dose psychostimulants may also merit inclusion in an optimized therapeutic TMS regimen.

Finally, regarding target, although personalized targeting via resting-state functional MRI is emerging as a technique for improving treatment outcomes[5,37,45], such methods can be challenging to implement outside academic centers. If a non-personalized, scalp-based heuristic is the only option for logistical reasons, it would be reasonable to at least base this heuristic on a target derived from causal network-mapping methods (lesion and stimulation effects) that make no *a priori* assumptions about what seed regions or networks are ideally targeted. Siddiqi et al. [46] have recently applied a causal network mapping approach to major depression, and identified two targets in left DLPFC: one smaller and anterior, and one larger and posterior. Scalp-based heuristics are available for both[47], and as posterior scalp targets are typically more tolerable for patients, the more posterior of these left DLPFC targets may be optimal for a regimen that allows only a single day for habituation to the scalp discomfort of TMS.

With these considerations in mind, it is possible for practitioners to combine all of these evidence-based optimizations into a regimen for a single day of TMS treatment, which for convenience we refer to hereafter as an Optimized, Neuroplasticity-Enhanced Depression (ONE-D) treatment regimen. Importantly, this regimen does not involve any elements that fall outside the scope of evidence-based, off-label prescribing. A regimen such as ONE-D can therefore be considered by prescribers on a risk/benefit basis, for patients who are unresponsive to medication and suitable for TMS, but unable to attend multiple days of treatment, and therefore seeking to maximize the effect of a single day of TMS. For such patients and practitioners, it would be helpful to understand what such a regimen might accomplish clinically.

The aim of the present study was therefore to quantify the response and remission rates for a single-day course using the ONE-D regimen, under naturalistic conditions, among real-world community providers and patients, to determine whether such a regimen is sufficiently effective to be worth any further consideration. Specifically, it would be of interest to know whether the real-world effectiveness of a single-day, 20-session course of ONE-D falls above or below the aforementioned ~40% remission and ~70% response rates reported for a 20-session, once-daily, DCS-augmented regimen[41]. 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[48], add-on low-frequency right DLPFC-TMS[49], additional pulses[50] of high-frequency left DLPFC-TMS, shortened inter-train intervals for 10 Hz stimulation[51], and TMS in adolescents[52,53]. The present retrospective case series therefore similarly reports on real-world outcomes

for a series of TRD patients undergoing a single day of TMS, according to the ONE-D regimen outlined above.

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 that have a cumulative experience of >9,000 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 declined a standard multi-visit course of treatment for logistical reasons, and 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. The present sample included for analysis 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.

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 (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 an intensity of 120% of motor threshold for upper extremity; 5) target defined at the causal-network-mapping-derived left posterior DLPFC maximum of Siddiqi et al., 2021[46] [MNI X-46 Y+9 Z+31] and localized using the updated BeamF3-like scalp heuristic of Mir-Moghtadaei et al., 2022[47], 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 15x20 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)[47] above (Supplementary Figure S1). Patients received 3 minutes of TMS every 30 minutes 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)[54], Beck Depression Inventory-II(BDI-II)[55], Patient Health Questionnaire-9(PHQ-9)[56], and General Anxiety Disorder-7 Scale (GAD-7)[57]. 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 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), who was an experienced psychiatric nurse practitioner trained in the administration of a standardized form of the HDRS-17, the GRiD-HAMD[58].

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[5,31]. 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 weeks was also adopted as a supplementary outcome measure.

Comparisons among subgroups were performed using the two-sample t-test for continuous variables, Fisher's Exact Test for categorical variables. Multiple linear regression using the general linear model was used to assess the significance of correlations between HDRS-17 improvement and the continuous predictor variables of baseline symptom severity, episode duration length in months, and number of previous medication trials.

Results

Clinical and Demographic Characteristics

Clinical and demographic characteristics of the series are presented in Table 1. In summary, the series included 32 patients (ages 22-62 yrs, 9 male and 23 female) with unipolar major depression and a current episode duration of 14.6±SD16.3 months (range, 2-60), having failed an average of 4.16±SD 2.60 antidepressant medication trials (range 0-10), of whom 19/32 were TMS-naive and the remaining 13/32 had previously received TMS on a conventional regimen of once-daily treatment (N=11), and/or on 8x-daily treatment for 5 days (N=2). Comorbid diagnoses included anxiety disorders (N=27), 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.

Table 1. Demographic and clinical characteristics of patient sample

	Overall
# Patients	32
Male	9 (28.1%)
Age	41.9 ± 12.1
Previous TMS	13 (40.6%)
Previous ECT	1 (3.1%)
Previous Psychotherapy	31 (96.9%)
Current Psychotherapy	17 (53.1%)
Previous Pharmacotherapy	28 (87.5%)

ECT, electroconvulsive therapy.

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 the treatment sessions, rated at 5.8/10±SD2.1/10 on a numerical rating scale where 0 = no discomfort and 10 = the maximum tolerable level of 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 36.4%±SD6.9% 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 and 27/32 patients at week 12.

Table 2. Side effects and adverse events

	Overall
# Patients	32
Side Effect(s) Reported During Treatment	25
Headache	12 (48.0%)
Scalp Pain	6 (24.0%)
Jaw Pain	2 (8.0%)
Neck Tension	2 (8.0%)
Ringing In Ear	1 (4.0%)
Low appetite	1 (4.0%)
Lightheadedness	1 (4.0%)
Side Effect(s) Reported 1 Week After Treatment	9
Headache	7 (77.8%)

Jaw Pain/Soreness	1 (11.1%)
Neck Soreness	1 (11.1%)
Serious Adverse Events	0 (0.0%)
Treatment-limiting Serious Adverse Events	0 (0.0%)

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.

