JAMA Psychiatry | Original Investigation

Efficacy of Adjunctive D-Cycloserine to Intermittent Theta-Burst Stimulation for Major Depressive Disorder
A Randomized Clinical Trial

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IMPORTANCE The antidepressant effects of transcranial magnetic stimulation protocols for major depressive disorder (MDD) are thought to depend on synaptic plasticity. The theta-burst stimulation (TBS) protocol synaptic plasticity is known to be *N*-methyl-D-aspartate (NMDA)–receptor dependent, yet it is unknown whether enhancing NMDA-receptor signaling improves treatment outcomes in MDD.

OBJECTIVE To test whether low doses of the NMDA-receptor partial-agonist, D-cycloserine, would enhance intermittent TBS (iTBS) treatment outcomes in MDD.

DESIGN, SETTING, AND PARTICIPANTS This was a single-site 4-week, double-blind, placebo-controlled, randomized clinical trial conducted from November 6, 2019, to December 24, 2020, including 50 participants with MDD. Participants were recruited via advertisements and referral. Inclusion criteria were as follows: age 18 to 65 years with a primary diagnosis of MDD, a major depressive episode with score of 18 or more on the 17-item Hamilton Depression Rating Scale, a Young Mania Rating Scale score of 8 or less, and normal blood work (including complete blood cell count, electrolytes, liver function tests, and creatinine level).

INTERVENTIONS Participants were randomly assigned 1:1 to either iTBS plus placebo or iTBS plus D-cycloserine (100 mg) for the first 2 weeks followed by iTBS without an adjunct for weeks 3 and 4.

MAIN OUTCOMES AND MEASURES The primary outcome was change in depressive symptoms as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) at the conclusion of treatment. Secondary outcomes included clinical response, clinical remission, and Clinical Global Impression (CGI) scores.

RESULTS A total of 50 participants (mean [SD] age, 40.8 [13.4] years; 31 female [62%]) were randomly assigned to treatment groups: iTBS plus placebo (mean [SD] baseline score, 30.3 [4.2]) and iTBS plus D-cycloserine (mean [SD] baseline score, 30.4 [4.5]). The iTBS plus D-cycloserine group had greater improvements in MADRS scores compared with the iTBS plus placebo group (mean difference, −6.15; 95% CI, −2.43 to −9.88; Hedges *g* = 0.99; 95% CI, 0.34-1.62). Rates of clinical response were higher in the iTBS plus D-cycloserine group than in the iTBS plus placebo group (73.9% vs 29.3%), as were rates of clinical remission (39.1% vs 4.2%). This was reflected in lower CGI-severity ratings and greater CGI-improvement ratings. No serious adverse events occurred.

CONCLUSIONS AND RELEVANCE Findings from this clinical trial indicate that adjunctive D-cycloserine may be a promising strategy for enhancing transcranial magnetic stimulation treatment outcomes in MDD using iTBS requiring further investigation.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03937596

JAMA Psychiatry. 2022;79(12):1153-1161. doi:10.1001/jamapsychiatry.2022.3255
Published online October 12, 2022. Corrected on December 7, 2022.

Supplemental content

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Major depressive disorder (MDD) is a significant public health problem and leading cause of worldwide disability.[1] Treatment resistance is common in MDD,[2] however, for these individuals, targeted noninvasive brain stimulation is an alternative. Repetitive transcranial magnetic stimulation (rTMS) and more recently, theta-burst stimulation (TBS), are the noninvasive brain stimulation modalities with the largest evidence base in MDD.[3,4] Although efficacious, an unacceptable proportion of patients do not significantly improve, and several aspects of the TMS parameter space are under investigation to enhance clinical outcomes.

rTMS and TBS are believed to depend on synaptic plasticity in targeted circuits.[5] Yet, there are several lines of evidence to suggest that synaptic plasticity is not intact in MDD, such as impaired learning and memory[6-9] and lower expression of trophic factors.[10-12] Using TMS as a tool to probe synaptic plasticity, individuals with MDD have reduced long-term potentiation–like facilitation in the motor cortex[13-16] and prefrontal cortex.[17] Importantly, this is observed with the intermittent TBS (iTBS) protocol used in MDD treatment.[15,16] As such, iTBS treatment effects may be constrained by impaired synaptic plasticity in MDD.

One potential strategy to improve outcomes is to adjunctively target the *N*-methyl-D-aspartate (NMDA) receptor during stimulation, an ionotropic glutamate receptor and key regulator of synaptic plasticity.[18] Synaptic plasticity with continuous and intermittent TBS is NMDA-receptor dependent, as antagonists abolish the effects of both protocols.[19,20] We have shown that targeting the NMDA receptor with low doses of the partial agonist, D-cycloserine (DCS), normalizes long-term motor cortex plasticity in individuals with MDD.[16] Moreover, it results in greater persistence of iTBS-induced changes compared with placebo.[16] However, a demonstration that these physiological effects have an impact on treatment outcomes is lacking.

