# A Proof-of-Concept Study of Subanesthetic Intravenous Ketamine Combined With Prolonged Exposure Therapy Among Veterans With Posttraumatic Stress Disorder

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Prolonged exposure (PE) is a gold-standard trauma-focused therapy[1]; however, clinical trials of trauma-based therapies in the military and veteran populations showed that up to 50% of participants failed to attain clinically meaningful symptom improvement.[2] Emerging research indicates that PE efficacy may be improved by the use of adjunctive medications. The efficacy of single and repeated ketamine administration in posttraumatic stress disorder (PTSD) seems comparable with that in depression. Below, we present pilot data on the feasibility of combining standardized PE therapy with repeated ketamine administration in PTSD.

## Methods

In a 10-week pilot conducted April–June 2019, veterans aged 18–75 years with chronic (>6 months) and at least moderate PTSD (Clinician-Administered PTSD Scale for *DSM-5* [CAPS-5] score ≥ 23 and PTSD Checklist for *DSM-5* [PCL-5] score > 33) received intravenous (IV) ketamine (0.5 mg/kg) 24 hours prior to weekly PE for the first 3 weeks followed by up to 7 additional PE sessions. PE was delivered by nationally certified clinical therapists. Exclusion criteria were < 6 months of alcohol/substance use disorder, moderate/severe traumatic brain injury, bipolar disorder, or psychosis. Concurrent psychotropics were stable ≥ 4 weeks. The primary outcome was the change in CAPS-5 scores from baseline to the last PE session administered by an independent evaluator. Linear mixed model with intent-to-treat analysis included baseline CAPS-5 score, time as fixed effects, and random patient effect. Secondary outcomes, which included the Montgomery-Asberg Depression Rating Scale (MADRS), PCL-5, and Clinical Global Impression-Severity of Illness scale (CGI-S), were measured at baseline and weeks 1, 2, 3, 4, 6, 8, and 10. Informed consent was obtained from all participants. The study was approved by the Minneapolis Health Care System institutional review board and registered in ClinicalTrials.gov (NCT03960658).

## Results

In 4 months, out of 12 subjects who provided consent, 10 completed treatment infusions with at least 1 follow-up PCL-5 (N = 10) or CAPS-5 (N = 9) assessment. Demographic and clinical characteristics are shown in Supplementary Table 1. PCL-5 scores for each patient at several weeks of treatment are shown in Figure 1, and complete PE sessions and pre- and posttreatment scores of CAPS-5, PCL-5, MADRS, and CGI-S are shown in Supplementary Table 2. Scores significantly decreased from baseline to end of treatment in CAPS-5 ($t_{11} = 4.21$, $P = .001$, −15.25 [95% CI, 7.27–23.23], $d = 1.21$), PCL-5 ($t_{11} = 6.35$, $P < .001$, −30.75 [20.09–41.41], $d = 1.83$), and MADRS ($t_{11} = 4.68$, $P = .001$, −11.5 [6.09–16.91], $d = 1.35$). After controlling for mean change in MADRS score over time, changes in total PCL-5 scores ($F_{1,10} = 5.69$, $P = .038$, $h^2 = 0.36$) and PCL-5 Avoidance ($F_{1,10} = 6.31$, $P = .031$, $h^2 = 0.36$) remained significant. However, changes in PCL-5 Intrusion ($F_{1,10} = 4.48$, $P = .06$, $h^2 = 0.31$), Arousal ($F_{1,10} = 1.25$, $P = .29$, $h^2 = 0.11$), and Negative mood and cognition ($F_{1,10} = 3.83$, $P = .079$, $h^2 = 0.28$), as well as CAPS-5 ($F_{1,10} = 1.18$, $P = .30$, $h^2 = 0.11$), were no longer significant.

