

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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The Methodological Issue Being Addressed

- Ketamine provides rapid antidepressant and antisuicidal effects, but these typically last only about seven days, limiting its long-term utility.
- The potential risks of repeated ketamine infusions remain unclear, underscoring the need for safer, more sustainable strategies to extend its therapeutic benefits.
- Potential overlapping mechanism of action:

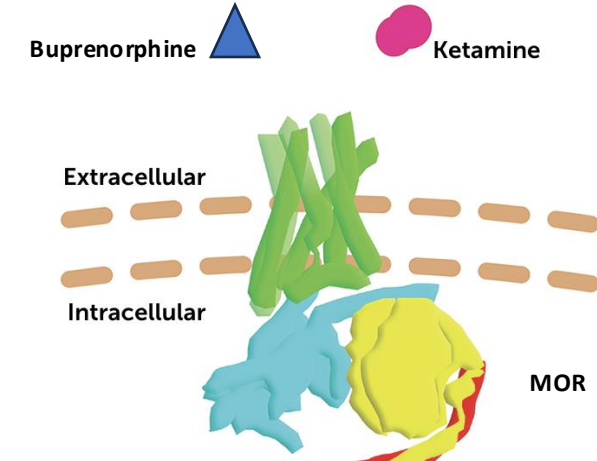


Image modified from Levinstein et al. Redefining Ketamine Pharmacology for Antidepressant Action: Synergistic NMDA and Opioid Receptor Interactions? Am J Psychiatry. 2025.

Introduction (Aims)

- 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

- Randomized, placebo-controlled, double-blinded, phase II clinical trial (NCT04116528)

Inclusion criteria

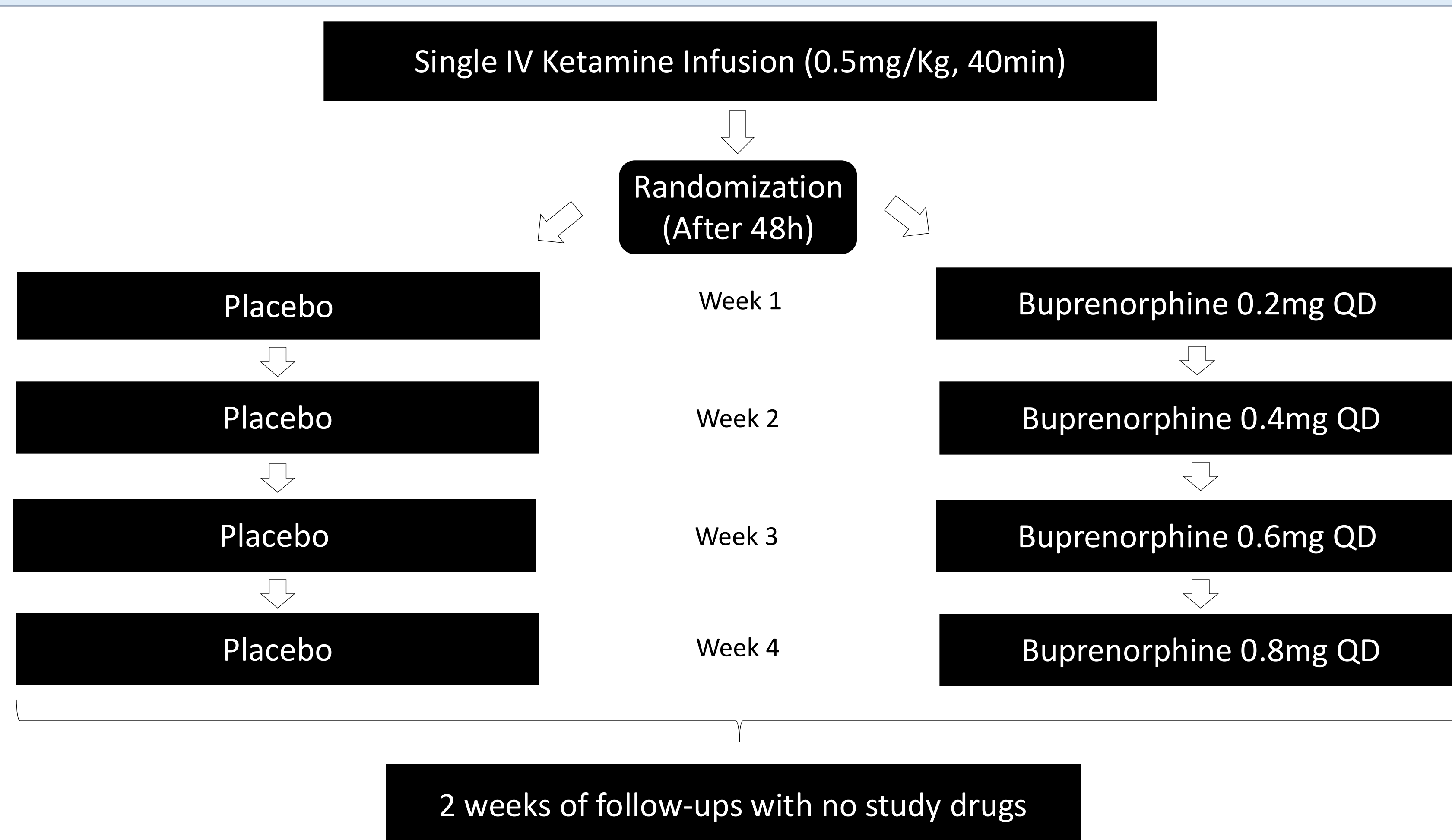
- Major depressive disorder or bipolar disorder type II in a major depressive episode (≥ 8 weeks)
- ≥ 1 antidepressant failure in the current episode or ≥ 2 intolerances
- Beck Scale for Suicidal Ideation (BSSI) total score ≥ 6