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 Figure 1A-D. These trajectories reveal a gradual onset of therapeutic effect that was delayed in most cases by 1-4 weeks from the day of treatment, and reaching a plateau around weeks 4-6 post-treatment. From baseline to week 6, scores improved on HDRS-17 from 22.6±SD5.3 to 5.5±SD4.2 (Cohen's *d*, 3.58), on BDI-II from 37.5±SD9.0 to 7.6±SD7.8 (Cohen's *d*, 3.73), on PHQ-9 from 18.4±SD3.5 to 4.6±SD4.2 (Cohen's *d*, 3.36), and on GAD-7 from 14.3±SD5.2 to 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 to 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.

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, 28/31(90.3%) of patients met response and 23/31(74.2%) met remission criteria. On BDI-II, 29/31(93.5%) of patients met response and 22/31(71.0%) met remission criteria. On the PHQ-9, 28/31(90.3%) of patients met response and 18/31(58.1%) met remission criteria. On the GAD-7, 29/31(93.5%) of patients met response and 24/31(77.4%) met remission criteria; if excluding six patients with baseline GAD-7<10, 23/25 (92.0%) were responders and 18/25 (72.0%) 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. 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 (Figure 2A-D).

In terms of durability, at 12 weeks, among the 27/32 patients for whom data was available, response and remission rates were 92.6% and 77.8% on the HDRS-17, 92.3% and 73.1% on the BDI-II, 88.5% and 65.4% on the PHQ-9, and 91.7% and

80.0% on the GAD-7 (90.0% and 75.0% if excluding six patients with baseline GAD-7<10). Likewise, the degree of improvement appeared stable at 78.3%±SD21.0% for HDRS-17, 79.2%±SD23.6% for BDI-II, 77.0%±SD22.8% for PHQ-9, and 78.8%±SD17.4% for GAD-7 (76.6%±SD16.9% if excluding six patients with baseline GAD-7<10). There were no significant differences in scores between the 6-week versus the 12-week timepoints on the HDRS-17 (5.5±SD4.2 vs. 5.4±SD5.0; paired t_{22}= -0.19; *p*=0.848), BDI-II (7.6±SD7.8 vs. 7.7±SD7.0; paired t_{21}=-0.58; *p*=0.567), PHQ-9 (4.6±SD4.2 vs. 4.5±SD4.6; paired t_{21}=-0.32; *p*=0.755), or GAD-7 (2.7±SD2.9 vs. 3.2±SD3.0; paired t_{20}=-1.24; *p*=0.229) (3.1±SD3.1 vs. 3.7±SD3.0; paired t16=-1.32; p=0.204 if six patients with baseline GAD-7<10 were excluded).

Regarding re-treatment, the series included one patient who achieved remission in 2 weeks but subsequently partially relapsed (HDRS-17 scores from baseline to week 6: 22, 15, 6, 4, 6, 9, 12), with full relapse by week 12 (HDRS-17 score: 21). This patient underwent a repeat treatment with the same ONE-D regimen, and once again showed a similarly rapid but more durable response to the second treatment (HDRS-17 scores from baseline to week 6: 21, 12, 5, 5, 5, 9, 7).

Regarding generalizability, one additional patient (not included in the main series) presented with OCD as a comorbidity to MDD. This individual underwent a variant of the ONE-D regimen targeting the DMPFC rather than the DLPFC, and showed an improvement in YBOCS score from 26 at baseline to 7 at 1 week, 7 again at week 6, and 7 again at week 12. Improvement in PHQ-9 score was from 15 at baseline to 1 at week 1, 1 again at week 6, and 1 again at week 12. This case is described in detail in the Supplementary Material.

