



# Marked reduction in suicidality and depression in a transcranial magnetic stimulation non-responder after augmenting with a standard available D-cycloserine dose

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## ABSTRACT

Promising clinical benefits were observed with d-cycloserine (DCS) augmentation of intermittent theta-burst stimulation (iTBS), presumably by enhancing long-term potentiation (LTP) through NMDA receptor agonism (Cole et al., 2022). However, the applicability of this trial and accessibility of this approach are unknown. We report the case of a 28-year-old woman whose psychiatric symptoms worsened during an initial course of 18-Hz rTMS using an H1-coil, and culminated in a suicide attempt and hospitalization. Upon discharge, she underwent a second course of rTMS augmented this time with DCS, and quickly experienced full remission of her suicidal thoughts and marked improvement in her symptoms of depression. This is the first real-world report of rTMS using the FDA-approved 250 mg dose of DCS without pharmaceutical compounding, employing a different coil and stimulation protocol than those used in prior clinical trials. This encounter suggests that this augmentation approach may be more broadly applicable than the dose and protocol used in previous trials, and could be a solution for TMS non-responders or for severe and suicidal patients.

## Introduction

Transcranial Magnetic Stimulation (TMS) has demonstrated a response rate of 40 % - 60 % in patients with treatment-resistant depression (TRD) (Carpenter et al., 2012; Sackeim et al., 2020; Vida et al., 2023), however, efficacy may be diminished in patients with greater severity of symptoms (Abo Aoun et al., 2023). Patients with TRD have disproportionately higher rates of suicidality and completed suicide (Mann et al., 2021; McIntyre et al., 2023), which has prompted the suggestion that clinical trials should have suicidality as a discrete outcome measure (Bergfeld et al., 2018). Therefore, finding more effective treatments for suicidality is paramount.

Recent improvements on the “standard-of-care” TMS may have the potential to reduce suicide risk through augmenting its mechanism of action (Sohn et al., 2025). TMS is purported to cause therapeutic changes by inducing a form of synaptic plasticity called long term potentiation (LTP), which depends on n-methyl-d-aspartate receptor (NMDAR) function (Brown et al., 2022). The potential of augmenting TMS with NMDAR agonism was first observed when d-cycloserine (DCS)

enhanced corticomotor plasticity (Brown et al., 2020, 2021; Kweon et al., 2022; Sohn et al., 2024). DCS is an antibiotic used to treat tuberculosis (TB) and at doses under 250 mg acts as a co-agonist on the NMDAR glycine binding site (Schade & Paulus, 2015; Sohn et al., 2024). In a groundbreaking study by Cole et al. (2022), patients were treated with DCS as an adjunct to intermittent theta burst stimulation (iTBS) for the treatment of MDD (Cole et al., 2022). After only two weeks of iTBS combined with either DCS or placebo followed by two weeks of TMS without medication augmentation, response rates increased from 29.3 % for iTBS with placebo to 73.9 % when combined with DCS (Cole et al., 2022). Similarly, remission rates improved from 4.2 % to 39.1 % with DCS (Cole et al., 2022).

Whether DCS augmentation can enhance other TMS protocols, like 18-Hz, has never been tested, nor has the non-compounded FDA-approved standard available dose of 250 mg (all studies have used 100 mg which requires compounding by a pharmacy). Moreover, access to DCS may be prohibitively expensive without insurance coverage in the United States (roughly \$1600 - \$2700 for 30 capsules), but international prices may vary), thereby limiting access, and real-world

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reports on this approach to augment TMS have not been reported ([PharmacyChecker.com](https://www.pharmacychecker.com), 2025). We present a patient who had worsening suicidal ideation and a suicide attempt by the end of her initial repetitive Transcranial Magnetic Stimulation (rTMS) course requiring hospitalization, who shortly after had complete remission of her suicidality after 23 rTMS sessions with DCS augmentation.

