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CASE REPORT

Combination therapy utilizing ketamine and transcranial magnetic stimulation for treatment-resistant depression: a case report

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In the present article, we report on the case of a 23-year-old woman with a history of treatment-resistant depression who achieved significant symptom improvement with a novel treatment consisting of ketamine, a dissociative anesthetic, and external neuromodulation with transcranial magnetic stimulation (TMS). This case highlights the need for further investigation of treatments pairing external neuromodulation with dissociative anesthetics.

KEYWORDS: ketamine, transcranial magnetic stimulation, depression

Despite advances in pharmacological treatment, approximately half of patients fail to achieve full remission, prompting researchers to look beyond conventional antidepressant medications [1]. Recent research has examined transcranial magnetic stimulation (TMS and its variant rTMS), in which an electromagnetic stimulator positioned at the scalp induces a change in local and distant electric field conditions and may cause an associated depolarization of neurons [2]. When used to stimulate the dorsolateral prefrontal cortex, rTMS has been associated with significant antidepressant effects [3], and is an FDA-approved treatment for depression. However, it is difficult to achieve remission with rTMS alone. A separate body of research has investigated intravenous ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist [4–8]. In contrast to typical antidepressant medications that take effect within several weeks, ketamine provides relief within 2 h and lasts between four and seven days, after which relapse is common [4,5]. To date, little is known about the possible synergistic effects of combined rTMS/ketamine treatment for depression.

One study found that a factor underlying treatment resistance in depression is abnormal function in a thalamocortical circuit involving the anterior cingulate cortex (ACC), among other areas [9,11]. Accordingly, the first author hypothesized stimulating the ACC with TMS would restore normal functioning in the relevant circuit, thereby improving response to ketamine. We report on a depressed patient treated with a novel combined ketamine/TMS technique who showed substantial improvement in depression symptomatology at the end of treatment, and again at follow-up 483 days later. An IRB exemption was obtained from an independent accredited agency.

Case Report. Patient X is a 23-year-old woman who presented with a 9-year history of depression that did not respond to treatment with sertraline, buprorion, paroxetine, or stimulants. She also presented with attention deficit disorder that was treated with amphetamine from intake through follow-up. Her past history included diagnoses of anorexia nervosa and substance abuse (cocaine) that were in full remission at intake. Patient X was systematically assessed for psychopathology by an independent licensed psychologist at the outset of treatment. The primary assessment instruments were the Beck Depression Inventory-II (BDI-II) and the Personality Assessment Inventory (PAI). PAI subscale scores greater than 70 indicate clinically significant difficulties. Results of this assessment suggested that Patient X exhibited moderate levels of depression (BDI-II = 17, PAI DEP T = 84) consisting predominantly of depressed mood (PAI DEP-A T = 83), low self-esteem (PAI DEP-C T = 87), and suicidal ideation (PAI SUI T = 62). In addition, the initial assessment suggested significant difficulties in developing and maintaining a sense of life

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purpose and self-identity (PAI BOR-I T = 80), problematic alcohol use (PAI ALC = 66), and concentration difficulties (PAI SCZ-T T = 73). After this comprehensive assessment, Patient X's mood was assessed during each treatment by the first author using a visual analog scale. In this measure, Patient X indicated where her mood fell along a continuum from "the worst I can imagine feeling" to "the best I can imagine feeling."

Prior to beginning combined treatment, Patient X was given 2 days of rTMS pretreatment (four treatments per day of 30 min with 45 min of rest between treatments). Combined ketamine/TMS treatment began the following day and continued at weekly intervals for 13 weeks. Fifteen years of observational evidence from our clinic suggested that this duration produced clinically significant results. Combined treatment consisted of 40 min of 1 Hz continuous TMS with an intravenous ketamine infusion administered concurrent to and bracketed within the middle 30 min of TMS, resulting in 5 min of TMS pre- and postinfusion. The dosage of infused ketamine increased gradually from 30 mg at the first treatment to 100 mg at the last treatment. During combined treatment, the TMS head coil (manufactured by Neotonus) was positioned at the midline of the scalp to achieve maximal stimulation of the medial prefrontal area that overlays the anterior cingulate, a region implicated in depression [10]. While direct stimulation of the anterior cingulate is not likely given its subcortical position and the limited electromagnetic field penetration of TMS coils [4], we hypothesized that indirect stimulation of the anterior cingulate via TMS applied to the overlaying scalp region would result in a beneficial effect.

Baseline brain scans were used to ensure accurate coil positioning at each treatment. TMS treatments were administered at 115% of motor threshold at 1 Hz continuous pulsation given that these settings were within safety guidelines and consistent with previous research. Using this method, we hypothesized that the dissociative effects of ketamine along with TMS activation of the anterior cingulate would help reestablish normal oscillatory rhythms in this region, leading to a decrease in depression symptoms.

After the treatment on week three, Patient X reported a substantial improvement in mood and energy levels. Patient X noted that these gains were maintained over the duration of treatment with some fluctuation in mood due to relationship difficulties. Soon after the last combined treatment, Patient X reported a nondepressed mood with increased motivation and diminished attention difficulties. Combined treatment was followed by regular psychiatric visits 1–2× /month for 14 months. Gains were generally maintained over this span, with Patient X reporting that she was able to begin graduate studies and sustain an intimate relationship. Four hundred and eighty three days after her initial assessment, Patient X was again systematically assessed for psychopathology by an independent licensed psychologist. Results showed substantial decreases in depression (BDI-II = 0, PAI DEP T = 41), suicidal ideation (PAI SUI T = 45), alcohol use (PAI ALC T = 49), and concentration difficulties (PAI SCZ T = 49), along with increased sense of self-purpose (PAI BOR-I T = 56).

Discussion. This case report adds to the literature on improving the efficacy of brain electromagnetic stimulation by administering pharmacological agents that modulate glutamatergic transmission. Whereas previous research suggests that rTMS is somewhat effective in treating depression [3], and that subanesthetic doses of ketamine are temporarily helpful with depression [5–9]; the present case report is the first to suggest that a combined ketamine/rTMS treatment may be a more efficacious treatment for refractory depression than either infused ketamine or rTMS alone. Future research should examine combined ketamine/TMS treatment in a randomized controlled trial.

Declaration of Interest

Dr. Best reports no biomedical financial interests or potential conflicts of interest. Brian Griffin reports no biomedical financial interests or potential conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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