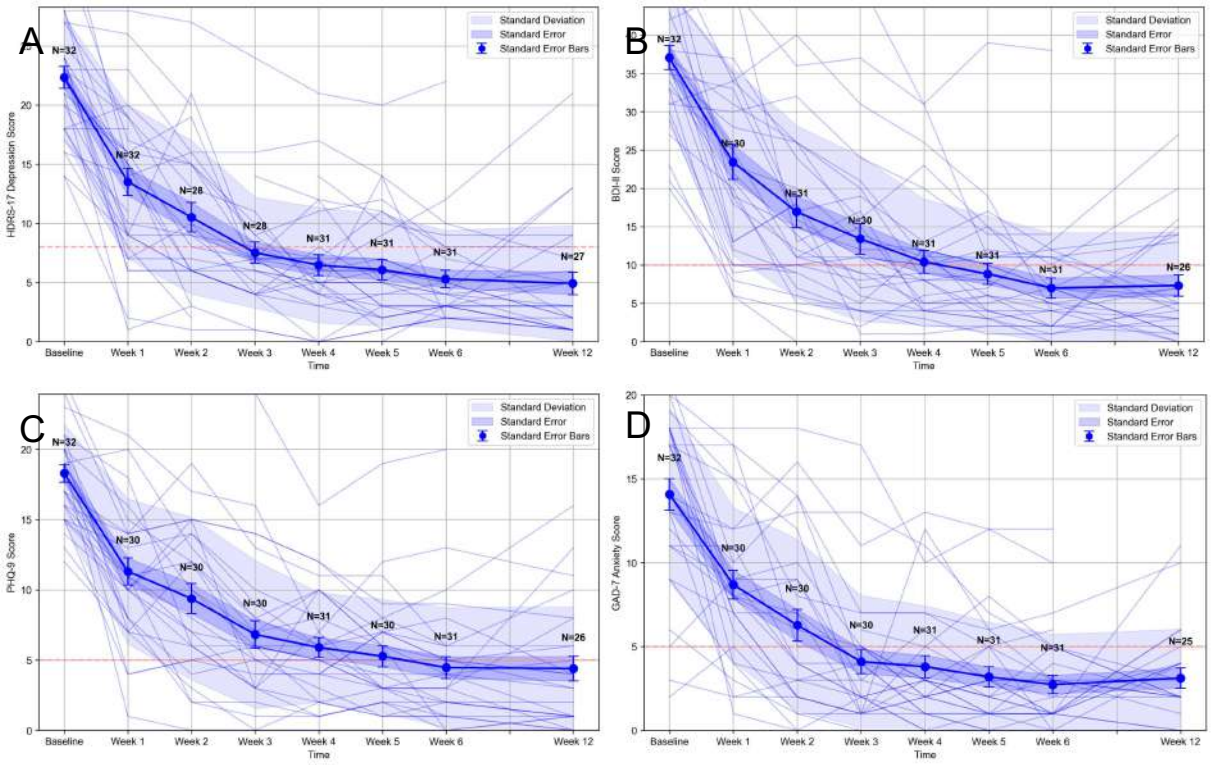

Figure 1. Trajectories of improvement following delivery of the ONE-D regimen on the HDRS-17 (A), BDI-II (B), PHQ-9 (C), and GAD-7 (D) symptom scales. Individual thin blue lines indicate trajectories for each individual patient; thick blue line indicates the mean, and shading indicates standard deviation 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 weeks for most patients on most scales.

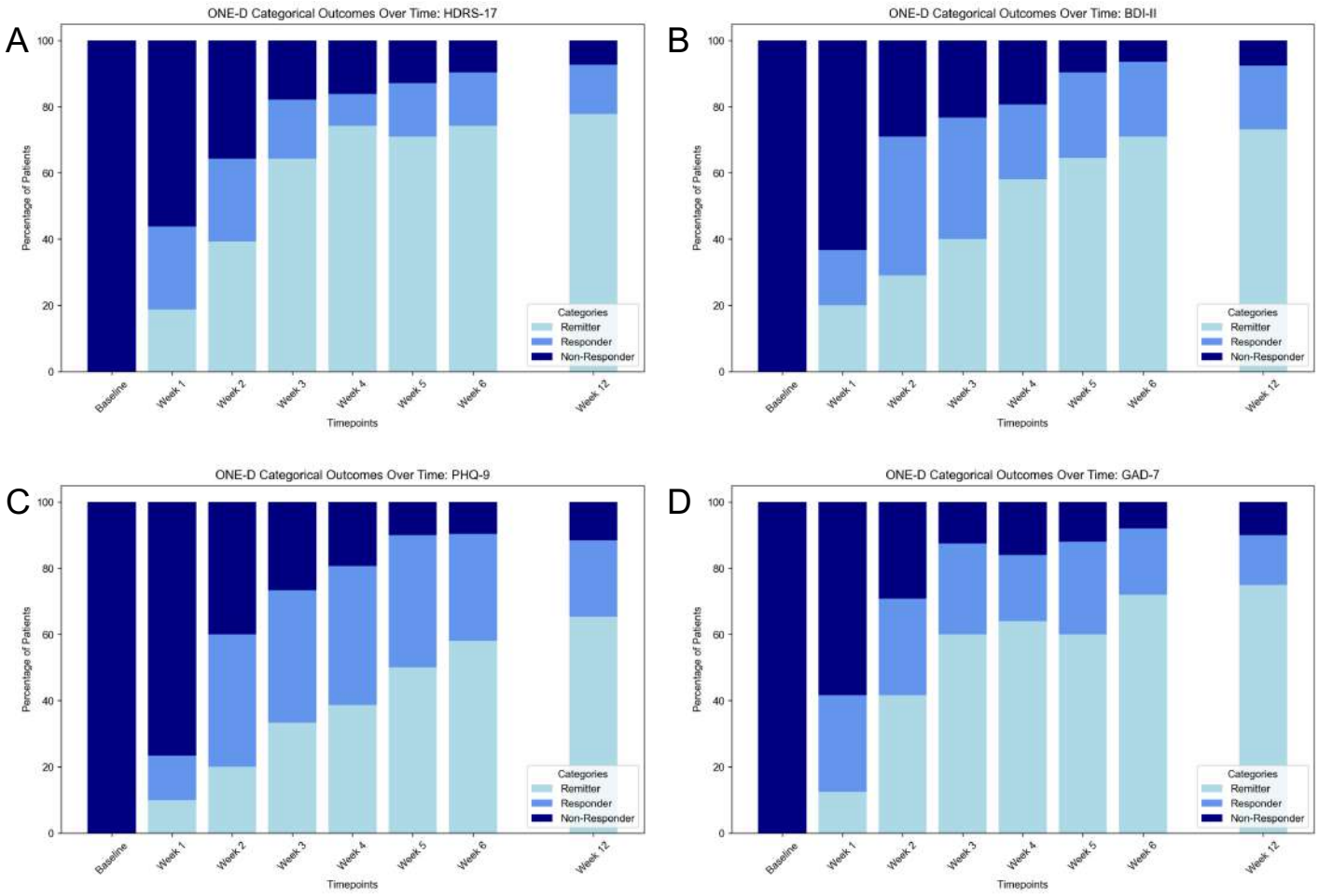

Figure 2. Categorical outcomes following delivery of the ONE-D regimen on the HDRS-17 (A), BDI-II (B), PHQ-9 (C), and GAD-7 (D) symptom scales. The proportion of patients meeting criteria for non-response, response, and remission at each week of follow-up (cross-sectional, not aggregated) are indicated 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.

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 t29=-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 75.3±SD16.9 (anxiety comorbidity, *n=27*) vs 73.9±SD20.8 (no anxiety comorbidity, *n=5*) (unpaired t29=-0.13; p=0.899). 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 t29=-0.99; p=0.329).

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

In terms of effectiveness, TMS is increasingly considered a preferred option in TRD, particularly following recent studies showing superiority of this intervention over conventional pharmacotherapy[6]. For many patients, however, it is simply not practical to attend long courses of treatment involving dozens of clinic visits. Even with accelerated regimens requiring only 5 days[5,24,29], patients who live far from treatment centers or who have limited mobility may still face significant logistical challenges in accessing TMS, regardless of how effective the treatment may be. In this context, it is reasonable to pose the open question of how much therapeutic benefit can be achieved in a single visit, under a treatment regimen optimized as far as possible using currently available evidence. Although the single-day ONE-D regimen may almost certainly be further optimized in various ways, the present case series indicates that a one-day TMS regimen is feasible, safe, well-tolerated, and effective, when administered under naturalistic community settings, to representative patients presenting for TMS treatment.