## Discussion

This small, open-label, proof-of-concept study suggests that repeated IV ketamine administration can be concurrently used with standardized PE therapy to treat PTSD. Previously, a single infusion of ketamine significantly decreased PTSD symptoms 24 hours postinfusion compared to midazolam.[3] Findings with repeat open-label IV ketamine administration in comorbid PTSD and refractory depression suggested that ketamine increases the efficacy for both PTSD and depressive symptoms beyond a single infusion.[4]

Clinical studies have demonstrated the feasibility of combining IV ketamine and cognitive-behavioral therapy in obsessive-compulsive disorder[5] and treatment-resistant depression.[6] PE efficacy may be improved through medications that target 1 or more mechanisms.[7] Ketamine

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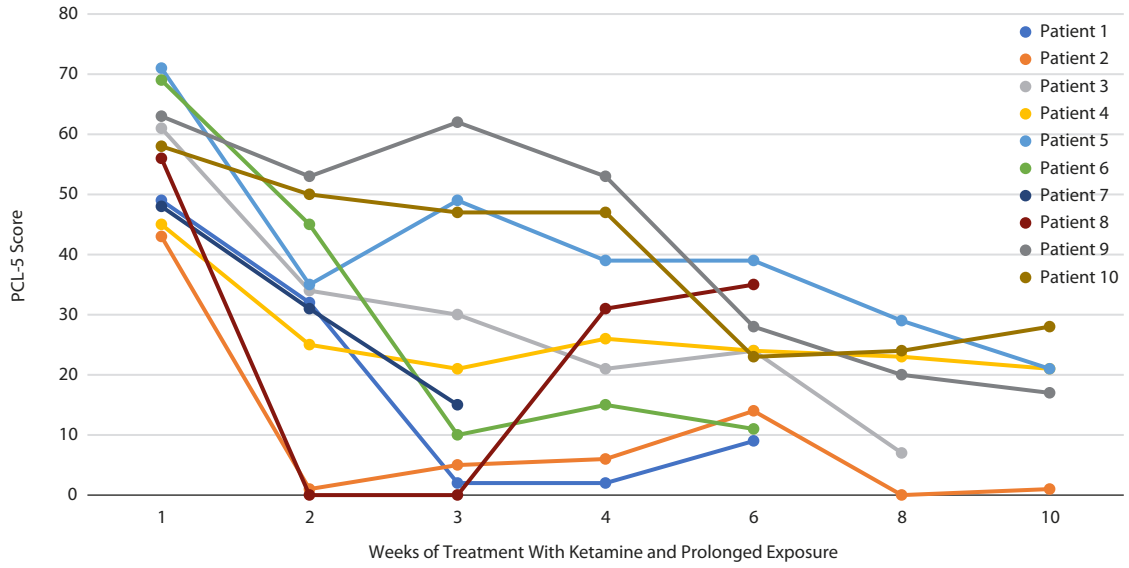
**Figure 1. Severity of PTSD Symptoms as Measured by PCL-5 Scores During Treatment With Ketamine and Prolonged Exposure (PE)[a]**




[a]Subjects started a 10-week course of PE therapy concurrently with intravenous ketamine at 0.5 mg/kg for 40 minutes 24 hours prior to the first 3 PE sessions. Subjects then completed up to a total of 10 weekly PE sessions. Standardized PE was delivered by clinical therapists.
Abbreviations: PCL-5 = PTSD Checklist for *DSM-5*, PTSD = posttraumatic stress disorder.

could augment the biological processes of extinction memory. In mice models of PTSD, a single dose of ketamine followed by extinction training enhances the recall of extinction learning and decreases fear renewal.[8] Ketamine plus extinction exposure increases synaptic protein promoter and neuronal activation in the medial prefrontal cortex,[8] exerting a possible top-down inhibitory drive over excitatory responses of fear conditioning such as the amygdala.

As an alternative, early gains by ketamine's rapid antidepressant and anxiolytic effects can strengthen confidence in the therapeutic approach, improve rapport, and increase treatment adherence. Rapid improvement in depression is associated with lower rate of dropout and lower posttreatment severity score during PTSD treatment.[9] A potential backfire of this rapid response is reducing the motivation to complete PE. Given preliminary findings, larger randomized clinical trials should prove whether ketamine has a synergistic effect over trauma-based therapy for PTSD.

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See supplementary material for this brief report at PSYCHIATRIST.COM.

