Pilot Study: Ketamine-Assisted Mindfulness-Based Cognitive Therapy for Treatment-Resistant Depression

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Background

- **Treatment-resistant depression (TRD) is a significant health challenge, as many patients do not respond to traditional treatments and continue to experience persistent depressive symptoms.**
- **Ketamine offers rapid antidepressant effects; however, its benefits are often short-lived.**
- **Mindfulness-Based Cognitive Therapy (MBCT) effectively prevents relapse in depression. MBCT strengthens the connectivity between the posterior cingulate cortex (PCC) and dorsolateral prefrontal cortex (dlPFC). This increased connectivity helps individuals redirect focus from negative thoughts, reducing distress and supporting long-term recovery.**

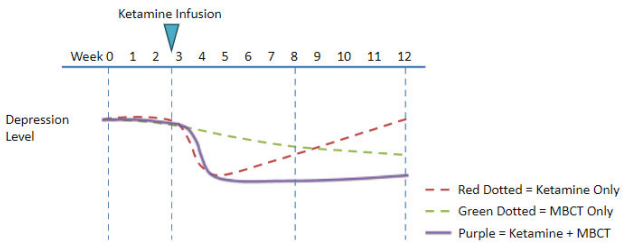

Figure 1: Model of depression level changes over 12 weeks with ketamine only (red dotted line), MBCT only (green dotted line), and combined ketamine + MBCT (purple line). The combined treatment shows rapid improvement from ketamine may be sustained by MBCT, potentially prolonging antidepressant outcomes in treatment-resistant depression.

Recruitment

- **This single-arm pilot study recruited adults (ages 18–72) with treatment-resistant depression (TRD) from OSU clinics and the community. Participants met DSM-5 criteria for major depressive disorder and had failed at least one FDA-approved antidepressant trials. Exclusion criteria included abnormal thyroid function, need for inpatient care, current substance use, pregnancy or breastfeeding, history of psychotic or bipolar disorder, abnormal ECG, previous cardiac surgery, hypertension (>140/90), unstable medical conditions (such as liver or kidney disease, uncontrolled diabetes), history of ketamine misuse or adverse reactions, obstructive sleep apnea, seizures, intellectual disabilities, and active suicidal ideation.**

Methods

- **Study Design: an 8-week Mindfulness-Based Cognitive Therapy (MBCT) program, with participants attending weekly 2-hour group sessions and completing daily home mindfulness practices. An IV ketamine infusion (0.5 mg/kg) was administered between weeks 2 and 3, followed by three "booster" mindfulness sessions. Primary MDD symptom and mindfulness outcomes were measured through weekly self-report assessments and clinician-administered interviews. EEG recordings were conducted at intake, post-ketamine infusion, and after the 8-week program to assess neurophysiological changes.**

- **EEG Laboratory Tests: Participants completed a series of non-emotionally arousing tasks during EEG recording, including**
  - **Rest (5 mins eyes open, 5 mins eyes closed)**
  - **Mindful Rest (5 minutes eyes open)**
  - **Error Monitoring Task (ERN), using Flanker paradigm**
  - **Doors Reward Task (LST), assessing reward reactivity**
  - **Auditory Tone Task (LTP), aimed at inducing auditory habituation.**

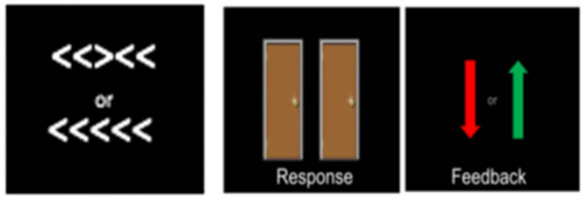

Figure 2: EEG tasks: In the Flanker Task (left), participants identify the direction of the central arrow to measure error response. In the Doors Reward Task (right), participants choose a door to receive reward or loss feedback, assessing reward reactivity.

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Results

- **N=14 adults with TRD have been enrolled, and N=6 have completed treatment and post-treatment assessments. These participants demonstrated a significant acute response to ketamine, with reduced depression symptoms observed from weeks 3-4 (p<.05). Ketamine response was sustained five weeks after infusion for participants that received MBCT. Participants who completed the program reported lower ratings for depression at follow-up.**

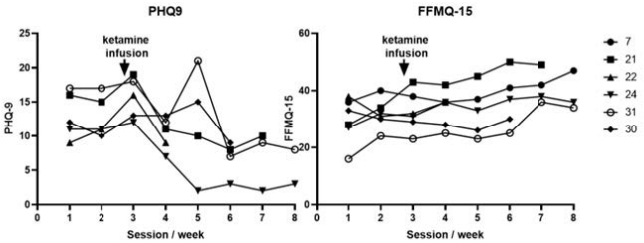

Figure 3: Effects of i.v. ketamine and MBCT (measured by PHQ-9 and FFMQ-15) shows improvement in depression and an increase in mindfulness.

Participant	Pre MADRS score	Post MADRS score
1	31	19
2	20	16
3	30	18
4	30	6
5	33	23

Figure 4: Pre- and post-treatment MADRS scores for participants, showing reductions in depressive symptoms following intervention.

Discussion

- **The findings are consistent with our hypothesis that ketamine may enhance the effects of MBCT, supporting the feasibility of combining IV ketamine with MBCT for extended antidepressant effects and improved treatment outcomes.**
- **In future studies, we aim to replicate these findings across multiple groups and investigate enhanced metacognitive regulation in the PCC and dlPFC regions using fMRI.**
- **We hope to observe increased neurogenesis following the ketamine infusion evidenced by an increase in theta band power in the LTP EEG task.**