Primary outcome

- Change in the BSSI total scores from day 3 to day 31 at the completion of the buprenorphine or placebo course.

Secondary outcomes

- Changes in the Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D-17) total scores over the same period.



Schedule of events	Baseline	Infusion day	Day 3	W1	W2	W3	W4	W5	W6
Clinician-rated scales									
Mini International Neuropsychiatric Interview (MINI)	X								
Beck Scale for Suicidal Ideation (BSSI)	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X
Montgomery-Åsberg Depression Rating Scale (MADRS)	X	X	X	X	X	X	X	X	X
Hamilton Depression Rating Scale (HAM-D-17)	X	X	X	X	X	X	X	X	X
Clinician-Administered Dissociative States Scale (CADSS)		X							
Clinician Opiate Withdrawal Scale (COWS)								X	X
Self-reports									
Beck Hopelessness Scale	X	X	X	X	X	X	X	X	X
Beck Depression Inventory II (BDI-II)	X	X	X	X	X	X	X	X	X
Adverse Childhood Experiences Questionnaire (ACE)	X	X	X	X	X	X	X	X	X
Brief Pain inventory (BPI)	X	X	X	X	X	X	X	X	X
Insomnia Severity Index (ISI)	X	X	X	X	X	X	X	X	X
Snaith-Hamilton Pleasure Scale (SHAPS)	X	X	X	X	X	X	X	X	X
Rumination Scale	X	X	X	X	X	X	X	X	X

Other outcomes

Pupillometry



Prolactin and drug metabolites

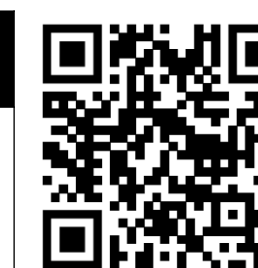


Implicit Association Test (IAT-Death/Escape)