### Clinical case

A 28-year-old female nurse with past medical history of migraines and gastroesophageal reflux disease and past psychiatric history of MDD, severe, recurrent, without psychotic features and post-traumatic stress disorder (PTSD), seven prior acute psychiatric hospitalizations, and three prior suicide attempts, who presented to TMS clinic for worsening symptoms of depression. She described neurovegetative symptoms of depression including feelings of low mood, poor sleep, tearfulness, hopelessness, guilt, low self-worth, poor appetite with associated unintended weight loss, anhedonia, poor concentration, decreased motivation, and increased daytime fatigue that had been worsening over the past year after the loss of a close friend to suicide. She reported suicidal ideation with a plan of overdosing or hanging herself, though she reported no intention to act on these plans. Initial (baseline) depression and anxiety scales indicated severe symptoms of depression including Patient Health questionnaire-9 (PHQ9) score of 25, Quick Inventory of Depressive Symptomatology (QIDS) score of 18, and General Anxiety Disorder –7 (GAD7) score of 8. She also reported active symptoms of PTSD including hypervigilance, flashbacks, and dissociative events that were occurring near daily that were related to a previous sexual assault. She reported nightly use of edible marijuana and occasional alcohol use, roughly a few drinks per month.

Her outpatient prescribed medication regimen included desvenlafaxine 100 mg daily, dextroamphetamine-amphetamine 20 mg in AM and 10 mg in afternoon, lorazepam 1 mg used approximately 2 times per week, cariprazine 1.5 mg daily, pantoprazole 40 mg daily for gastroesophageal reflux disease (GERD), propranolol 80 mg LA for migraines, junel fe for oral contraception, naratriptan for migraines, galcanezumab injections for migraines, and topiramate 25 mg daily for migraines. She had previously failed to respond to 5 antidepressants (2 selective serotonin reuptake inhibitors, 2 serotonin-norepinephrine reuptake inhibitors, and bupropion), 4 prior antipsychotics for mood augmentation, and 3 prior stimulant trials for ADHD and mood augmentation. rTMS was delivered at McLean Hospital with a Brainsway (Jerusalem, Israel) H1 coil targeting the left dorsolateral prefrontal cortex with 18 Hz frequency, 55 trains per session, and 1980 pulses per session.

Throughout rTMS treatment, she described worsening suicidal ideation occupying more than “90 %” of her thoughts. The patient’s prescribed outpatient medications were continued throughout the treatment course with the only change made by her outpatient prescriber being an increase in her dextroamphetamine-amphetamine to 20 mg two times daily after the fifth rTMS treatment. Despite the medication adjustment and rTMS treatment, her depression continued to worsen and following her 34th session, she intentionally overdosed on lorazepam and was admitted to McLean Hospital. She was discharged on the desvenlafaxine 150 mg (increased from 100 mg), dextroamphetamine-amphetamine 20 mg two times daily, cariprazine 1.5 mg daily, bupropion 150 mg daily, quetiapine 25 mg every six hours as needed for anxiety, and hydroxyzine 25 mg every four hours as needed for anxiety. bupropion, quetiapine and hydroxyzine were initiated as new medications during the inpatient admission.

Before her inpatient admission, DCS augmentation of rTMS was discussed as a way to help with her worsening thoughts of death. A detailed discussion of risks and possible benefits, including the off-label and investigational nature of the treatment were discussed and informed consent was obtained. The hospital pharmacist assisted with obtaining insurance coverage resulting in a nominal cost, and no prior authorization was required. Of note, her local pharmacy did not have the

medication in stock and further, they were “blocked” from ordering the medication due to the very high costs. Ultimately, the outpatient academic pharmacy special ordered the DCS directly from the distributor.