Here, we present randomized, placebo-controlled trial data testing low-dose adjunctive DCS as a strategy to improve iTBS treatment outcomes in MDD. We hypothesized that adjunctive DCS would lead to greater reductions in depressive symptoms than placebo.

Key Points

Question Can the efficacy of transcranial magnetic stimulation in major depressive disorder be enhanced with a pharmacological adjunct?

Findings In this double-blind, placebo-controlled, randomized clinical trial that included 50 participants, those receiving intermittent theta-burst stimulation with adjunctive D-cycloserine (100 mg) had significantly greater improvements in depressive symptoms compared with stimulation with a placebo.

Meaning Adequately powered multisite studies are required to confirm whether adjunctive D-cycloserine enhances antidepressant treatment outcomes with intermittent theta-burst stimulation transcranial magnetic stimulation in major depressive disorder.

Methods

Between November 6, 2019, and December 24, 2020, we conducted a 4-week, double-blind, placebo-controlled, randomized clinical trial at the University of Calgary (Supplement 1). The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary and Health Canada, and participants provided written informed consent. A Health Canada clinical trial application amendment was made to rectify exclusion criteria omissions identified during the screening process. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Participants

Recruitment involved advertisements and referral. Race and ethnicity data were collected to inform generalizability and external validity by self-report questionnaire. Participants from the following race and ethnicity groups were included: Asian, Black, Hispanic, Middle Eastern, White, and mixed.

Eligibility criteria were male and female individuals aged 18 to 65 years with a primary diagnosis of major depressive disorder by *DSM-5* criteria, experiencing a major depressive episode (MDE) with score of 18 or more on the 17-item Hamilton Depression Rating Scale (HRDS-17), a Young Mania Rating Scale score of 8 or less, and normal blood work (complete blood cell count, electrolytes, liver function tests, and creatinine level). Failure of at least 1 adequate antidepressant trial or psychotherapy was required for eligibility but not more than 4 adequate trials of antidepressants in the current episode as determined by the antidepressant treatment history form. Medications must have remained unchanged for 4 weeks before enrollment and throughout the study.

Exclusion criteria were allergy to DCS, acute suicidality, potential harm to self or others, psychosis, a substance use disorder within the last 3 months, benzodiazepine use, seizures, pacemaker or metallic implant, unstable medical condition, pregnancy or lactation, a history of nonresponse to rTMS or electroconvulsive therapy, comorbid psychiatric conditions that were deemed primary, and the initiation of psychotherapy within 3 months of enrollment or during the trial.

Adjunctive DCS

DCS was purchased as Seromycin (Parsolex Gmp Center), 250-mg capsules, and repackaged as capsules containing 100 mg of DCS. Placebo capsules contained 100 mg of microcrystalline cellulose. Participants were provided with the study drug at randomization and instructed to take their capsules at least 60 minutes before their scheduled treatments.[21] Participants self-reported time of capsule ingestion.

Participants were provided with blinded placebo or DCS, 100 mg, for the first 2 weeks of the 4-week study. This aligns with DCS treatment courses for urinary tract infection in the interest of antimicrobial stewardship. Adjunctive DCS was not paired with iTBS for the full treatment course as there was a priori concern that repeated pairings of DCS and iTBS could engage homeostatic mechanisms, occlude plasticity, and potentially decrease treatment efficacy based on (1) our own data

in healthy individuals in which it blunted iTBS motor plasticity,[22] (2) inconsistent data from previous healthy motor plasticity studies[23] (J. Wrightson, PhD, personal communication, August 19, 2022), and (3) ex vivo slice physiology indicating NMDA-receptor internalization with glycine or D-serine.[24] Moreover, this design affords an opportunity to examine clinical course in the absence of a placebo effect for the final 2 weeks.

Randomization and Blinding

A 1:1 random number sequence was generated. Eligible participants were randomly assigned to treatment group with allocation concealment. Eligible participants, treatment team, and outcome assessors remained blind to treatment condition throughout the duration of the study.

iTBS

We used a MagPro X100 stimulator (MagVenture) and a COOL-B70 coil. Targeting of the left dorsolateral prefrontal cortex used the Beam F3 method.[25] Although anatomical and functional neuroimaging was collected as part of the study protocol, targeting using surface anatomy was chosen to increase generalizability to clinical settings where neuroimaging derived targets are not feasible. The Beam F3 target was registered to the participant's anatomical MRI or a template brain (Visor2, ANT Neuro). Resting motor threshold (rMT) was determined using electromyographic electrodes placed over the first dorsal interosseous muscle, defined as the minimal intensity eliciting greater than 50-μV responses in at least 5 of 10 stimulations.

