

Repeated Ketamine Treatment to Accelerate Efficacy of Prolonged Exposure in PTSD

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Ketamine-enhanced Prolonged Exposure Therapy in PTSD
CORE PROTOCOL
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1. BACKGROUND

1.1. Limitations of Pharmacological Interventions for PTSD.

Currently, only 02 selective serotonin reuptake inhibitors, sertraline and paroxetine, are FDA- approved as pharmacological treatment for PTSD. The 2017 VA/DoD Clinical Practice Guideline for The Management of PTSD and Acute Stress Disorder added fluoxetine and venlafaxine as monotherapy. Unfortunately, even after an adequate medication trial, response and remission rates are approximately 60% and 30%, respectively⁹. Randomized controlled trials (RCTs) investigating the use of alternative drugs or combination of mainstream pharmacological interventions including atypical antipsychotics, anticonvulsants, and benzodiazepines have shown limited to no benefit¹⁰, leaving considerable room to improve treatment options for PTSD. On the other hand, the VA/DOD clinical practice guidelines recommend individual, manualized trauma-focused psychotherapy, such as Prolonged Exposure (PE) therapy, over other pharmacologic interventions for the primary treatment of PTSD. Moreover, when given a choice, most patients will select psychotherapy treatment for PTSD rather than medications.

1.2. Limitations of Trauma-based Psychotherapy in the veteran/military populations.

PE is considered a first-line evidence-based treatment for PTSD with compelling evidence to effectively reduce PTSD symptoms relative to waiting list¹¹. A multi-center study¹ showed that female veterans and active duty military personnel with PTSD were more likely than those in the present-centered therapy (PCT) group to no longer meet PTSD diagnostic criteria (41% vs 28%); however, PE achieved only an overall remission rate of 15% (vs 7% in PCT), the dropout rate was almost double in PE (38%) than in PCT (21%), and there was no significant difference rates of PTSD remission at 6-month follow-up with at 40% in PE and 33% in PCT. A recent review of clinical trials of trauma-based therapies for PTSD² (PE and Cognitive Processing Therapy (CPT) in the military and veteran population found that between 30% to 50% of participants failed to attain clinically meaningful symptom improvement (defined as a 10- to 12-point decrease in interviewer- assessed or self-reported symptoms). The mean posttreatment scores for CPT and PE remained at or above clinical criteria for PTSD, and approximately two-thirds of patients retained their PTSD diagnosis after treatment (range, 60%-72%)². These results suggest that despite its efficacy, PE (and CPT) in the military/veteran population is suboptimal to relieve PTSD as an elevated number of patients drops out from treatment and most patients remain with considerable post-treatment residual symptoms.

1.3. Medication-enhanced psychotherapy.

Medication-enhanced psychotherapy (MEP) has re-emerged as one of the most exciting areas in the treatment of PTSD. Current work in this area has been driven by the translation of preclinical research on the biology of fear learning and memory into human clinical trials (i.e., d-cycloserine, propranolol, MDMA, yohimbine, methylene blue, rapamycin, hydrocortisone). Cumulative research³ indicates that PE may be improved by administering medications that target one or more therapeutic mechanisms such as 1) augmenting the biological processes of extinction memory formation (“*cognitive enhancer*”); 2) disrupting the reconsolidation of feared memories (“*memory disrupter*”); or 3) enhancing the trust in the therapist by reducing the anxiety of re-engaging with traumatic material (“*therapy facilitator*”). Non-conventional drugs such as $\pm$ 3,4- methylenedioxymethamphetamine (MDMA)¹² and d-cycloserine (DCS)¹³ have been already tested using a MEP strategy to catalyze the efficacy of the most widely recognized methods of psychotherapy in PTSD. The treatment paradigm for DCS and MDMA uses the acutely timed medication to integrate therapy sessions. The medication then, assists therapy interventions during its bioavailability (e.g., half-life of 4-6 hours for DCS). Ketamine, an FDA-approved anesthetic with potent non-competitive glutamatergic NMDA antagonistic properties, has shown to enhance neuroplasticity in mood disorders⁴ and PTSD⁵ in pre-clinical studies beyond its blood concentration. Recently, a MEP study showed that a single IV ketamine enhanced subsequent brief course of CBT (i.e., 10 one-hour exposure sessions) by achieving 63% response rate among patients with OCD. CBT sessions followed ketamine treatment within the putative time interval when a single ketamine facilitates extinction learning (within 14 days)¹⁴.

