Study Protocol

Official Title: Ketamine plus mindfulness for depression

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Scientific Background

Depression is one of the most prevalent and costly mental health conditions, with a collective public disease burden of staggering proportions. While efficacious treatments have been available for decades, remission rates are low, relapse rates are high, and disorder prevalence rates remain notably consistent, with only 12.7% of patients receiving minimally adequate treatment.

Ketamine is a glutamatergic agent used routinely for induction and maintenance of anesthesia. In randomized controlled trials, subanesthetic (typically, 0.5mg/kg) intravenous ketamine exhibits well-replicated, rapid, potent (i.e., metaanalytic Cohen's d=1.4, a large effect) antidepressant effects, even in difficult-to-treat conditions such as treatment-resistant depression and bipolar depression. Antidepressant effects begin app. 2 h post-infusion (after acute dissociative and euphoric side effects subside) and continue far beyond the drug's elimination half-life of 2.5-3h.

The rapidity and magnitude of ketamine's effects on depressive-like behavior are attributed, at the neurobiological level, to its ability to rapidly and profoundly reverse neuroplasticity deficits. However, little is known regarding whether ketamine's mechanisms of antidepressant action also involve psychological shifts in the patient's state of consciousness which are evident during the infusion itself. One such theorized mechanism involves a possible amplification of present-moment mindful awareness, which is a psychological state that has also been strongly linked with protection against depression in prior work. For example, during and just after a ketamine infusion, awareness of present-moment perceptual experiences may be enhanced due to their deviations from normal consciousness, and these shifts are experienced by some patients as 'mystical,' 'holy,' or 'spiritual' and as fostering meaningful insights that they view as linked to therapeutic benefits. However, many other patients do not spontaneously report such experiences, suggesting that the infusion may interact with other pre-

disposing factors to produce a more mindful and/or 'mystical' state in some patients than in others.

Furthermore, although effective, ketamine as a stand-alone treatment may not be fully optimized, as it leads to a robust treatment response only in 50-70% of depressed patients, and the impact is relatively short-lived, with symptoms generally returning to baseline within 1-2 weeks.

In this study, we will utilize ketamine as a rapid-acting experimental probe to decrease clinical symptoms and enhance neuroplasticity, and will experimentally assess (through a randomized design) whether the resulting effects on depression, as well as on a neurocognitive battery of performance-based and psychological measures, are amplified by explicitly invoking a mindful state of awareness just before, during, and after the infusion. In particular, we will test whether the adjunctive mindfulness exercises lead to a larger and/or more enduring benefit in terms of depression symptoms, self-reported mindful awareness, and neurocognitive performance-based markers.

Findings will help in building a more integrative model of depression mechanisms and possible synergistic treatment approaches. In particular, anticipated heightened perceptual experiences and anomalies, as well as generalized increases in flexible processing across cognition, information processing, and neural networks which we posit will be induced by IV ketamine, may acutely promote the achievement of a mindful state of awareness, which may in turn yield larger and/or more enduring downstream improvements in depression.

The aims of the project are innovative in several key respects. First, although prior studies among substance use disorder patients have incorporated mindfulness training/exercises into the context of a single ketamine infusion and have reported correlational findings linking corresponding 'mystical' experiences during the infusion with abstinence following the infusion, no prior study has examined the role of mindful awareness or mystical experiences during ketamine infusion in

potentially promoting antidepressant benefits among depressed patients. There is considerable debate regarding whether the altered state of consciousness that ketamine induces during the infusion itself is therapeutically relevant at all. This is noteworthy considering that depression has been a key clinical target for stand-alone IV ketamine treatments as well as for behavioral mindfulness-based interventions. Furthermore, no prior study (in any clinical population) has used a randomized design to experimentally manipulate mindful awareness during a ketamine infusion. This information is vital for the development and assessment of novel, potentially synergistic interventions and to inform practice guidelines for ketamine therapy, which in community-based clinical settings routinely espouse to induce a "transformative," "trance"-like, mindful and/or mystical/spiritual experience.
Second, little prior work has examined the degree to which a range of neurocognitive performance-based biomarkers may be altered by a single dose of ketamine, with or without adjunctive mindfulness exercises. Thus, our study has the potential to illuminate the neurocognitive mechanisms underlying ketamine's rapid antidepressant effects, which could yield an improved understanding both of ketamine's mechanisms of action as well as the pathophysiology of depression itself.

Study Objectives

In this project, we will administer a single infusion of IV ketamine to depressed patients and randomize the patients to receive either a) usual/typical infusion conditions or b) mindfulness training and exercises in conjunction with the infusion. We will test whether the conjunction of ketamine + mindfulness enhances the reductions in depression following a single ketamine infusion.