Participants all received active iTBS, consisting of 600 pulses per session delivered in 20 trains of triplets at 50 Hz repeated at 5 Hz (2 seconds on, 8 seconds off) at 80% rMT. Participants received daily treatments Monday through Friday for a total of 20 treatments.

Assessments

For enrollment and all clinician ratings, participants were assessed by a blinded investigator psychiatrist (A.M.). The primary outcome of the study was change in Montgomery-Åsberg Depression Rating Scale (MADRS[26]) depressive symptoms from baseline to the 4-week end point. The MADRS was administered at baseline, after 2 weeks, and after 4 weeks of treatment. Clinician-rated secondary outcomes included rates of clinical response (≥50% reduction in MADRS score) and clinical remission (≤10 MADRS score). The Clinical Global Impression (CGI[27]) was administered to assess overall illness severity and improvement at baseline, 2 weeks, and 4 weeks. The protocol was twice amended to align with registration incongruities.

Self-reported depressive symptoms were rated weekly using the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR[28]), as were anxiety symptoms using the 7-item Generalized Anxiety Disorder (GAD-7[29]). Participants' perception of well-being was evaluated with a visual analog scale (VAS) for overall well-being (score, 0-100), and quality of life was assessed with the World Health Organization (WHO) Quality of Life (WHOQOL-BREF[30]) instrument at baseline and after 2 and 4 weeks. Anhedonia, measured with the Snaith Hamilton Pleasure Scale (SHAPS), and illness perception, measured by the Brief Illness Perception Questionnaire (BIPQ), were assessed at baseline and after 4 weeks.

Cognitive function was assessed at baseline and after 2 weeks using self-report measures and neuropsychological testing, and these data will be reported elsewhere. Daily adverse effects were rated on a scale from 0 to 10, ranging from absent to adverse effects causing significant distress.

To measure blinding integrity, participants were asked whether they believed they received placebo or DCS. The blinding integrity of the clinical raters and iTBS administrators was not measured.

Sample Size Determination

As there are no previous studies using an adjunct to enhance iTBS, we determined our sample size based on a moderate effect size of 0.5, 95% power, and $\alpha \leq .05$. This revealed a required sample of 44 participants. In planning the final sample size, we included previous dropout rates in iTBS trials of 5.9%.[31]

Statistical Analysis

Analyses were performed blind to treatment allocation using Stata software, version 17 (StataCorp). Baseline demographic and clinical characteristics were analyzed with *t* test for normally distributed variables or Fisher exact test for categorical variables. Normality was assessed using histograms and tested with the Shapiro-Wilks test, and if normality was violated, we used a Mann-Whitney test.

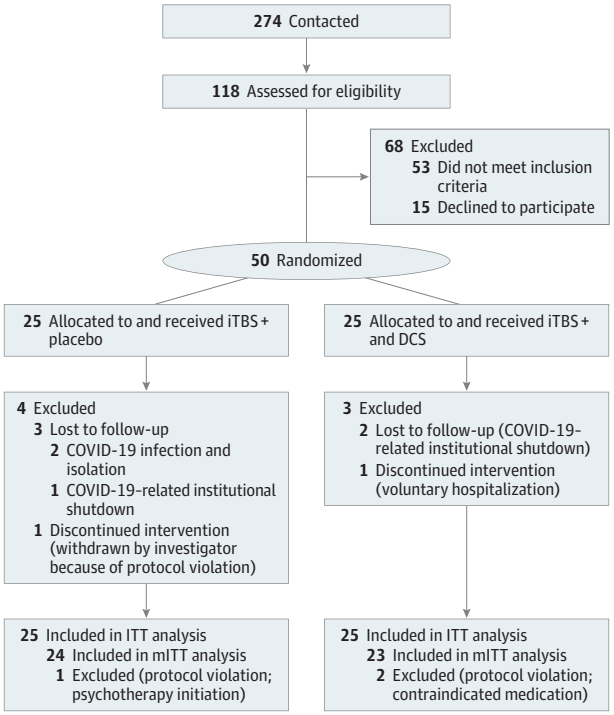
Intention-to-treat (ITT) analyses for the primary analysis of MADRS change scores from baseline to week 4 used a *t* test comparing difference scores in the 2 groups with last observation carried forward for missing data. To better account for missing data, a secondary analysis was conducted using random intercept mixed models. Here, time by group interactions were used to estimate the treatment effect. Other secondary outcomes used similar mixed-effects models with maximum likelihood estimation in which treatment group, visit (time), and treatment group-by-visit interaction were included. Effect size of the primary outcome was calculated with Hedges *g*. Response and remission rates were compared at 2 weeks and 4 weeks using logistic regression with the last observation carried forward to compute odds ratios (OR). *P* values were 2-sided, and $P < .05$ was considered statistically significant. Results are reported as mean (SD) or 95% CI.

