Protocol for a Randomized, Double-Blind, Midazolam-Controlled Phase II Clinical Trial Investigating Repeated Ketamine Infusions for Treatment Resistant Bipolar Disorder (NCT05004896)

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SUBMISSION DETAILS

Request for Proposals Psychedelics

Abstract: Introduction: Treatment resistant bipolar depression (TRBD) is a significant clinical challenge with an urgent need for novel treatments. Growing evidence supports rapid and robust antidepressant effects with sub-anesthetic doses of intravenous (IV) ketamine for treatment resistant depression. The majority of completed randomized controlled trials (RCTs) to date have been in major depressive disorder samples, excluding participants with history of mania or hypomania. Only small single dose pilot RCTs have evaluated ketamine for bipolar depression. No completed RCTs have evaluated the effects of repeated doses of IV ketamine for TRBD. Based on this minimal evidence, most guidelines consider IV ketamine to be a third-line option for acute bipolar depression.

Methods: A multi-site (University Health Network (UHN) and Ontario Shores (OS)), randomized, double-blind, midazolam-controlled, phase II clinical trial will evaluate the efficacy, safety and tolerability of four flexibly dosed ketamine infusions (0.5 – 0.75 mg/kg infused over 40 minutes) for acute treatment of moderate to severe TRBD (BDI and BDII). Exclusion criteria will include active psychosis, mania, substance use and severe medical comorbidity. Target enrollment is 70 participants (n=35 per group) to be adequately powered. The primary outcome will be change in Mongomery-Asberg Depression Rating Scale (MADRS) scores from baseline to Day 14, using analysis of covariance (ANCOVA), with 14-day MADRS as the outcome and baseline MADRS and stratification variable (sex, bipolar diagnosis) as covariates. Secondary outcomes include response and remission rates, safety (adverse events), tolerability (treatment emergent mania), suicidality, anxiety, quality of life, function and duration of effects (to Day 28).

Results: Enrollment began June 2022 at UHN and April 2024 at OS. Recruitment is ongoing with 51 participants currently enrolled (n=44 UHN, n=7 OS) and is expected to be completed by November 2025. Current recruitment rate is 2-3 participants completed per month. The mean age of the total sample is 45.0 (SD=10.8) with 52.9% female participants (n=27). 20 participants have a diagnosis of bipolar I and 31 are diagnosed with bipolar II.

Discussion: There is an urgent need to evaluate the efficacy, safety and tolerability of repeated IV

ketamine for TRBD. If results find ketamine to be effective and safe, this novel intervention will have the potential to address the current lack of sufficient pharmacotherapies for TRBD and hold hope of improving clinical outcomes in this difficult to treat population. Our trial will provide critical evidence to support or refute the use of IV ketamine for TRBD to inform clinical care guidelines.

Learning Objectives:

Learning Objective 1 Describe the need for clinical trials investigating novel pharmacotherapies for patients with treatment resistant bipolar depression.

Learning Objective 2 Discuss study protocol of the first RCT evaluating IV ketamine for treatment resistant bipolar depression and current recruitment status.

DISCLOSURE

Financial Relationships

Disclosure No, I have nothing to disclose.