1.4. Glutamate Dysregulation in PTSD.

mPFC in the enhancement of fear extinction by ketamine, optogenetic stimulation of the IL-mPFC produces behavioral and synaptic responses similar to the antidepressant actions of systemic ketamine³⁰. Other mouse studies³¹ of PTSD have revealed that the long-term treatment with ketamine in combination with extinction training may accelerate extinction of fear memories by normalization of DNA methylation of BDNF gene leading to an increase in the levels of BDNF in the mPFC and hippocampus.

1.6.2. Ketamine as a Therapy Facilitator of PE: Co-occurrence of PTSD and major depressive disorder (MDD) or anxiety disorders is closely to 50% across diverse epidemiological samples^{32,33,34}. Higher dropout rates are more likely in comorbid PTSD suggesting that strategies specifically target depression and/or anxiety may increase retention by enhancing delivery of the trauma-focused interventions. Several studies reported an exacerbation of PTSD, anxiety, and depression symptoms (10.5%-20%, 21.1%, and 9.2%-22%, respectively) after the introduction of imaginal exposure (IE) in PE session^{35,36}. Given ketamine's robust and rapid antidepressant and anxiolytic effects, another MEP approach would be to facilitate the initial stages of engagement in the therapeutic process by diminishing the severity of comorbid depression as well as the initial fear, anxiety, and avoidance associated to emotionally intense trauma-based therapies. Rapid improvements in depression symptom (Beck Depression Inventory score >7 in one between session interval) was associated with lower rates of dropout and lower post-treatment severity score during PTSD treatment (PE or sertraline)³⁷. In addition, patients experiencing sudden gains early could have significant impact on a patient's course of treatment, strengthening their confidence in therapeutic approach, improving therapeutic alliance, and increasing motivation to be adherent with treatment.

2. PRELIMINARY STUDIES

2.1. Research Team is Well Qualified to Undertake this Clinical Trial.

The proposed clinical trial builds directly on the previous experience from Minneapolis VA Medical Center (MVAMC). **Dr. Shiroma**, PI for this proposal, is a VA physician investigator with experience in conducting clinical studies using IV ketamine in depression and PTSD^{7,39,40,41,42}. Dr. Shiroma recently completed a 4-year Merit Review Award (NCT02360280) aimed to investigate serial ketamine in refractory depression. The estimated sample size for this single site study was surpassed denoting a strong recruiting pipeline for clinical studies. Dr. Shiroma was also the P.I. (Co-P.I. by Dr. Albott) in the most recent study of serial ketamine and PTSD (*see Appendix 8*). **Dr. Polusny**, Co-I, is a nationally certified trainer for PE and senior PTSD investigator in the Center for Chronic Disease Outcomes Research (CCDOR) at MVAMC. Dr. Polusny will oversee PE training and adherence of nationally-certified therapists. She will also be the primary supervisor for individual and group consultation of the study PE therapists. **Dr. Disner**, Co-I, serves as a staff psychologist in the Mental Health Service Line at the MVAMC where he conducts assessment and therapy for veterans, with a focus on those experiencing post-deployment and/or trauma-related symptomatology. He is also the PI for the Predicting Rehabilitation Outcomes Using DNA (PROUD) and Genetic Analysis of Mechanisms underlying Brain Injury and Traumatic Stress (GAMBIT) studies, as well as the leader of the Psychiatric Genomics Consortium-PTSD TBI working group. He will supervise adherence and calibration of CAPS-5 administration. **Dr. Kehle-Forbes**, is a Core Investigator in the CCDOR at MVAMC. Her recent VA HSR&D Merit Award explored providers' and Veterans' perceived causes of early termination from trauma-focused psychotherapies. She is also the co-investigator on a randomized clinical trial examining the impact of family involvement in treatment on patient engagement in PE therapy. She will provide fidelity rating and checks for the PE therapists to ensure adherence to PE treatment standard and inter-rater reliability for measurements. **Dr. Thuras**, Co-I, is a biostatistician with more than 20 years of experience at the MVAMC. Dr. Thuras has provided expertise in study design, power, data management, and analysis using multilevel and latent variable models examining change over time in multiple clinical trials .