Blinded statistical analyses were performed from May 2021 until April 2022. These were conducted as ITT analyses for the primary outcome and modified ITT (mITT), excluding 3 participants who were determined to be ineligible for the study (benzodiazepines [n = 2] and psychotherapy initiation [n = 1]). Benzodiazepine use was identified by reviewing provincial pharmacy dispensation records, and psychotherapy initiation was disclosed by the participant.

Results

Recruitment and participant flow are illustrated in **Figure 1**. The final sample consisted of 50 participants (mean [SD] age, 40.8

Figure 1. Participant Enrollment Flowchart



DCS indicates D-cycloserine; iTBS, intermittent theta-burst stimulation; ITT, intention to treat; mITT, modified intention to treat.

Table 1. Demographic and Clinical Characteristics of Randomized Participants

Characteristic	No. (%)	
	iTBS + placebo (n = 25)	iTBS + DCS (n = 25)
Age, mean (SD), y	40.9 (13.4)	40.6 (13.6)
Sex		
Female	15 (60.0)	16 (64.0)
Male	10 (40.0)	9 (36.0)
Years of education, mean (SD)	16.44 (2.10)	16.44 (4.16)
Married/common law	13 (52.0)	12 (48.0)
Employed	11 (44.0)	14 (56.0)
Ethnicity		
Asian	3 (12.0)	4 (16.0)
Black	0	0
Hispanic	0	3 (12.0)
Middle Eastern	1 (4.0)	0
White	20 (80.0)	17 (68.0)
Mixed	1 (4.0)	1 (4.0)
Have children	12 (48.0)	9 (36.0)
Clinical characteristics		
No. of MDEs, mean (SD)	6.71 (4.94)	5.42 (6.23)
Previous suicide attempt	5 (20.0)	8 (32.0)
No. of suicide attempts, mean (SD)	0.45 (1.28)	0.68 (1.31)
Previous TMS	0	0
HRDS-17, mean (SD)	21.16 (2.59)	22.40 (2.94)
MADRS, mean (SD)	30.32 (4.23)	30.36 (4.45)
CGI-severity, mean (SD)	4.24 (0.59)	4.28 (0.67)
QIDS-SR, mean (SD)	17.59 (3.23)	16.78 (3.19)
GAD-7, mean (SD)	10.63 (5.87)	13.69 (4.53)
Concomitant treatment		
Psychotherapy	10 (40.0)	4 (16.0)
Selective serotonin reuptake inhibitor	7 (28.0)	11 (44.0)
Selective norepinephrine reuptake inhibitor	12 (48.0)	10 (40.0)
Tricyclic/monoamine oxidase inhibitor	2 (8.0)	0
Atypical antipsychotic	3 (12.0)	7(28.0)
No. of failed adequate antidepressant trials in the current MDE, mean (SD)	1.92 (0.75)	1.52 (0.82)
Stimulation characteristics		
Resting motor threshold, % stimulator output, mean (SD)	39.60 (7.29)	42.12 (8.94)

Abbreviations: CGI, Clinical Global Impression score; DCS, D-cycloserine; GAD-7, 7-Item Generalized Anxiety Disorder; HRDS-17, 17-item Hamilton Depression Rating Scale; iTBS, intermittent theta-burst stimulation; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-Report; TMS, transcranial magnetic stimulation.

[13.4] years; 31 female [62%]; 19 male [38%]) who were randomly assigned to the treatment groups iTBS plus placebo (n = 25) or iTBS plus DCS (n = 25). Demographic and clinical variables had similar values with no statistically significant differences across treatment groups (**Table 1**). The iTBS plus placebo group included participants of the following race and ethnicity categories: 3 Asian (12%), 20 White (80%), and 2 other (8%). The iTBS plus DCS group included participants of the following race and ethnicity categories: 4 Asian (16%), 3 Hispanic (12%), 17 White (68%), and 1 other (4%). The participants in this trial presented with moderate-severe depressive symptoms as measured by both the HRDS-17 and the MADRS. Blinding integrity was preserved, with 11 participants (44%) in the iTBS plus placebo group vs 7 (28%) in the iTBS plus DCS group believing that they had received adjunctive DCS (OR, 0.43; 95% CI, 0.12-1.48; P = .18). rMT did not significantly differ between groups at baseline (t_{48} = 1.09; P = .28) or between the weeks with or without an adjunct (t_{45} = 1.47; P = .14).