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# Supplementary Material

**Article Title:** A Proof-of-Concept Study of Subanesthetic Intravenous Ketamine Combined With Prolonged Exposure Therapy Among Veterans With Posttraumatic Stress Disorder

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## List of Supplementary Material for the article

1. Table 1 — Demographic and Clinical Characteristics of Veterans with PTSD
2. Table 2 — Number of Prolonged Exposure Sessions, and Severity of Post-traumatic Stress Disorder, Major Depressive Disorder, and Clinical Global Impression at Baseline and Post-Treatment

## Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Demographic and Clinical Characteristics of Veterans with PTSD

| Patient N | Age[¥] | Sex | Type of Trauma | Duration of PTSD[¥] | MDD | Anxiety Disorder | PPH | Past SUD/AUD | SA |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 54 | M | Combat | 15 | Yes | Yes | No | No | No |
| 2 | 38 | M | Sexual | 23 | No | No | No | No | Yes |
| 3 | 42 | F | Sexual | 6 | Yes | Yes | No | No | No |
| 4 | 34 | M | Combat | 14 | No | Yes | No | No | No |
| 5 | 72 | M | Combat | 52 | Yes | Yes | No | Yes | No |
| 6 | 38 | M | Combat | 15 | Yes | No | Yes | Yes | Yes |
| 7 | 24 | F | Sexual | 15 | No | Yes | No | No | No |
| 8 | 36 | M | Combat | 5 | Yes | No | No | No | No |
| 9 | 47 | F | Sexual | 28 | Yes | Yes | Yes | No | Yes |
| 10 | 66 | M | Physical | 44 | Yes | Yes | Yes | Yes | Yes |

Abbreviations: M, Male; F, Female; [¥] in years. MDD: Major Depressive Disorder. PPH: Past Psychiatric Hospitalization. SUD, Substance Use Disorder; AUD, Alcohol Use Disorder: SA, Suicidal Attempt.

Supplementary Table 2. Number of Prolonged Exposure Sessions, and Severity of Post-traumatic Stress Disorder, Major Depressive Disorder, and Clinical Global Impression at Baseline and Post-Treatment

| Patient N | N of PE sessions | CAPS-5 Baseline | CAPS-5 Post-treatment[¥] | PCL-5 Baseline | PCL-5 Post-Treatment | MADRS Baseline | MADRS Post-treatment | CGI-S Baseline | CGI-S Post-Treatment |
|---|---|---|---|---|---|---|---|---|---|
| 1[#] | 7 | 30 | 2 | 49 | 9 | 30 | 4 | 5 | 3 |
| 2[#] | 7 | 34 | 1 | 43 | 1 | 18 | 4 | 4 | 2 |
| 3[#] | 7 | 48 | 22 | 61 | 7 | 18 | 6 | 5 | 2 |
| 4 | 10 | 33 | 16 | 45 | 21 | 18 | 15 | 4 | 3 |
| 5 | 10 | 56 | 25 | 71 | 21 | 34 | 15 | 5 | 3 |
| 6 | 6 | 45 | N/A* | 69 | 11 | 27 | 4 | 5 | 3 |
| 7 | 3 | 37 | 5 | 48 | 15 | 21 | 5 | 5 | 2 |
| 8[π] | 10 | 53 | 14 | 56 | 25 | 32 | 21 | 5 | 2 |
| 9[μ] | 10 | 50 | 15 | 63 | 17 | 26 | 11 | 5 | 2 |
| 10[π] | 10 | 42 | 18 | 58 | 28 | 26 | 22 | 5 | 3 |

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for DSM-5; PCL-5, PTSD Checklist for DSM-5; MADRS, Montgomery-Åsberg Depression Rating Scale. CGI-S: Clinical Global Impression Severity. [¥]CAPS-5 post-treatment was administered within one week after the last PE sessions. *Missed CAPS-5 after PE session 4 and lost follow-up after PE session 6. [π] Asymptomatic elevation of systolic and diastolic blood pressure of subjects #8 (173/119) and #10 (163/103) required administration of 5 mg of labetalol once at infusion 1 and 3, respectively. [μ] Subject required 2 mg of ondansetron IV stat after experiencing nausea without vomiting during infusion 1 and 2. [#] Subjects who ended PE therapy after session 7 as therapists considered that clinical goals were achieved.