

Title: Adjunctive D-Cycloserine with Intermittent Theta-Burst Transcranial Magnetic Stimulation Improves Suicidal Ideation and Implicit Suicide Risk in Major Depressive Disorder

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Abstract

Background: Intermittent theta-burst stimulation (iTBS) to the dorsal lateral prefrontal cortex (DLPFC) is a non-invasive treatment for Major Depressive Disorder (MDD). We have shown that pairing iTBS with a mechanistically informed adjunct, the partial NMDA receptor agonist D-Cycloserine, improves antidepressant outcomes in MDD. Given that the DLPFC has also been implicated in suicide, we sought to test whether this adjunctive treatment influences suicidal ideation and implicit suicide risk measured on the Death-Implicit Association Test (D-IAT).

Methods: In this four-week randomized double-blind placebo-controlled trial, fifty participants with MDD received adjunctive D-Cycloserine or placebo with iTBS for the first two of four weeks. Suicidal ideation was measured by the suicide items of the clinician-rated Montgomery Asberg Depression Rating Scale (MADRS) and the self-reported Quick Inventory of Depressive Symptoms (QIDS-SR). At baseline and 2 weeks of iTBS+adjunctive D-Cycloserine or placebo, participants completed the D-IAT.

Results: Treatment groups did not differ on baseline suicide metrics. iTBS+D-Cycloserine improved on clinician-rated ($-2LL = 18.13$, $p = .006$) but not self-reported ($-2LL = 22.49$, $p = 0.22$) suicidal ideation. There was a Group*Time interaction such that only iTBS+D-Cycloserine treatment resulted in reduced suicide risk on the D-IAT ($F(1,45) = 5.07$, $p = .03$), an effect which persisted after controlling for improvements in depressive symptoms and suicidal ideation ($F(1,45) = 4.08$, $p = .049$).

Conclusion: D-Cycloserine enhances the effects of iTBS to mitigate suicide risk in adults with MDD. Future studies should determine the utility of this strategy in acutely suicidal individuals.