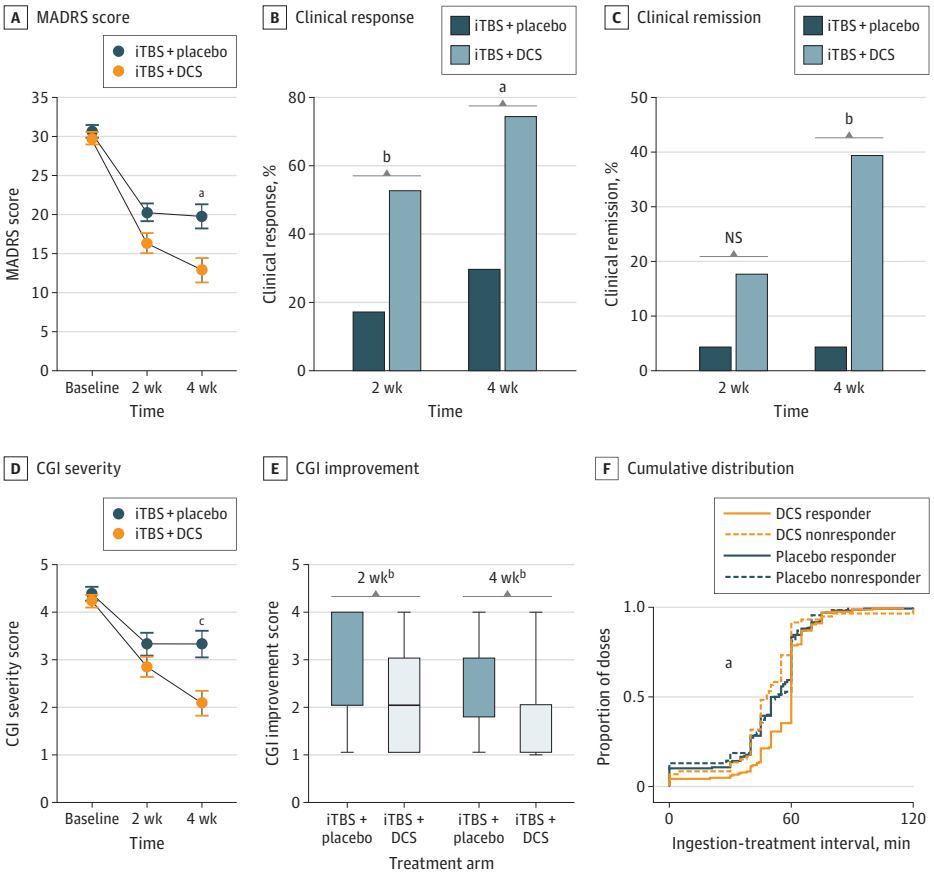
mITT analyses were performed on 24 participants (96%) in the iTBS plus placebo group and 23 participants (92%) in the iTBS plus DCS group. Protocol completer analyses were conducted on 20 participants (80%) in the iTBS plus placebo group and 21 participants (84%) in the iTBS plus DCS group.

Primary Outcome

The primary ITT analysis of mean (SD) change in MADRS score rejected the null hypothesis of equal change in the 2 groups between baseline and 4 weeks (iTBS plus placebo, −10.20 [7.79] vs iTBS plus DCS, −16.16 [6.99]; t_{48} = 2.84; P = .007).

mITT analyses examining change in MADRS scores demonstrated greater reductions in depressive symptoms in the iTBS plus DCS group compared with the iTBS plus placebo group (mixed-model likelihood ratio [MMLR] χ^2 = 9.97; P = .007) (**Figure 2**A). This corresponds to a mean difference of 6.15

Figure 2. Clinical Outcomes in Participants Who Received Intermittent Theta-Burst Stimulation (iTBS) Plus Placebo and iTBS Plus D-Cycloserine (DCS)



A, Participants randomly assigned to receive iTBS plus DCS had significantly greater improvements as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) at 4 weeks. This was reflected in higher rates of clinical response (B) and clinical remission (C), as well as greater improvements in Clinical Global Impression (CGI)–severity (D) and greater CGI-improvement (E) scores. F, Cumulative distribution plot illustrating all 940 self-reported ingestion-treatment intervals for 47 participants divided according to treatment allocation and responder status. Those who responded clinically to iTBS plus DCS treatment were more likely to ingest the adjunct at least 1 hour before scheduled treatments than iTBS plus DCS clinical responders as well as both iTBS plus placebo responders and nonresponders.

[a] $P < .001$.

[b] $P < .01$.

[c] $P < .05$.

(95% CI, 2.43-9.88; $P = .001$) on the MADRS and a Hedge g of 0.99 (95% CI, 0.34-1.62).

One notable feature of the course of improvement is a larger treatment effect after 4 weeks than after 2 weeks of treatment, despite the adjuvant being present for the first 2 weeks. We speculate that despite ongoing iTBS, this reflects an erosion of the placebo effect, as 15 of 25 participants (60%) in the iTBS plus placebo group plateaued or had a worsening MADRS score compared with 9 of 25 participants (36%) in the iTBS plus DCS group.

