Evaluating Augmentation of Anti-Suicidal Effects of Intravenous Ketamine by Low Oral Doses of Opioid Receptor Partial Agonism

Submission ID 3005948

Submission Type Pharmaceutical Pipeline

Topic Depressive Disorders

Status Submitted

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SUBMISSION DETAILS

Request for Proposals Psychedelics

Abstract Background: Ketamine has demonstrated rapid-onset antidepressant and anti-suicidal properties. Most mechanistic studies attribute the therapeutic properties of ketamine to NMDA receptor antagonism. Our group previously demonstrated that mu opioid receptor antagonism attenuates intravenous ketamine's acute antidepressant effects. Others have found that ultra-low oral doses of a partial mu receptor agonist have potent antidepressant and anti-suicidal properties. To reduce the burden and risk of repeated ketamine dosing needed to maintain therapeutic efficacy, we explored whether low dose opioid receptor agonism with buprenorphine could extend the anti-suicidal and antidepressant properties of a single administration of intravenous ketamine.

Methods: In an ongoing, double-blinded trial to be completed by mid March 2025, 42 participants to date (average age 37.5 +/- 10.9 years, 75% female) diagnosed with treatment resistant depression have received open-label IV ketamine infusion (0.5mg/kg), followed by randomization two days later to receive either dose-escalated buprenorphine (0.2-0.8 mg QOD) or placebo for 4 weeks, followed by a post taper follow up for 2 weeks. Study entry criteria include a major depressive episode lasting ≥ 8 weeks, a history of at least one treatment failure in the current episode, a Beck Scale for Suicidal Ideation (BSSI) score ≥ 6 and a minimum score of 3 on the Columbia-Suicide Severity Rating Scale (CSSRS). The primary measure outcome was change in the BSSI. Pre-defined secondary outcomes include changes from baseline on the Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD-21). The time course was analyzed via mixed-effects ANOVA and Bonferroni correction.

Results: Of the 42 participants infused thus far with a single dose of IV ketamine, 33 participants have completed the day 45-day time course. On day 3 post infusion, 52.1% of participants achieved ≥ 50% reduction of BSSI; response and remission rates were 35/17.5% on the HAM-D-21 and 37.5/25% on the MADRS respectively. With recruitment ongoing, the intervention allocation remains blinded, but preliminary results for the entire study are provided here. At day 45, BSSI decreased from 15.81 to 7.15 ($F_{4,139} = 28.40$, $p < 0.0001$); mean HAM-D-21 decreased from 24.88

to 16.94 ($F_{4,128} = 20.98$, $p < 0.0001$), and mean MADRS decreased from 33.98 to 22.45 ($F_{3,117} = 18.56$, $p < 0.0001$). At day 45, 21% of participants continued to remit using HAMD, with 27% continuing to remit using MADRS criteria. As of this submission recruitment is ongoing and blinded to buprenorphine treatment but completion will be before the ASCP meeting.

Conclusion: A single dose IV ketamine infusion substantially reduced depression and suicidality at day 3, with somewhat greater effect observed for suicidality than depression. The overall therapeutic benefits were largely maintained out to day 45, beyond what has been typically reported in the literature. While this outcome could be consistent with our hypothesis that low dose mu opioid agonism in the buprenorphine arm will prolong the therapeutic benefits of ketamine greater than placebo, we can only speculate until study completion and unblinding. The study will be completed prior to the ASCP meeting, and unblinded results will be presented at ASCP.

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