One unexpected outcome was the relatively delayed response to treatment. Pharmacological single-day interventions for TRD, such as ketamine/esketamine[59] or scopolamine[60,61], 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 large majority of these patients maintaining their response out to at least 3 months (Figure 2).

The delayed response to ONE-D is particularly striking given the complete lack of any further psychosocial or other intervention over the 6 weeks following treatment. Conventionally, the therapeutic effect of TMS treatment has been attributed not only to the magnetic pulses themselves but also to nonspecific beneficial factors associated with attending a series of clinic visits: behavioral activation, social interaction, therapeutic contact, structure and daily routine, as well as concomitant psychotherapy in some cases[62]. Thus it is unexpected that, with such nonspecific therapeutic factors removed, the effectiveness of the ONE-D intervention is still rather high. Similarly, it is unexpected that the response trajectory for a single-day intervention would still appear to follow the same delayed, exponential decay curve that has recently been described for once-daily TMS regimens[63].

The delay in response with the ONE-D regimen also stands in contrast to the much more rapid improvement in symptoms that has been described for the 5-day accelerated SAINT protocol[5,28]. 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[28]. The SAINT protocol includes additional features not present in the ONE-D regimen, including both a higher number of pulses and sessions as well as personalized target selection via functional MRI; it is possible that these features, alone or in combination, allow for substantially faster treatment response. Combining elements of SAINT and ONE-D might therefore be a fruitful approach in future.

It is also notable that the ONE-D regimen ultimately achieved unexpectedly high response rates of ~90% on all 4 outcome scales, along with unexpectedly high remission rates of >70% on 3 of the 4 scales, despite the lack of any personalized DLPFC targeting, and despite the delivery of only 20 sessions of treatment. However, the high response and remission rates are in keeping with the results of the previous work of Cole et al. [41], which also used only 20 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%. By extrapolation, DCS augmentation of all 20 sessions could potentially yield even further increases, in line with the present findings.

The ONE-D regimen is, of course, only one possible approach to optimizing a single-day treatment regimen, and simpler or alternative approaches should be considered for future study. For example, it is unclear whether there is additive benefit to using both lisdexamfetamine and DCS as neuroplastogens, or whether only one of

these agents would suffice on its own. Likewise, it remains to be clarified whether DCS is the only viable neuroplastogen targeting the NMDA receptor. Clinical studies have also investigated other, non-prescription agents in this role, including D-serine[64,65] and sarcosine[66,67]. If viable as alternatives to DCS, such agents would further improve the cost, scalability, and accessibility of neuroplastogen-enhanced TMS in various indications.

It is also unclear whether the combination of neuroplastogens with multiple daily sessions at short intervals is useful only with iTBS, or whether it may apply also to brief conventional sessions using 1 Hz[24] or 10 Hz[22,40] as per previous work. Finally, it is also unclear whether the 30-minute inter-session interval is truly the minimum possible, or whether even shorter intervals could be attempted in the presence of neuroplastogen augmentation. Recent work on the mechanisms of LTP and LTD induction in cell culture preparations suggests that 4 x 3-minute inductions achieve a robust cumulative effect at intervals of 30, 20, and 10 minutes, but not 0 minutes[68].

Given the large parameter space still to be optimized, it is worth considering whether current physiological proxies for TMS-induced neuroplasticity are truly generalizable to the actual therapeutic effects of TMS in clinical populations. Although this topic is large enough to merit a review all on its own, we note that most current characterizations of TMS protocols as ‘excitatory’ or ‘inhibitory’ remain based on transient (<90 min) effects in primary motor cortex, and not on any metrics of longer-term plasticity over days or weeks, which now appears to be the more relevant timescale for therapeutic TMS. Likewise, studies seeking to optimize factors such as the inter-session interval have also often employed transient effects in motor cortex as a proxy[30,32]. However, the present findings suggest that the sort of long-term plasticity that is most relevant to clinical outcomes may develop over days to weeks, not minutes to hours, from the time of induction.

Although neural populations can be difficult to monitor continuously over such timescales, recently developed models of learning and memory leveraging non-neural human embryonic kidney (HEK) cells suggest that schedules of multiple inductions at 10 minute intervals can achieve strong facilitation effects at >24 hours, despite relatively weak effects observed at 1-4 hours post-induction[68]. In this context, it is possible that some of our current assumptions about minimally effective or ineffective parameters (e.g., inter-session interval) will have to be re-examined and confirmed or disconfirmed via empirical findings in clinical populations. A single-day treatment regimen, quite aside from any clinical advantages, also offers practical advantages for future empirical research on parameter optimization for therapeutic TMS.

On the translational side, single-day regimens such as ONE-D may be particularly useful if they prove to generalize to other indications aside from TRD. For example, TMS is well-established as efficacious for chronic pain[69], but impractical for many patients due the limited durability of each session[70]. Neuroplastogen-

enhanced, accelerated regimens could potentially reduce the number of required clinic visits and increase the therapeutic duration of each visit. Likewise, although TMS now shows encouraging efficacy in Parkinson's disease[18] and Alzheimer's dementia[19,71], the need for dozens of clinic visits renders this intervention impractical for most patients with mobility and/or driving restrictions; an occasional, single-day regimen could improve feasibility (and perhaps also efficacy) substantially. Patients with medical conditions impairing mobility (e.g., dialysis, palliative care[72], or post-amputation phantom limb pain[70]) may also find a single-day regimen more feasible. The supplementary observation of a case of rapid and sustained remission from OCD and MDD, following a DMPFC-target variant of ONE-D (Supplementary Material), is encouraging regarding the possible generalizability of single-day regimens to other indications.