Protocol completer analyses revealed that the iTBS plus placebo group and the iTBS plus DCS group had significantly different MADRS scores at both 2 weeks (mean difference, 3.97; 95% CI, 0.43-7.51; $P = .01$) and 4 weeks (mean difference, 7.09; 95% CI, 2.66-11.52; $P = .001$).

Secondary Outcomes

All secondary outcomes were analyzed with mITT analyses (**Table 2**). iTBS plus DCS was associated with a higher rate of clinical response than iTBS plus placebo at both 2 weeks (iTBS plus placebo, 16.7% vs iTBS plus DCS, 52.2%; OR, 5.45; 95% CI, 1.41-21.03; $P = .01$) and 4 weeks (iTBS plus placebo, 29.2% vs iTBS plus DCS, 73.9%; OR, 6.88; 95% CI, 1.91-24.77; $P = .003$) (Figure 2B). Rates of clinical remission did not separate at 2 weeks (iTBS plus placebo, 4.2% vs iTBS plus DCS, 17.4%) but were statistically significantly different by 4 weeks (iTBS plus placebo, 4.2% vs iTBS plus DCS, 39.1%; OR, 14.78; 95% CI, 1.68-129.52; $P = .01$) (Figure 2C). The CGI-severity scale demonstrated greater improvements in the iTBS plus DCS group compared with the iTBS plus placebo group (MMLR $\chi^2 = 13.13$; $P = .001$) (Figure 2D). When analyzing CGI-improvement scores, these were not normally distributed, and therefore, we used a Mann-Whitney test. This revealed greater improvement in the iTBS plus DCS group relative to the iTBS plus placebo group at 2 weeks ($z = 2.38$; $P = .02$) and 4 weeks ($z = 3.24$; $P = .001$) (Figure 2E).

There was no statistically significant group difference on self-reported depressive symptoms as measured by the QIDS-SR despite a high correlation with clinician rated MADRS scores ($r = 0.74$; $P < .001$). Anhedonia as measured by the SHAPS did not reveal any significant group differences.

Self-reported anxiety symptoms using the GAD-7 revealed a greater improvement in the iTBS plus DCS group compared with the iTBS plus placebo group (MMLR $\chi^2 = 6.67$; $P = .04$).

A VAS score for overall well-being showed a greater improvement in the iTBS plus DCS group compared with the iTBS plus placebo group (MMLR $\chi^2 = 7.94$; $P = .02$); however, statistical significance was not reached for the WHOQOL-BREF subdomains or illness perception.

Table 2. Primary and Secondary Outcomes

Outcome	Mean (SD) [No.]		Group × time mixed model likelihood ratio χ^2	*P* value
	iTBS + placebo (n = 25)	iTBS + DCS (n = 25)		
MADRS				
Baseline	30.63 (4.04) [24]	29.83 (3.89) [23]	9.97	.007
2 wk	20.32 (5.42) [22]	16.35 (6.29) [23]		
4 wk	20.00 (6.85) [20]	12.90 (7.14) [21]		
CGI-severity				
Baseline	4.25 (0.60) [24]	4.22 (0.60) [24]	12.11	.002
2 wk	3.36 (0.79) [22]	2.83 (1.07) [23]		
4 wk	3.35 (1.13) [20]	2.10 (1.17) [21]		
CGI-improvement				
2 wk	2.64 (0.95) [22]	1.91 (0.94) [23]	$z = 2.38$	.02
4 wk	2.60 (1.04) [21]	1.52 (0.81) [21]	$z = 3.24$	.001
QIDS-SR				
Baseline	17.59 (3.23) [22]	16.78 (3.19) [23]	3.17	.20
2 wk	12.55 (4.31) [22]	12.35 (3.57) [23]		
4 wk	11.90 (6.28) [20]	9.33 (5.03) [21]		
GAD-7				
Baseline	10.64 (5.87) [22]	13.70 (4.53) [23]	6.67	.04
2 wk	9.27 (5.24) [22]	8.91 (4.53) [23]		
4 wk	7.95 (5.39) [20]	8.43 (5.12) [21]		
VAS well-being				
Baseline	56.86 (21.77) [22]	46.00 (15.27) [23]	7.94	.02
2 wk	54.57 (15.38) [21]	58.83 (16.56) [23]		
4 wk	52.60 (19.67) [20]	55.81 (17.45) [21]		
WHOQOL-BREF-physical				
Baseline	11.37 (2.31) [22]	11.41 (2.33) [23]	2.98	.22
2 wk	11.76 (2.70) [21]	12.52 (2.68) [23]		
4 wk	12.16 (3.18) [20]	13.19 (3.50) [21]		
WHOQOL-BREF-psychological				
Baseline	7.14 (1.94) [22]	6.95 (1.91) [23]	1.48	.47
2 wk	8.16 (2.54) [21]	8.17 (1.59) [23]		
4 wk	8.51 (2.68) [20]	9.12 (2.42) [21]		
Social				
Baseline	10.00 (3.53) [22]	10.98 (2.49) [23]	0.57	.75
2 wk	10.72 (3.73) [21]	11.13 (2.11) [23]		
4 wk	11.00 (4.25) [20]	12.06 (3.27) [21]		
Environmental				
Baseline	13.54 (2.08) [22]	13.89 (2.77) [23]	2.06	.35
2 wk	14.65 (2.10) [21]	14.31 (2.51) [23]		
4 wk	15.05 (2.33) [20]	14.58 (2.54) [21]		
SHAPS				
Baseline	8.32 (3.44) [22]	8.22 (3.42) [23]	$t = 0.28$	.78
4 wk	6.25 (4.98) [20]	5.81 (5.10) [21]		
BIPQ				
Baseline	54.32 (5.96) [22]	54.91 (6.23) [23]	0	.94
4 wk	50.05 (12.71) [20]	52.14 (7.12) [21]		

