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

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Background

- **Treatment-resistant depression (TRD) is a serious health concern that affects about 44% of patients who have tried at least two consecutive antidepressant therapies.**
- **Ketamine is a NMDA receptor antagonist that 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.**

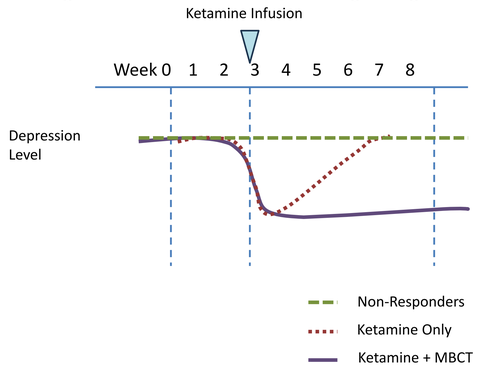

Figure 1: Hypothetical Model of Depression Trajectories Across Treatment Conditions Illustration of expected trends in depression symptoms over time in response to Ketamine Only, combined Ketamine + MBCT treatment, and non-responders.

Methods

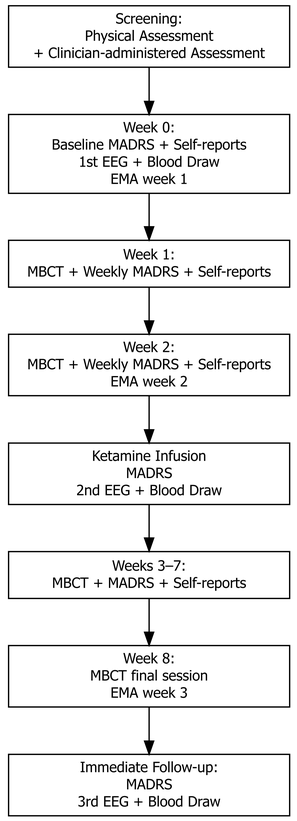

Figure 2: Study Procedure Timeline. Overview of Ketamine MBCT intervention schedule

- **Study Design: an 8-week Mindfulness-Based Cognitive Therapy (MBCT) program, with participants attending weekly 2-hour virtual 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.**
- **Participants completed weekly self-report measures (PHQ-9), clinician-administered interviews (MADRS), and Ecological Momentary Assessments (EMA).**
- **Electroencephalogram (EEG) and blood draws were completed at baseline, post-infusion, and post-therapy.**
- **This single-arm pilot study recruited adults (ages 18–72) with TRD.**
  - **Inclusion criteria:**
    - **Participants met DSM-5 criteria for major depressive disorder**
    - **Failure of at least one adequate trial of antidepressant medication**
    - **>= 20 on Montgomery-Asberg Depression Rating Scale (MADRS)**
  - **Exclusion criteria:**
    - **Meets DSM-5 criteria for PTSD, bipolar disorder, any psychotic illness, OCD, and more**
    - **Previous participation in MBCT or MBSR group**
    - **Current risk of suicide**
    - **Significant physical health risks**

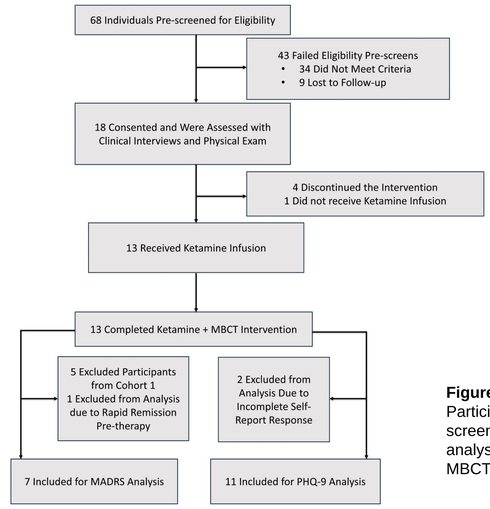

Figure 3: Participant Flow Diagram. Participant recruitment, eligibility screening, enrollment, intervention, and analysis inclusion for the Ketamine MBCT study.

Discussion

- **MBCT extended antidepressant effect of a <u>single</u> ketamine infusion in most participants to 6 weeks or longer, rather than typical time course of depression relapse in 1-2 weeks**
- **Combining Ketamine and MBCT may produce a fast-acting and sustained antidepressant response for TRD.**
- **Longer term follow-up is needed to assess if MBCT can reliably increase the long-term durability of ketamine**
- **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.**

Results

- **18 participants enrolled, 14 completed MBCT group therapy. Only 11 participants were included in analysis due to dropouts and incomplete assessment collection.**
- **Figure 4 displays PHQ-9 scores over course of treatment, responses reflect experiences in the past two weeks.**
- **MADRS scores reflect experiences in the past one week and are used as the primary outcome measure.**
- **Comparison of all participants across all timepoints (Figure 5) reveal three trends in response to treatment, these trends are separately presented in Figure 6.**
  - **Responded to both ketamine and MBCT (N=4)**
  - **Responded to ketamine only (N=1)**
  - **Non-Responder (N=2)**
- **N=3 reached remission at the end of therapy (MADRS <= 10)**

1. Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A, Denys D. Treatment-resistant depression and suicidality. J Affect Disord. 2018;235:362-367. doi:10.1016/j.jad.2018.04.016
2. Wan LB, Levitch CF, Perez AM, et al. Ketamine Safety and Tolerability in Clinical Trials for Treatment-Resistant Depression. J Clin Psychiatry. 2015;76(03):247-252. doi:10.4088/JCP.13m08852
3. Kuyken W, Warren FC, Taylor RS, et al. Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials. JAMA Psychiatry. 2016;73(6):565. doi:10.1001/jamapsychiatry.2016.0076
4. Kral TRA, Imhoff-Smith T, Dean DC, et al. Mindfulness-Based Stress Reduction-related changes in posterior cingulate resting brain connectivity. Soc Cogn Affect Neurosci. 2019;14(7):777-787. doi:10.1093/scan/nsz050
5. Kuyken W, Hayes R, Barrett B, et al. The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: results of a randomised controlled trial (the PREVENT study). Health Technol Assess. 2015;19(73):1-124. doi:10.3310/hta19730

PHQ-9 Scores Over Time

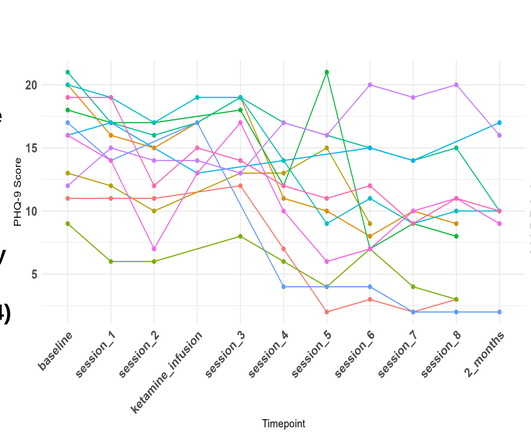

Figure 4: Weekly Progression of Depressive Symptoms (PHQ-9) This figure presents PHQ-9 scores from both Cohort 1 and Cohort 2 participants. Each line represents one participant, representing the change in depressive symptom changes throughout treatment.

MADRS Scores Over Time

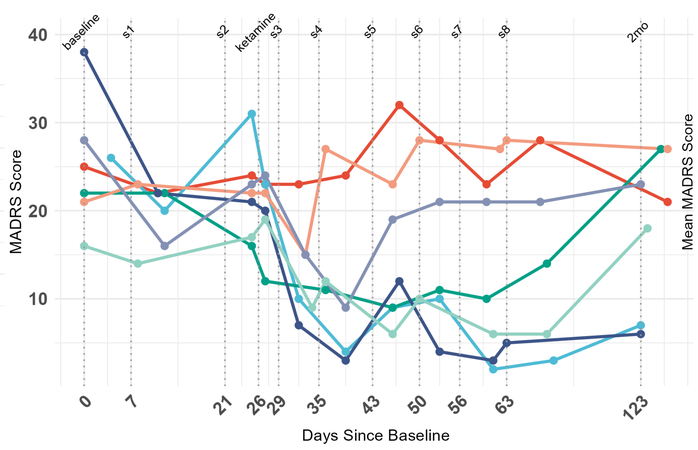

Figure 5: Individual MADRS Score Trajectories Across Study Days (Cohort 2) This figure displays individual trajectories of MADRS scores for participants in Cohort 2. The x-axis represents days since baseline, with vertical dotted lines marking session timepoints. Each colored line represents an individual participant's MADRS scores across the course of intervention.

MADRS Scores by post-hoc "Response Type"

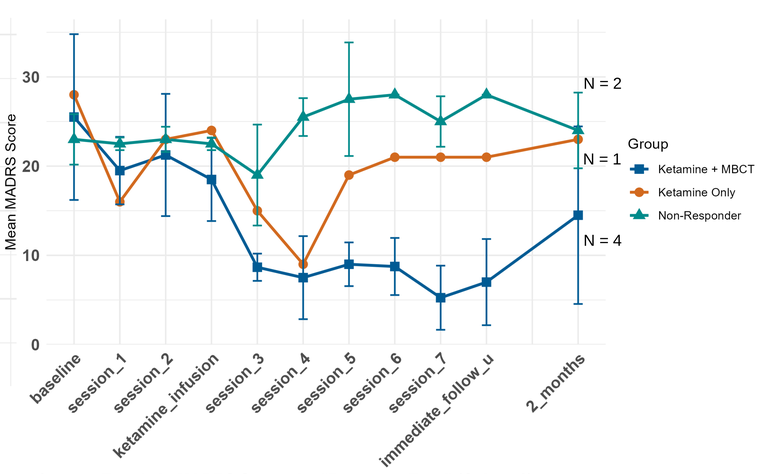

Figure 6: Trends in MADRS Scores by "Response Type" (Cohort 2) This figure illustrates the mean ± standard deviation of MADRS scores over time for participants in Cohort 2, categorized by clinical response patterns: Responders to both Ketamine and MBCT, Ketamine-Only Responders, and Non-Responders. Sessions are plotted along the x-axis, from baseline through immediate follow-up. Ketamine responders show initial improvement with relapse, while combined treatment responders demonstrate sustained reduction in depression severity.