Building on our prior work, we will examine how a single dose of ketamine, with vs. without adjunctive mindfulness training, alters depressive symptoms, self-reported mindfulness, and neurocognitive performance-based markers related to depression risk.

Aim 1) To examine the extent to which adjunctive mindfulness exercises, delivered in conjunction with a single dose of ketamine, enhances the effect size and/or duration of ketamine's rapid antidepressant effect.

Aim 2) To examine the extent to which adjunctive mindfulness exercises, delivered in conjunction with a single dose of ketamine, enhances self-reported mindful awareness and 'mystical' experiences, during and just after the infusion.

Aim 3) To examine the extent to which adjunctive mindfulness exercises, delivered in conjunction with a single dose of ketamine, enhances the effect size of post-infusion shifts in neurocognitive performance-based markers related to depression risk.

Study Design & Methods

Enroll 60 adults to complete 40 patients in final sample. Participants will complete baseline clinical, self-report, and neurocognitive performance-based assessments, followed by a single dose of ketamine. Patients will be randomly allocated to receive either standard/typical infusion conditions, or adjunctive training in mindfulness exercises. All patients will then complete post-infusion assessments over a 1-month follow-up interval.

Eligibility Criteria:

Inclusion Criteria:

All participants will:

1) be between the ages of 18 and 65 years,

2) score ≥ 14 on the modified Hamilton Depression Rating Scale (Ham-D)

3) possess a level of understanding sufficient to agree to all tests and examinations required by the protocol and must sign an informed consent document

Exclusion Criteria:

1) Presence of lifetime bipolar, psychotic, or autism spectrum; current problematic substance use (e.g., ongoing moderate-to-severe substance use disorder);
2) Acute suicidality or other psychiatric crises requiring treatment escalation. We will use the Columbia Suicide Severity Rating Scale (CSSRS) as both an initial exclusion criteria (CSSRS "Baseline/Screening" Version for past 1month period) and as grounds for rescue/removal (CSSRS "Since Last Visit" form). The CSSRS will be administered using a paper form by an experienced and thoroughly trained clinical assessor on the study team. Subjects with CSSRS suicide ideation scores scored "yes" on items 4 (active suicidal ideation with some intent to act) and/or 5 (active suicidal ideation with specific plan and intent) will be excluded from the study, and if enrolled, will be exited from the study and referred immediately to the nearest emergency mental health facility for additional thorough assessment and appropriate treatment referral.
3) Changes made to treatment regimen within 4 weeks of baseline assessment.
4) Reading level <6th grade as per patient self-report.
5) Patients who have received ECT in the past 2 months prior to Screening.
6) Current pregnancy or breastfeeding
7) Patients must be reasonable medical candidates for ketamine infusion, as determined by a physician co-investigator. Serious, unstable medical

illnesses including respiratory [obstructive sleep apnea, or history of difficulty with airway management during previous anesthetics], cardiovascular [including ischemic heart disease and uncontrolled hypertension], and neurologic [including history of severe head injury] will be exclusions.

8) Clinically significant abnormal findings of laboratory parameters [including urine toxicology screen for unreported drugs of abuse], vitals, or ECG. Patients with prolonged QT or Torsade will not be eligible to receive Zofran PRN, but remain eligible for all other study procedures
9) Uncontrolled or poorly controlled hypertension, as determined by a physician co-investigator's review of vitals collected during screening and any other relevant medical history/records.
10) Patients with one or more seizures without a clear and resolved etiology.
11) Patients starting hormonal treatment (e.g., estrogen) in the 3 months prior to Screening.
12) Past intolerance or hypersensitivity to ketamine.
13) Patients taking medications with known activity at the NMDA or AMPA glutamate receptor [riluzole, amantadine, memantine, topiramate, dextromethorphan, D-cycloserine], or the mu-opioid receptor [opiate medications--morphine, oxycodone, heroin, fentanyl)]. However, lamotrigine will not be a study exclusion given that it has been shown not to impact ketamine's safety profile or its antidepressant efficacy.
14) Patients taking any of the following medications: St John’s Wort, theophylline, tramadol, metrizamide.
15) Patients who report meditating with mindfulness techniques >1 hour weekly (on average) for the past 6 months or longer.

Statistical Considerations and Statistical Analysis Plan

This is a pilot study, designed to develop novel study infrastructure and novel intervention methods, leading to small numbers of patients in each treatment arm. Descriptive statistics (means, standard deviations) will be reported without statistical analysis to directly compare the two groups (mindfulness training vs. academic training), given the small number of patients within each group, which yields low statistical power for between-group comparisons. Exploratory inferential statistical analyses

and effect size comparisons (with 95% CIs) will include appropriate comparisons of groups on all primary and secondary endpoints, and on other pre-specified outcomes as warranted.