Abbreviations: BIPQ, Brief Illness Perception Questionnaire; CGI, Clinical Global Impression; GAD-7, 7-item Generalized Anxiety Disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-report; SHAPS, Snaith Hamilton Pleasure Scale; VAS, visual analog scale; WHOQOL-BREF, World Health Organization Quality of Life.

Fidelity to Study Protocol and Clinical Outcomes

Participants ingested the adjunct at least 60 minutes before treatment for only 48.5% of doses (Figure 2F). We examined whether there was an association between fidelity to the protocol and treatment outcome in an unplanned analysis comparing clinical responders and nonresponders in the 2 intervention groups. A Kruskal-Wallis *H* test examined the time between ingestion and treatment and found a significant effect of group ($H_3 = 25.2$, $P < .001$). Bonferroni post hoc comparison revealed that iTBS plus DCS responders had longer

Table 3. Adverse Effects Reported After Any Treatment When Intermittent Theta-Burst Stimulation (iTBS) Was Paired With and Without an Adjunct

Adverse effect	No. (%)			
	With adjunct (first 2 wk)		Without adjunct (last 2 wk)	
	iTBS + placebo (n = 25)	iTBS + D-cycloserine (n = 25)	iTBS + placebo (n = 23)	iTBS + D-cycloserine (n = 22)
Headaches	19 (76)	23 (92)	12 (57.1)	12 (52.1)
Tenderness at stimulation site	4 (16)	0 (0)	1 (4.7)	0 (0)
Fatigue	7 (28)	8 (32)	5 (23.8)	6 (26.0)
Increased anxiety	5 (20)	4 (16)	4 (19.0)	4 (17.3)
Concentration difficulties	1 (4)	1 (4)	0 (0)	0 (0)
Dizziness/vertigo	4 (16)	2 (8)	1 (4.7)	0 (0.0)
Lightheadedness	3 (12)	2 (8)	0 (0)	1 (4.3)
Nausea	1 (4)	2 (8)	1 (4.7)	0 (0)

intervals between ingestion and treatment than iTBS plus DCS nonresponders (H_1 = 85.9; P < .001), iTBS plus placebo responders (H_1 = 50.8; P = .04), and iTBS plus placebo nonresponders (H_1 = 55.8; P < .001). No other post hoc comparison reached statistical significance. This tentatively suggests that treatment outcome was related to DCS presence in the brain when iTBS was delivered.

Adverse Events

There were no serious adverse events during the study, including allergic reactions, seizures, or psychotomimetic adverse effects. One participant in the iTBS plus placebo group doubled their dose of the adjunct for the first week.

The adverse events reported by participants are described in **Table 3**. The most common adverse effect was a headache, reported by 76% of participants (19 of 25) in the iTBS plus placebo group and 92% of participants (23 of 25) in the iTBS plus DCS group after at least 1 treatment during the first 2 weeks. This, however, was mild, with an average maximal severity rating of 2.9 of 10 in both conditions. The proportion of participants reporting a headache decreased as the trial progressed, with half of participants reporting a headache in the final 2 weeks of the study, with an average severity of 1.5 of 10 in the iTBS plus placebo group and 1.6 of 10 in the iTBS plus DCS group.

Discussion

This single-site, double-blind, placebo-controlled, randomized clinical trial demonstrated that noninvasive neurostimulation treatment outcomes can be enhanced using mechanistically informed adjuncts. In individuals with moderate-severe MDD, the primary outcome of the study demonstrated superiority of iTBS plus DCS, with greater improvements in MADRS score with a large effect size and clinically meaningful difference. This was paralleled in several secondary outcomes, including clinical global impression, higher rates of both clinical response and clinical remission, and effects on self-reported anxiety and overall well-being; however, it was not paralleled in self-reported depressive symptoms. These findings are important, because if replicated in large multicenter studies, an adjunct is deployable within existing TMS and health systems infrastructure to improve outcomes in MDD.