2.2. Pilot study suggest need for adjunctive intervention to PE.

Drs. Kehle-Forbes and Polusny, Co-Is in this proposal, conducted semi-structured qualitative interviews (VA HSR&D Merit Award-IIR14-030) with 30 Veterans who dropped out of PE prior to session 6 and 30 Veterans who completed the treatment. Ongoing analysis demonstrates that **dropouts reported lack of treatment gain prior to discontinuation and worsening anxiety and depression**. As one male OEF/OIF Veteran who discontinued PE after three sessions stated, "I wasn't okay. I was frustrated, I was angry, I was sad, I was depressed every day, I didn't want to be there anymore, I didn't want to go, and I stopped wanting to be anywhere. And so, my original goal was just go to PE , I thought it'll help you, but it made

everything worse.” While symptom worsening was not unique to treatment dropouts as exacerbation following IE was also commonly reported by completers, dropouts were characterized by **fear of the consequences of increased symptomology (e.g., suicidal ideation, aggression towards other) and low self-efficacy for coping with symptom exacerbation**. As another male OEF/OIF Veteran who dropped out after the third session of PE stated, “it’s too risky for me because I don’t want to freak my family out and hurt somebody.” These findings suggest that an adjunctive intervention that lowers both anticipating anxiety and negative emotional reactions following exposure would reduce dropout rates and improve outcomes among veterans initiating a course of PE.

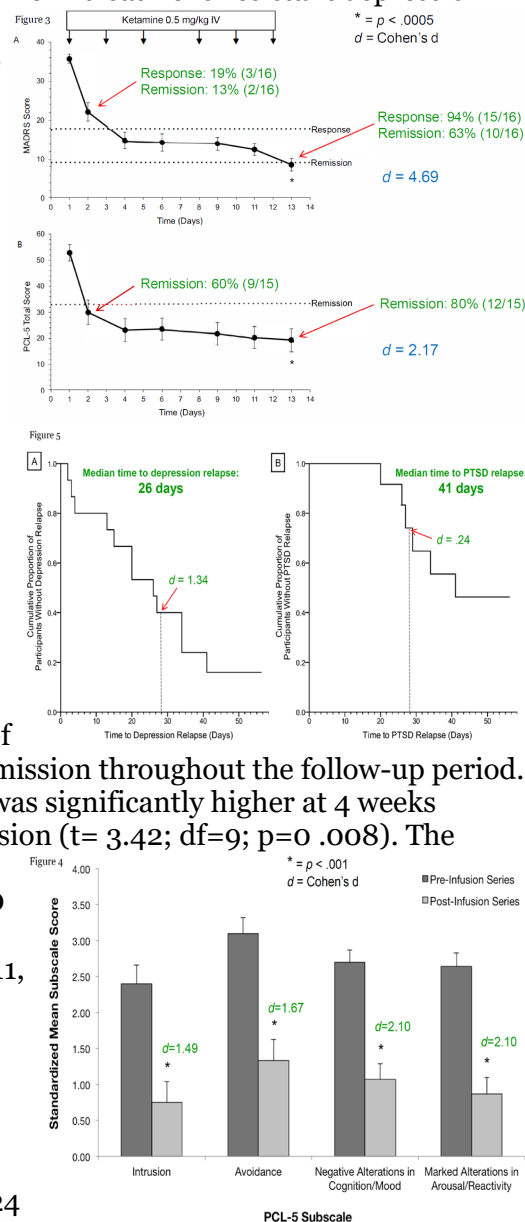
2.3. Research Experience on Ketamine and PTSD.