Upon discharge from the acute inpatient unit, her scores were QIDS of 18, PHQ9 of 24, and GAD7 of 18. Her Clinical Global Impression-Severity Scale (CGI-S) score was a 6. The medications prescribed at discharge were continued during the second course of rTMS treatment, which was delivered with the same device and protocol as her initial rTMS course. By the time the second course of rTMS was going to start, the special ordered DCS had arrived and rTMS was re-initiated 10 days after her last treatment. Although all prior work was done with 100 mg, we used the smallest standard available dose of 250 mg with a strategy to give it early enough (6–8 h prior to rTMS) to allow levels to approximate 100 mg serum levels ([van Berckel et al., 1997](#)). After five consecutive days of DCS her serum concentration levels were obtained to determine accumulation effects at steady state, and resulted in a cycloserine level of 11.40 µg/mL at roughly 7.5 h after administration.

Only five treatments into her augmented course of rTMS, she noted improved mood and anxiety and significantly decreased severity and frequency of suicidal ideation, although these changes were not yet reflected on psychometrics. After 11 augmented treatments, her suicidal thoughts further decreased and were now limited largely to evenings. During the second round of rTMS treatment her medications prescribed at discharge from the acute inpatient unit were continued. The only medication adjustment made during her second course of rTMS was the discontinuation of her cariprazine, which was discontinued after 9 treatments. She ended her 2nd augmented rTMS course at 23 sessions with QIDS reduction from 18 to 10 in line with mild symptoms of depression. QIDS sub-domain scores improved in energy, anhedonia, concentration, sleep, self-attitude, and sadness. Her PHQ9 improved from 24 to 16, and GAD7 improved from 18 to 15. Despite her report of feeling “a lot better,” her self-assessment scores were less than her observed clinical assessments. Her CGI-S improved from 6 to 3, and CGI-improvement (I) score was a 2 denoting a very substantial change in psychiatric symptoms. Her CGI-S score remained a 3 due to persistent anxiety despite marked improvement in symptoms of depression. Importantly, while some mild depression and especially anxiety remained, her suicidality was considerably improved. The patient described feeling “surprised” by the rapid improvement of her intrusive thoughts of death and reported complete resolution of suicidal ideation, which is consistent with a recent report from [Sohn et al. \(2025\)](#) ([Sohn et al., 2025](#)). In fact, the last intrusive thought of death had occurred 3 days prior to her final treatment at which time she described the thought as “brief,” passive, and easily redirected.

### Discussion

We have described the first real-world report of a patient treated with rTMS augmented by DCS. It demonstrates the potential utilization of a standard pharmaceutical dose without compounding requirements, which has not previously been tested with rTMS. Additionally, it is also the first report of this augmentation approach with an 18-Hz protocol using an H1 coil, suggesting that therapeutic benefits may span protocols and devices.

Most importantly, however, the patient’s treatment results demonstrated a remarkable remission of her suicidality which had previously occupied a self-reported “90 %” of her thoughts near the end of her initial rTMS course and had culminated in a suicide attempt. Her improvement in suicidality is consistent with [Sohn et al. \(2025\)](#) who reported a rapid reduction in suicidal ideation, as well as, a reduced implicit suicide risk based on the Death-Implicit Association Test (D-IAT) in patients treated with DCS augmentation ([Sohn et al., 2025](#)). Suicidal depression may represent a more severe phenotype of depression with “less frequent depression remission, suicidal ideation persistence and higher suicide attempt risk, despite antidepressant treatment” ([Nobile et al., 2024](#)). Thus, TMS augmented by DCS may fill an unmet

need to treat more severe forms of depression and reduce suicidality. Moreover, DCS augmentation could also serve as a future strategy for TMS non-responders as she had no improvements after her initial 34-sessions of rTMS.