Sample size

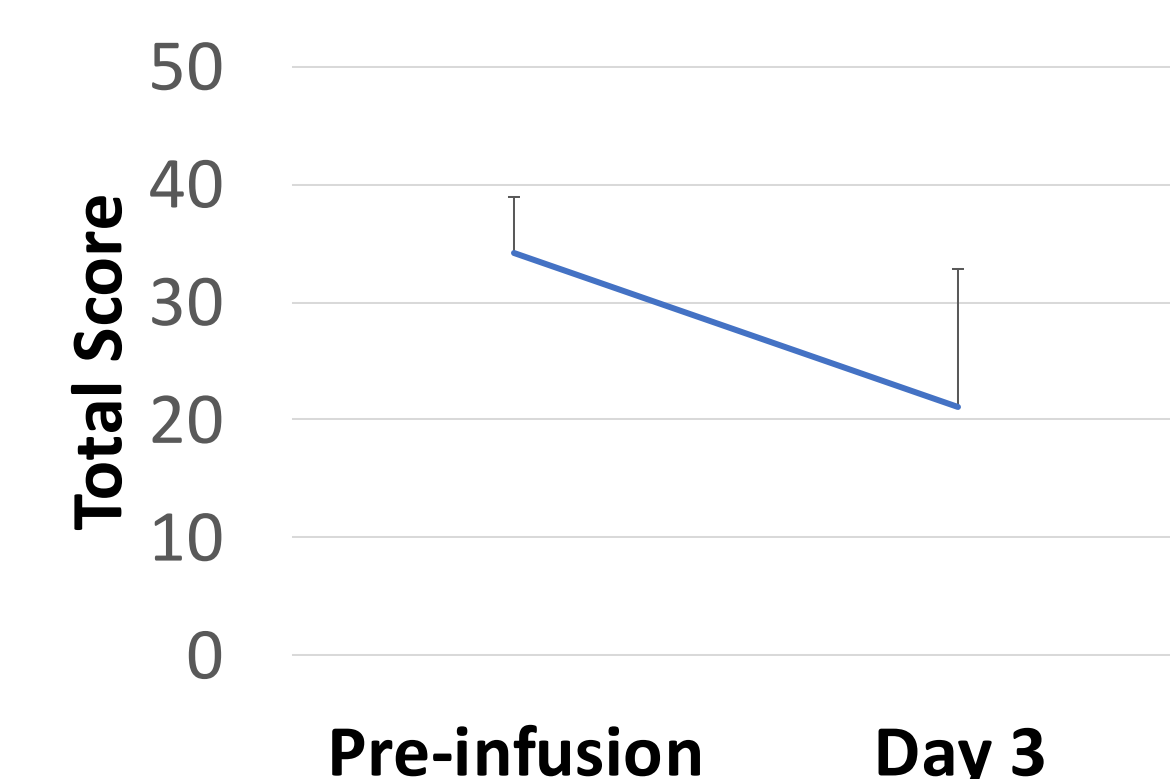
- With a sample size of 60, a two-tailed test will have 80% power to detect an effect size of 0.35 or greater.



Results

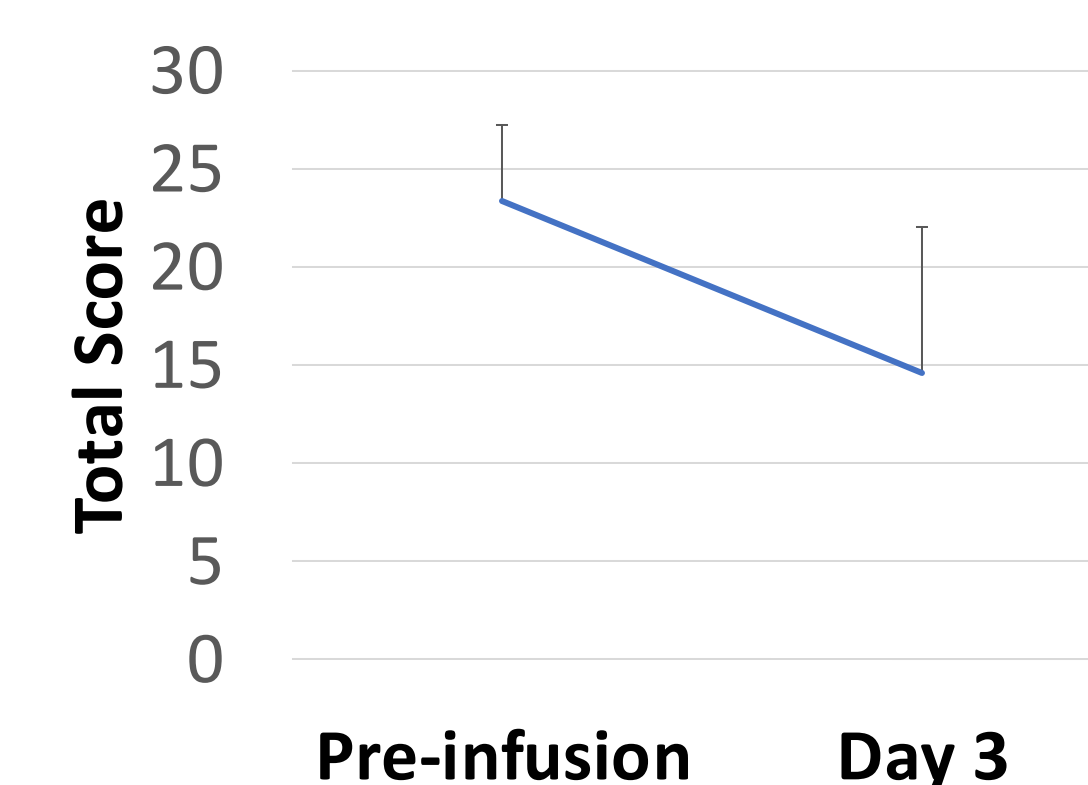
Baseline characteristics	n=48
Age, M (SD)	37.58 (11.23)
Sex, n (%)	
Female	33 (68.75)
Race, n (%)	
White	34 (72.34)
Ethnicity, n (%)	
Hispanic or Latino	9 (18.75)