Important limitations of this small, open-label retrospective case series bear acknowledgment. No placebo comparator group was present for either the neuroplastogens or the TMS, limiting firm conclusions on efficacy or the relative contributions of each. Neither patients nor prescribers or assessors were blinded to the nature of the intervention. Only 19 of the 32 patients were TMS-naive; the remainder were previous TMS responders, in whom a higher remission rate would be expected. Although the overall difference in improvement was fairly small and non-significant (78% HDRS-17 score reduction in previous TMS responders, versus 73% in TMS-naive patients), 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 outcomes in this small, outpatient sample may not generalize to broader populations with more severe illness, or more acute treatment settings. Finally, the issues of durability beyond 3 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, if not more so. The delayed onset of effect was an unexpected feature, and suggests that regimens resembling ONE-D might be less ideal for acute or inpatient settings, where rapid response is required and other accelerated protocols such as SAINT may be better positioned to deliver remission in days rather than weeks. However, the triple combination of multiple daily sessions, personalized targeting, and pharmacological augmentation of plasticity could potentially offer the best of all possible worlds, enabling both rapid response and robust, durable remission in a high proportion of patients. Moreover, the supplementary observation of rapid and durable remission from severe OCD, using a dorsomedial ONE-D variant, suggests that the viability of the ONE-D regimen may generalize to other indications beyond TRD. If replicated under more formal randomized controlled conditions, the efficacy of a single-day, neuroplastogen-enhanced treatment regimen could substantially increase the value of

TMS as a practical treatment option for more patients under real-world conditions. If the high rates of remission do indeed replicate and generalize to other conditions, then single-day TMS protocols could potentially achieve a meaningful impact on the overall prevalence of TRD and other TMS-treatable conditions, in the years to come.

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Disclosures and Competing Interests

DV is a co-founder of Ampa Health, and holds equity in Ampa Health and Arc Health Partners. BM is employed by Kind Health Group and Ampa Health. AE is employed by Neurostim TMS Centers. AD is employed by Ampa Health. NW is employed by Neurostim TMS Centers and holds equity in Arc Health Partners and Ampa Health. FVR has received support from Seedlings Foundation, CIHR, and Brain Canada. He is a volunteer director with the BC Schizophrenia Society board of directors, and he has received in-kind equipment support from Magventure for investigator-initiated research. JD has received grant support from the National Institutes of Health (NIH), Canadian Institutes of Health Research (CIHR), Brain Canada, and the Ontario Brain Institute. He has received in-kind equipment support from Magventure for investigator-initiated research. He has also received consulting fees from TMS Neuro Solutions and Arc Health Partners. He is a co-founder of Ampa Health, and holds equity in Ampa Health and Arc Health Partners.

SUPPLEMENTARY MATERIAL

Supplementary Case Report: Dorsomedial prefrontal ONE-D regimen in comorbid MDD/OCD

M was a 51 year old woman who presented with a chief complaint of “depression”. Over the previous four years she had developed increasingly severe dysphoric and irritable mood, anhedonia, self-critical ruminations, low motivation, impaired concentration, both initial and middle insomnia and consequent daytime exhaustion. She had become increasingly socially isolated, rarely leaving her house. She cherished her family deeply, particularly her grandchildren, but had come to dread spending time with them because of the feelings of anxiety and self-reproach it engendered.

On assessment she was found to struggle with nearly incessant thoughts about neatness, cleanliness and symmetry. She often babysat her young grandchildren, but spent the majority of her time with them rearranging all the toys and other objects immediately after they began playing with them, as it was intolerable for her to have any of these items “out of place.” If she was unable to clean and rearrange these objects immediately she would become intensely anxious and irritable and would be unable to focus on any other topic. She was also frequently bombarded with preoccupations about the possibility of there being some sort of dirt or contaminants in her eyes or ears. In response, she would typically spend over three hours daily cleaning her eyes and ears with q-tips, causing severe irritation of her eyes, periorbital skin and external ear canal because of excessive cleaning and scraping.

As part of the study assessment, a Y-BOCS was completed by author NW and M’s score was found to be 26. The Hamilton Depression rating scale score was 18, BDI-II was 17 and PHQ-9 was 15. Diagnoses of OCD and Major Depressive Disorder were assigned.

M was able to complete all components of the study procedure on the day of treatment, which included administration of lisdexamfetamine and d-cycloserine prior to 20 sessions of 600-pulse iTBS to the DMPFC (scalp target: Fz) delivered every 30 minutes. On follow up one week later, she reported a marked improvement in depression, sleep and OCD symptoms. She reported that she had just spent time with her nieces and nephews and had enjoyed it greatly because she “wasn’t dominated by this need to clean and straighten immediately after they touched anything.” For the last few days, she reported being free of preoccupations about dirt or contaminants in her eyes or ears and had not felt the need to clean them with Q-tips. The Y-BOCS total score was found to be 7 and the PHQ-9 was 1.

Over the next 5 weeks of follow up, M continued to show overall improvement in both OCD and depression symptoms. She experienced a temporary flare in OCD symptoms during week 3 of follow up, with a recurrence of excessive and harmful cleaning of her eyes and ears with Q-tips. This occurred after finding out that her husband was showing signs concerning for a recurrence of a prior cancer. That week the Y-BOCS increased to 17 and the PHQ-9 to 6. However, by the following week’s assessment this flare in OCD symptoms had resolved and the Y-BOCS was 6. At the end of the 6 week follow up she had a Y-BOCS of 7 and a PHQ-9 of 1. At week 12, her YBOCS score remained at 7, PHQ-9 at 1, and BDI-II at 0.

Figure S1. Custom scalp cap with pre-marked motor hotspot grid and treatment targets. The three targets visible at left are BeamF3, and the anterior and posterior left DLPFC targets of Siddiqi et al., 2021. The posterior DLPFC target, designated PF3, was employed for all patients in the present report.