On the other hand, it is important to note that her anxiety limited her CGI rating and her overall mental health. Cole et al. (2022) noted increased anxiety in 4 patients getting DCS compared to 5 getting placebo. Interestingly, however, the patient described her suicidal thoughts as intrusive and compulsive in nature, occupying an overwhelmingly large portion of her cognitive thought process. Our patient's obsessional (90 %) thoughts about suicide appeared to be differentially and preferentially rescued relative to her depression and anxiety symptoms. Considering recent findings that DCS augmentation of TMS robustly improves OCD response rates over DCS or TMS alone (McGirr et al., 2025), it is intriguing to speculate that modulation of pathology linked to OCD, such as cortico-striatal-thalamo-cortical loops, could contribute to her cessation of suicidal thinking.

The patient did not report any adverse effects from treatment with DCS, which is consistent with reports from prior trials using DCS (Brown et al., 2020; Cole et al., 2022; Kweon et al., 2022). Cole et al. (2022) observed similar effect rates between placebo and DCS including headache, lightheadedness, dizziness/vertigo, nausea, fatigue, anxiety, and difficulty concentrating (Cole et al., 2022). Other reported side effects are primarily associated with high doses and include depression, confusion, memory loss, lethargy, rash, allergy, fever, and gastrointestinal and cardiovascular problems including arrhythmia (Schade & Paulus, 2015). Current recommended serum concentrations range from 20 to 35 mg/liter for standard TB treatment which typically ranges from 500 mg – 750 mg per day, and up to as high as 1000mg maximum per day (Alghamdi et al., 2019). Rare seizures have been observed particularly when blood levels are above 35 µg/mL (Schade & Paulus, 2015). Patients taking DCS daily have a theoretical risk of accumulation over time, however studies in individuals being treated with 250 mg of DCS daily for TB demonstrated a maximum peak concentration of 16 mg/liter over 24 h, which is well below serum levels of concern (> 35 mg/liter) (DeMayo et al., 2025; Alghamdi et al., 2019). Our patient taking 250 mg 6–8 h before rTMS had a serum concentration levels of 11.4 µg/mL. When augmenting TMS with DCS serum concentration monitoring is suggested as there may be a minimum serum concentration necessary for a clinical response (DeMayo et al., 2025). Although further research is needed to fully elucidate the optimal dosing and blood serum levels of DCS for TMS augmentation, open label data suggests that serum levels > 7 ng/mL may be associated with greater likelihood of clinical remission (DeMayo et al., 2025).

We report these findings to illustrate that in this case DCS was obtained, covered by insurance, safe and beneficial at a standard FDA-approved dose without pharmaceutical compounding. DCS was also used with good effect in this case with a different device and protocol compared to previously published TMS augmentation strategies. Being a single case, this patient's results cannot be assumed to be generalizable but does raise a new treatment possibility. It is important to remember that with more sessions of TMS alone, a patient can convert from being a non-responder into a responder (Hutton et al., 2023; Razafsha et al., 2023; Yip et al., 2017) and presents one possible confounding variable to explain her clinical response. Additional confounders may include the patient's concurrent use of amphetamines during treatment. Evidence suggests that amphetamines enhance neuroplasticity during TMS by increasing dopaminergic and noradrenergic activity, thereby facilitating long-term potentiation LTP-like mechanisms and cortical excitability (Carter et al., 2003; Nitsche et al., 2004). However, this is unlikely to explain the patient's marked improvement during her second course of DCS augmented rTMS, as her amphetamine dose was previously increased within the first five sessions of her initial rTMS course yet her depressive symptoms worsened, culminating in a suicide attempt. Furthermore, the same amphetamine dose was maintained throughout the DCS augmented rTMS course that ultimately led to her clinical

improvement.

In conclusion, this severely suicidal patient was a rTMS non-responder before experiencing a full remission of suicidality after an additional abbreviated course of 18-Hz rTMS augmented with a DCS dose that did not require pharmaceutical compounding.

## CRediT authorship contribution statement

**Joshua Brown:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Sanjali Kumar:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Sabra Sullivan:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Alesia Cloutier:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Co-Author JB receives an editorial stipend from Elsevier, and serves as the Editor-in-Chief of the Transcranial Magnetic Stimulation Journal. 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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