MADRS



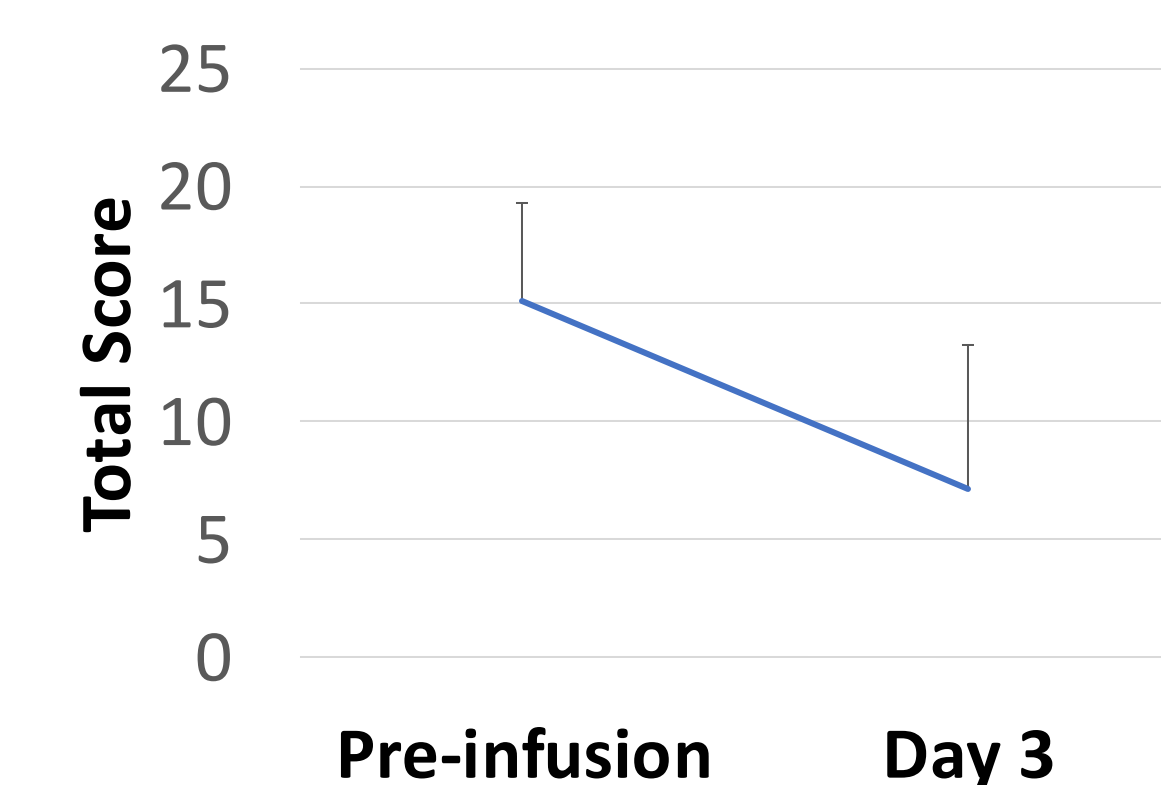
p < 0.0001
Response rate: 37.5%
Remission rate: 25%

HAMD-17



p < 0.0001
Response rate: 31.25%
Remission rate: 18.75%

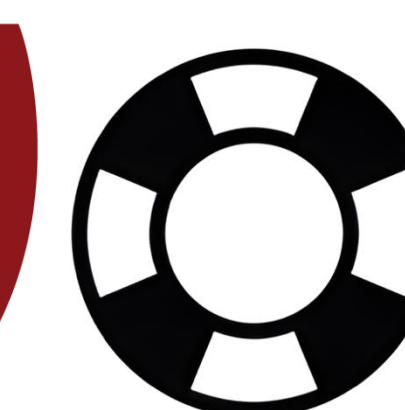
BSSI



p < 0.0001
Response rate: 54.17%

Conclusions

- The ketamine infusion led to substantial reductions in depressive symptoms and suicidal ideation by day 3, with a particularly strong impact on suicidal thoughts.
- 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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