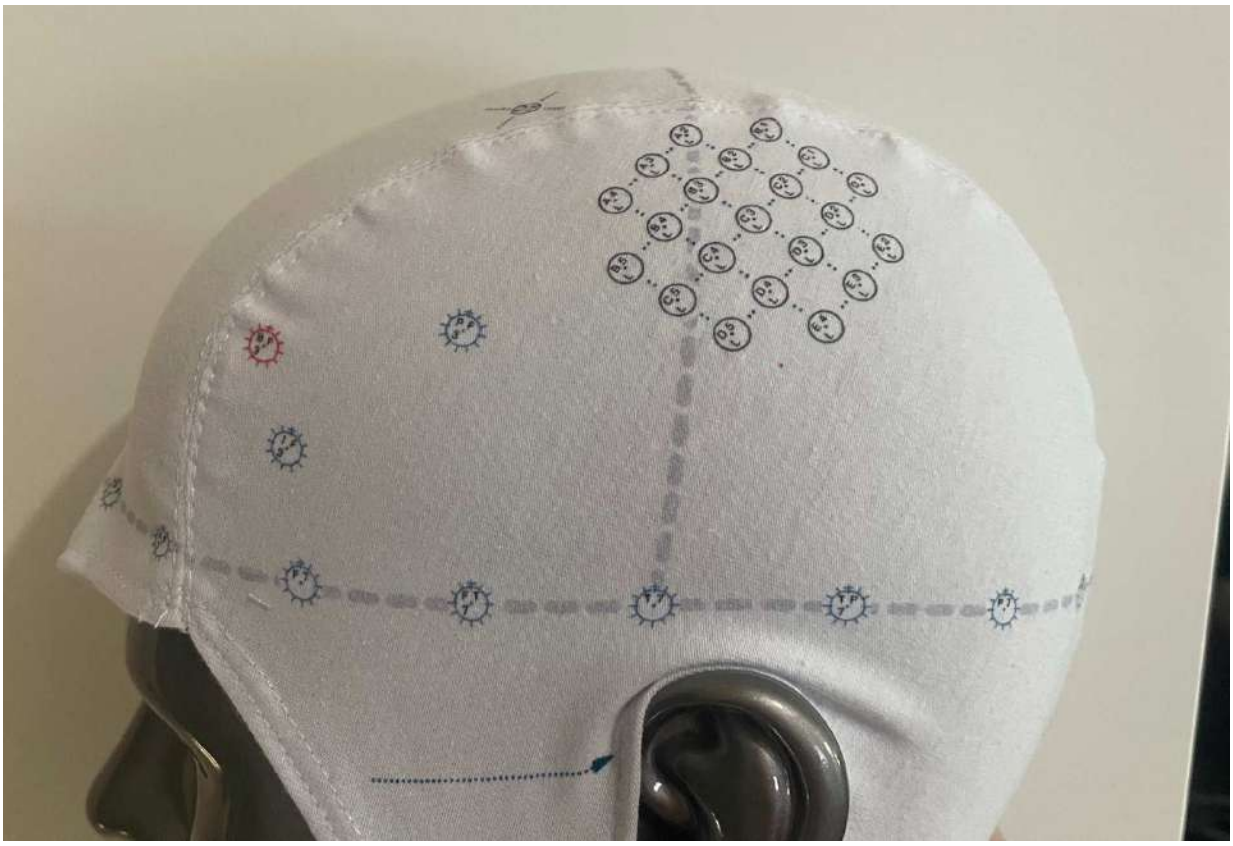

Figure S2. Treatment coil with integrated endoscope camera. The centrally-placed, 4 mm diameter endoscope camera on the underside of the coil enables accurate placement of the coil over the intended target, indicated on the cap with a pre-printed circle inscribed with an alphanumeric identifier.

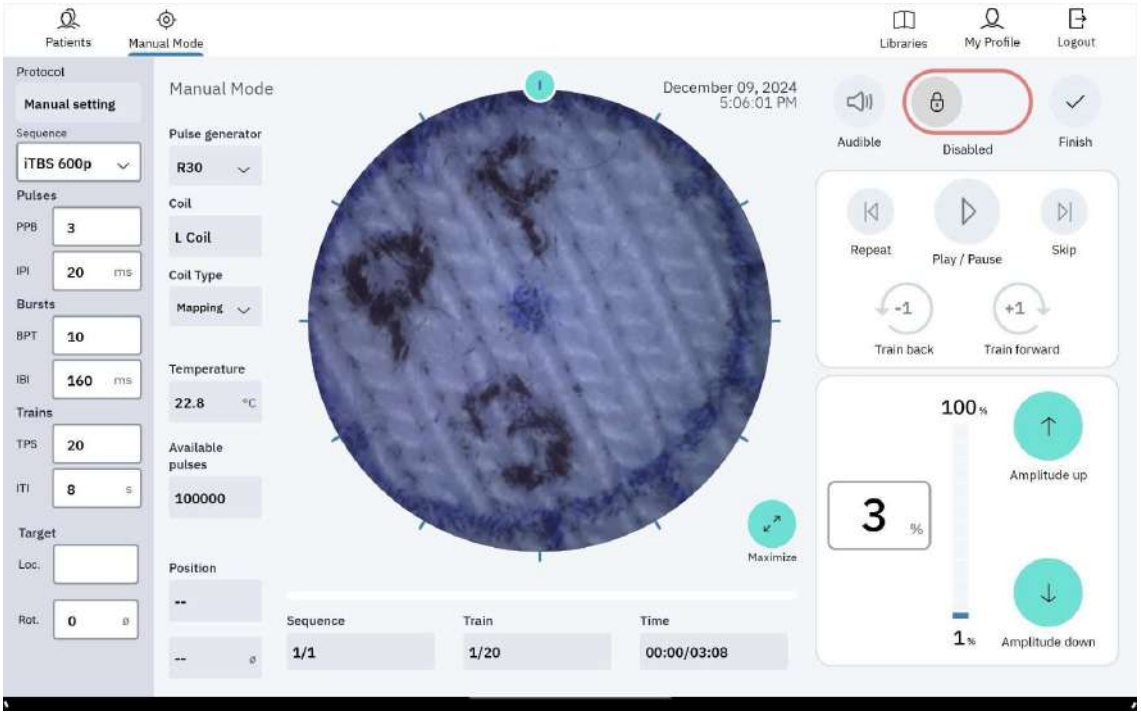

Figure S3. Percent improvement from baseline, by symptom scale. When expressed in terms of percent reduction from the baseline score, the trajectories of improvement showed close agreement across all four scales at all timepoints of assessment.

