

Combined Ketamine/Transcranial Magnetic Stimulation Treatment of Severe Depression in Bipolar I Disorder

To the Editor:

I report on the first case of treatment of severe depression in a patient with bipolar I disorder using a combined ketamine/transcranial magnetic stimulation (TMS) technique. The patient had been largely nonresponsive to electroconvulsive therapy (ECT), repetitive TMS (rTMS), or vagal nerve stimulation. Ketamine is an *N*-methyl D-aspartate antagonist that has been shown to provide rapid relief for depressive symptoms.¹ Transcranial magnetic stimulation, a noninvasive brain stimulation technique, has been shown to possibly reduce symptoms of depression and mania.^{2,3}

The patient, a 31-year-old white man, had presented to my clinic after a 2-month psychiatric hospitalization earlier in that year. He reported that, at the time of the hospitalization, he had been under extreme stress from working 80 to 90 hours per week. He was diagnosed with bipolar I disorder on the basis of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria by the attending psychiatrist and was administered with ECT 14 times during the course of 2 months. The patient reported that the first 4 ECT treatments had been successful in reducing his acute suicidality but that he returned to feeling suicidal after the fourth treatment and did not experience any gains from the subsequent 10 treatments. Thereafter, he consulted in my clinic and began rTMS with relief but not quiescence. After a year, vagal nerve stimulation was added to the existing rTMS strategy. This addition resulted in some improvement, but the patient still did not attain symptomatic quiescence. I therefore described to him the option of pursuing combined ketamine/TMS. After weighing the potential risks and benefits, the patient decided to undergo the combined treatment. Institutional

review board approval was obtained from an independent accredited agency.

Before the onset of the combined treatment of TMS applied during infused ketamine, the patient underwent a systematic psychodiagnostic assessment conducted by an independent licensed clinical psychologist. As part of the assessment, the patient completed a valid Personality Assessment Inventory (PAI) and a Beck Depression Inventory (BDI) II. These measures revealed marked elevations in depression (PAI depression scale T score = 87, BDI-II = 24) and anxiety (PAI anxiety scale T score = 74). Furthermore, the patient showed problems with attention, concentration, and clear thinking (PAI schizophrenia scale T score = 81). Largely consistent with the results of these assessments, the patient described himself as feeling severely depressed, including having frequent thoughts of suicide. In terms of functioning, the patient was severely debilitated, being unable to read or speak in complete sentences. He was on leave from his job and had withdrawn from all of his personal and social relationships, including spending time with his wife and volunteering at his church.

In preparation for the combined treatment, the patient received 2 days of rTMS consisting of 4 treatments per day, each of which lasted 30 minutes separated by a 45-minute rest period. The combined treatment then began the following day and was administered approximately once weekly for 3 years. The ketamine dosage varied from 40 to 80 mg per treatment. At each treatment, 40 minutes of 1-Hz continuous rTMS was administered at 115% of motor threshold and intravenous ketamine infusion was administered concurrent to and bracketed within the middle 30 minutes of TMS. Preinfusion and postinfusion, there were 5 minutes of TMS. The TMS head coil, manufactured by Neotonus, was positioned at the midline of the scalp. This position was selected to maximally stimulate the medial prefrontal area that overlays the anterior cingulate region, which has been implicated in depression.⁴ All stimulation levels fell within published safety guidelines.

A follow-up psychodiagnostic assessment, which included a valid PAI and BDI-II, was conducted a year after the beginning of the combined treatment by the same psychologist who administered the pretreat-

ment battery. This assessment revealed a partial remission of symptoms with partial functional improvement. Specifically, the results showed improvements in depression (PAI depression scale T score = 74, BDI-II = 18) and anxiety (PAI anxiety scale T score = 61) as well as attention, concentration, and clear thinking (PAI schizophrenia scale T score = 74). Although these scores were still elevated, they nonetheless represented substantial decreases from the baseline levels. Consistent with these changes in scores, the patient reported experiencing substantially improved mood, including the absence of any suicidal ideation. He said that he had largely regained his ability to read and speak clearly. Although he remained unemployed, he had returned to spending more time with his wife as well as volunteering approximately 10 to 20 hours per week for his church.

These findings are the first of which I am aware to show that a combined ketamine/TMS treatment can be used to treat severe depression in bipolar I disorder. Future research should systematically examine whether the combined treatment of bipolar I symptoms offers benefits over either ECT or ketamine administered independently of TMS.

Steven Richard Devore Best, MD

The Neuroscience Center
Deerfield, IL
srdbest@neuroscience.md

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