

Ultra-Low Dose Buprenorphine to Sustain Antidepressant and Antisuicidal Effects of Intravenous Ketamine in Treatment-Resistant Depression with Suicidal Ideation: Protocol Design and Preliminary Results from a Randomized Controlled Trial

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Methodological Issue Being Addressed Ketamine provides rapid antidepressant and antisuicidal effects, but these typically last only about seven days, limiting its long-term utility. Moreover, the potential risks of repeated ketamine infusions remain unclear, underscoring the need for safer, more sustainable strategies to extend its therapeutic benefits. This study explores whether ultra-low doses of buprenorphine, a partial mu-opioid receptor agonist, administered after a single ketamine infusion, can prolong or enhance its effects by engaging overlapping receptor pathways, building on evidence suggesting ketamine's action via mu-opioid mechanisms.

Introduction This study addresses a critical limitation in the use of ketamine for treatment-resistant depression (TRD) and high suicide risk: the transient nature of its therapeutic effects. TRD and suicide represent significant public health challenges, highlighting the need for innovative and effective treatments. Ketamine has demonstrated rapid—but transient—antidepressant and antisuicidal effects, often fading within a week or two. Ultra-low doses of buprenorphine have been reported to be significantly more effective than placebo in reducing suicidal activity, but the differences are observed beginning at 2 weeks. This study explores a novel approach of pairing intravenous ketamine with follow-on ultra-low doses of oral buprenorphine, which may produce significantly greater or longer-lasting antisuicidal effects than with ketamine followed by placebo.

Methods This is an ongoing randomized clinical trial (ClinicalTrials.gov Identifier: NCT04116528). Participants first received a 40-minute ketamine infusion (0.5 mg/kg), followed 48 hours later by random assignment to a four-week course of either dose-escalated buprenorphine (0.2–0.8 mg daily) or a placebo. The trial visits include weekly follow-ups over the four-week treatment phase and an additional two-week follow-up period with no study drugs. Eligible participants included individuals experiencing a unipolar or bipolar type II major depressive episode lasting at least eight weeks, with prior failure on at least one antidepressant treatment or history of intolerance to at least two antidepressant therapies, and a Beck Scale for Suicidal Ideation (BSSI) score of 6 or higher. The primary outcome is change in the BSSI total scores from day 3 to day 31 after the buprenorphine or placebo course. Secondary outcomes include changes in the Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D-17) total scores over the same period. With a sample size of 60, a two-tailed test will have 80% power to detect an

effect size of 0.35 or greater. Data analysis will use linear mixed models in R software.

Results Since this ongoing study is a placebo-controlled RCT, the results focus on data related to pre-ketamine infusion and day 3 after a ketamine infusion but before initiating the buprenorphine phase. Forty-eight participants experiencing a major depressive episode with suicidal ideation took part in the study, with an average age of 37.58 years (SD = 11.23), of whom 68.75% were female, and one participant had bipolar disorder type II. The MADRS scores showed significant improvement, decreasing from an average of 34.12 to 21.06 ($p < .0001$), with 37.5% meeting the response criteria (a 50% reduction in MADRS total score) and 25% achieving remission (a score of 10 or below). HAMD-17 scores also decreased significantly from 23.47 to 14.68 ($p < .0001$), with 31.25% meeting response criteria and 18.75% achieving remission (a score of 7 or below). BSSI scores dropped from 15.1 to 7.12 ($p < .0001$), with 54.17% achieving a response defined as a 50% reduction in the BSSI total score.

Conclusion The ketamine infusion led to substantial reductions in depressive symptoms and suicidal ideation by day 3, with a particularly strong impact on suicidal thoughts. These findings, combined with ketamine's favorable safety profile, suggest its potential as a rapid-acting intervention for individuals at high suicide risk. The study's next phase, investigating whether prolonged opioid receptor activation via buprenorphine extends ketamine's therapeutic effects, is ongoing and will offer insights into a promising combined treatment approach for TRD and suicidality.

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