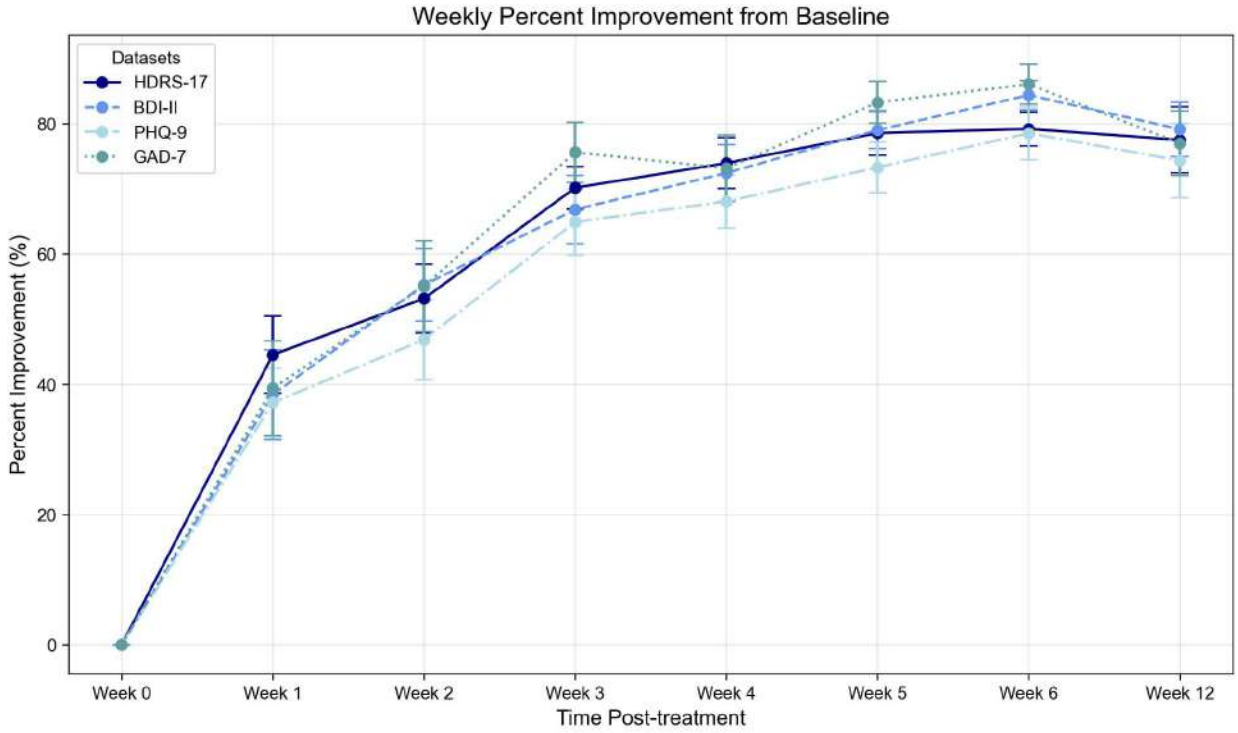

Table S1. Weekly Symptom Score Summaries, by Scale

	Weekly Assessments							
Outcome Measure	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 12
HDRS-17								
N	32	32	28	28	31	31	31	27
Mean Score	22.6	13.5	10.6	7.9	6.6	6.3	5.5	4.9
SD	5.3	6.4	6.4	4.9	4.9	4.8	4.2	4.8
SE	0.9	1.1	1.2	0.9	0.9	0.9	0.8	0.9
Mean % improvement	0.0	40.5	53.1	65.3	70.8	72.3	75.6	78.4
% Responders (≥ 50% improvement)	0.0	43.8	64.3	82.1	83.9	87.1	90.3	92.6
% Remitters (≤7 score)	0.0	18.8	39.3	64.3	74.2	71.0	74.2	77.8
BDI-II								
N	32	30	31	30	31	31	31	26
Mean Score	37.5	23.8	17.1	14.1	11.0	9.5	7.6	7.4
SD	9.0	12.2	11.1	11.2	8.7	8.2	7.8	6.8
SE	1.6	2.2	2.0	2.0	1.6	1.5	1.4	1.3
Mean % improvement	0.0	36.5	54.4	62.5	70.8	74.8	79.7	80.3
% Responders (≥ 50% improvement)	0.0	36.7	71.0	76.7	80.6	90.3	93.5	92.3
% Remitters (≤9 score)	0.0	20.0	29.0	40.0	58.1	64.5	71.0	73.1
PHQ-9								
N	32	30	30	30	31	30	31	26
Mean Score	18.4	11.4	9.4	6.9	6.0	5.3	4.6	4.3