Concomitant medications are already considered when prognosticating TMS success, however, with the exception of psychostimulants,[32] the focus is on negative prognostication. Medications affecting resting membrane threshold, such as anticonvulsants,[33] have been excluded from TMS clinical trials due to efficacy concerns. Agonists of the γ-aminobutyric acid receptor, such as benzodiazepines and gabapentin, have been associated with decreased effectiveness of TMS in MDD.[32,34] Yet, there has been limited attention to how medications might be used to enhance treatment outcomes in MDD, and our data highlight the potential for mechanistically informed adjuncts.

DCS has been examined in other psychiatric applications, such as trauma, anxiety-related disorders, and obsessive-compulsive disorder, to manipulate NDMA-receptor function and synaptic plasticity. Despite inconsistent results across studies, DCS is associated with a small but statistically significant efficacy signal in meta-analyses for these conditions.[35] One consideration in these studies is the variability in DCS dosing, ranging from 50 to 500 mg, which includes doses that reduce endogenous full activation, or antagonize, the NMDA receptor. When exploring adjuncts to noninvasive neurostimulation, dosing considerations will be of critical importance.

An important consideration for DCS, as a partial agonist, is whether it is an appropriate adjunct in populations where NMDA-receptor expression and function are intact. Partial agonism might reduce endogenous full activation, as highlighted in healthy motor plasticity experiments where DCS plus iTBS has either changed the direction of plasticity,[23] blunted plasticity,[22] or had mixed effects (J. Wrightson, PhD, personal communication, August 19, 2022). It will be crucial to test the applicability of adjunctive strategies in different pathologies and TMS indications.

Limitations

There are several limitations and caveats to this study. First, the sample size was small, and the study was conducted in a

single institution. Replication in a larger multisite trial is required to determine where within the CI the true effect lies. Second, participants only received the adjunct for 2 weeks, and longer treatment courses require dedicated study. Pairing DCS with full courses of iTBS may or may not be beneficial, given possible homeostatic plasticity mechanisms[36] and internalization of the NMDA receptor.[24] Similarly, the safety of prolonged courses with this antimicrobial requires dedicated testing. Third, our superiority trial was only 4 weeks in length to minimize risk of a floor effect, and longer treatment durations remain to be studied to differentiate treatment acceleration from treatment enhancement, both of which are possible interpretations of our data. Fourth, the timing of ingestion and iTBS is based on self-report, and an additive effect of iTBS and DCS is possible, though unlikely given small or null effects from previous studies examining high-dose adjunctive DCS in MDD.[37,38] Fifth, blinding of clinical raters and TMS operators was not assessed. Sixth, it is unclear why large effects in clinician-rated symptoms were not paralleled by similar effects in self-reported symptoms, although they qualitatively tracked the same trajectory. Previous literature suggests that self-report and clinician-rated measures provide unique lenses on clinical symptoms.[39] Finally, although it is tempting to conclude that DCS would enhance all TMS protocols[40] and all TMS indications, this is an empirical question that requires dedicated study.

Conclusions

Results of this randomized clinical trial suggest that adjunctive DCS may be a promising strategy for improving TMS treatment outcomes in MDD using iTBS. Replication in a larger multisite study is required, as is additional investigation into intersectional approaches with other dosing regimens and precision medicine targeting approaches.

ARTICLE INFORMATION

Accepted for Publication: August 16, 2022.

Published Online: October 12, 2022. doi:10.1001/jamapsychiatry.2022.3255

Correction: This article was corrected on December 7, 2022, to fix an error in Figure 2.

Author Contributions: Dr McGirr had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Harris, Bray, McGirr.
Acquisition, analysis, or interpretation of data: Cole, Sohn, Patten, McGirr.
Drafting of the manuscript: Cole, Harris, McGirr.
Critical revision of the manuscript for important intellectual content: Cole, Sohn, Harris, Bray, Patten.
Statistical analysis: Patten.
Obtained funding: McGirr.
Administrative, technical, or material support: Cole, Sohn, Harris.
Supervision: McGirr.

Conflict of Interest Disclosures: Dr Sohn reported receiving grants from the Canadian Institutes of Health Research Canada Graduate Scholarship Masters Award during the conduct of the study. Dr McGirr reported having a patent for PCT/CA2022/050839 pending with MCGRx Corp and being a shareholder of MCGRx Corp. No other disclosures were reported.

Funding/Support: This study was supported in part by the 2018 Young Investigator Award (AM-27548) from the Brain and Behavior Research Foundation and the Campus Alberta Innovates Program Chair in Neurostimulation (Dr McGirr).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

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