SD	3.5	5.1	5.7	5.2	3.9	4.0	4.2	4.3
SE	0.6	0.9	1.0	1.0	0.7	0.7	0.8	0.8
Mean % improvement	0.0	38.2	49.1	62.3	67.4	71.0	75.1	76.4
% Responders (≥ 50% improvement)	0.0	23.3	60.0	73.3	80.6	90.0	90.3	88.5
% Remitters (≤4 score)	0.0	10.0	20.0	33.3	38.7	50.0	58.1	65.4
<u>GAD-7</u>								
N	32	30	30	30	31	31	31	25
Mean Score	14.3	8.7	6.4	4.3	3.8	3.3	2.7	3.2
SD	5.2	4.5	5.0	4.0	3.6	3.3	2.9	2.9
SE	0.9	0.8	0.9	0.7	0.6	0.6	0.5	0.6
Mean % improvement	0.0	38.7	55.3	70.1	73.5	76.7	81.0	77.8
% Responders (≥ 50% improvement)	0.0	43.3	73.3	86.2	87.1	90.3	93.3	91.7
% Remitters (≤4 score)	0.0	20.0	50.0	63.3	71.0	67.7	76.7	80.0
<u>GAD-7 (excluding patients scoring <10)</u>								
N	26	24	24	25	25	25	24	20
Mean Score	16.2	9.7	7.3	4.7	4.4	3.9	3.1	3.8
SD	3.2	4.4	5.0	4.1	3.7	3.4	3.1	2.9
SE	0.6	0.9	1.0	0.8	0.7	0.7	0.6	0.6
Mean % improvement	0.0	40.4	55.3	70.9	72.9	76.1	81.0	76.9
% Responders (≥ 50% improvement)	0.0	41.7	70.8	87.5	84.0	88.0	92.0	90.0

% Remitters (≤4 score)	0.0	12.5	41.7	60.0	64.0	60.0	72.0	75.0

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

Table S2. Comorbidities for Individual Patients

Patient #	Comorbidities
KHG1	GAD
KHG2	GAD, PTSD
KHG3	GAD
KHG4	PTSD
KHG5	PTSD, ADHD, unspecified eating disorder
KHG6	GAD
KHG7	GAD
KHG8	GAD
KHG9	GAD
KHG10	None
KHG11	GAD, PTSD
KHG12	GAD, PTSD
KHG13	GAD, ADHD
NS1	GAD, PTSD, Anorexia Nervosa
NS2	GAD
NS3	GAD, ADHD
NS4	GAD
NS5	PTSD, unspecified eating disorder
NS6	GAD
NS7	None
NS8	GAD
NS9	GAD
NS10	None
NS11	None
NS12	ADHD
NS13	GAD, ADHD
NS14	Binge Eating Disorder
NS15	None
NS16	GAD
NS17	PTSD, Panic Disorder
NS18	GAD, PTSD
NS19	GAD, PTSD

Patients KHG4, KHG8, and NS16 were considered non-responders (Week 6 HDRS score >= 10) while patients KHG1-3, KHG5-7, KHG9-13, NS1-14, and NS17-19 were considered responders (Week 6 HDRS-17 score <10 and/or 50% improvement HDRS-17 score by Week 6). Patient NS15 did not complete the HDRS-17 on Weeks 3-6 but was considered a remitter with a final HDRS-17 score of 3.

Table S3. Medication List for Individual Patients

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Patient #	Medications taken (dosage per day)
KHG1	Duloxetine (60 mg)
KHG2	Escitalopram (5 mg), Propranolol (10 mg, *as needed*),
KHG3	None
KHG4	None
KHG5	Fluoxetine (20 mg), Adderall XR* (20 mg, *as needed*)
KHG6	Sertraline (250 mg), Trazodone (100 mg)
KHG7	None
KHG8	Duloxetine (40 mg), Alprazolam (0.5 mg, *as needed*)
KHG9	Adderall IR* (5 mg)
KHG10	Bupropion (450 mg)
KHG11	None
KHG12	None
KHG13	Escitalopram (20 mg), Adderall XR* (5 mg), Alprazolam (0.25 mg, *as needed*)
NS1	Bupropion (450 mg), Concerta* (54 mg), Lorazepam (1 mg, *as needed*), Trazodone (200 mg), Zolpidem (12.5 mg)
NS2	Topiramate (50 mg)
NS3	Duloxetine (60 mg), Vyvanse* (60 mg), Bupropion SR (100 mg), Zolpidem (10 mg, *as needed*)
NS4	Adderall XR* (10 mg)
NS5	Gabapentin (300 mg), Clonidine (0.3 mg), Buspirone (2 x 15 mg), Prazosin (1 mg), Citalopram (40 mg), Trazodone (100 mg)
NS6	Prazosin (6 mg**), Escitalopram (25 mg), Bupropion XL (450 mg), Trazodone (50-100 mg, *as needed*), Lorazepam (1 mg, *as needed*)
NS7	Vilazodone (20 mg), Modafinil (100-150 mg)
NS8	None
NS9	Vyvanse* (70 mg), Sertraline (200 mg)
NS10	Escitalopram (20 mg), Venlafaxine (75 mg)
NS11	Bupropion (450 mg***), Trazodone (200 mg)
NS12	Citalopram (40 mg), Bupropion XL (150 mg), Aripiprazole (5 mg), Hydroxyzine HCl (25 mg, *as needed*), Vyvanse* (30 mg)
NS13	Bupropion XL (300 mg), Desvenlafaxine (100 mg)
NS14	Vortioxetine (10 mg)
NS15	Citalopram (40 mg)
NS16	Zolpidem (5 mg, *as needed*), Adderall IR* (2 x 20 mg)
NS17	Sertraline (200 mg), Propranolol (120 mg), Alprazolam (2 mg, *as needed*)
NS18	Alprazolam (0.5 mg), Zolpidem (10 mg)
NS19	Fluoxetine (40 mg), Hydroxyzine HCl (12.5 mg, *as needed*)

Patients KHG4, KHG8, and NS16 were considered non-responders (Week 6 HDRS score >= 10) while patients KHG1-3, KHG5-7, KHG9-13, NS1-14, and NS17-19 were considered responders (Week 6 HDRS-17 score <10 and/or 50% improvement HDRS-17 score by Week 6). Patient NS15 did not complete the HDRS-17 on Weeks 3-6 but was considered a responder with a HDRS-17 score of 3.

*Not taken day of treatment, **3 mg in the morning, 3 mg in the evening, ***300 mg in the morning, 150 mg in the evening,