3.3.1. Preliminary data found rapid effect of ketamine in depressive and PTSD symptoms: Several studies have been published by the P.I. research group on the use of repeated ketamine in treatment-resistant depression (TRD)³⁹⁻⁴². Expanding previous investigations, a pilot study⁷ examined the safety and efficacy of repeated ketamine treatment among veterans with comorbid TRD and PTSD. Sixteen Veterans completed 6 ketamine infusions at 0.5 mg/kg for 40 minutes per treatment during a 12-day period. The mean within-subject change in self-reported PTSD symptoms, as assessed by PCL-5 total score, significantly decreased from baseline 52 (S.D.=12) to 19 (S.D.=17) at 24 hours after the sixth ketamine infusion (F6, 90= 54.49, $p < 0.0005$) (Cohen’s $d' = 2.17$) (Figure 3B). The remission rate for PTSD defined by PCL-5 total symptom score < 33 was 80.0 %. PTSD symptom severity assessed by clinician interview (CAPS-5) also demonstrated a significant reduction in total score from a PTSD baseline of 39.7 (S.D.=9.3) to 20.8 (S.D.=7.2) after treatment (Cohen’s $d' = 1.85$). Figure 4 showed PCL-5 sub-clusters which significantly decreased after completion of treatment. Regarding depression, Montgomery- Åsberg Depression Rating Scale (MADRS) total score decreased over the course of treatment (F2.62, 36.70= 30.17, $p < 0.0005$), and was associated with a large effect size ($d' = 4.69$) (Figure 3A). The remission rate for depression defined by MADRS total score ≤ 9 was 62%.

3.3.2. Pilot data suggest that response to ketamine is short-term: Of the 12 individuals in remission from PTSD after the infusion series, the median time to relapse was 41 days (Figure 5B). Six individuals (50% of the individuals who remitted; 40% of the total sample) remained in remission throughout the follow-up period. Paired samples t-tests showed that the mean PTSD symptom severity was significantly higher at 4 weeks follow-up ($n=10$), compared to symptoms 24-hours after the sixth infusion ($t= 3.42$; $df=9$; $p=0.008$). The median time to depression relapse was 26 days with the 25th and 75th percentiles at 34 and 13 days, respectively (Figure 5A). The mean MDD symptom severity was also significantly higher at follow-up ($n=12$), compared to symptoms 24-hours after the sixth infusion ($t= 5.08$; $df=11$, $p < 0.0005$).

2.4. Pilot Study on Ketamine-PE Intervention among Veterans with PTSD

2.4.1. Pilot data suggests feasibility of ketamine-enhanced PE intervention: Out of 12 consented Veterans with PTSD in a 4-month period, we present preliminary data from 07 Veterans who started combined intervention (i.e., single ketamine infusion followed within 24 hrs. by PE session for the first 3 weeks) by the time of submission of this application. We had two dropouts who were consented but failed inclusion criteria of CAPS-5 score ≥ 23 (i.e., moderate to severe PTSD). Table 1 showed demographics and clinical characteristics. Below graphics include CAPS-5 (Figure 6), PCL-5 (Figure 7), Subjective Units Of Distress (SUDS) (Figure 8), and MADRS (Figure 9)

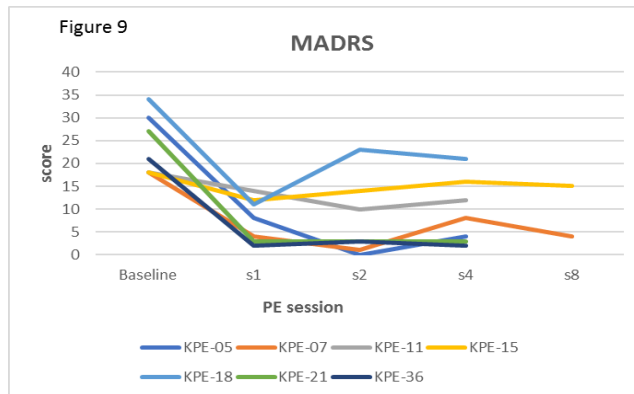
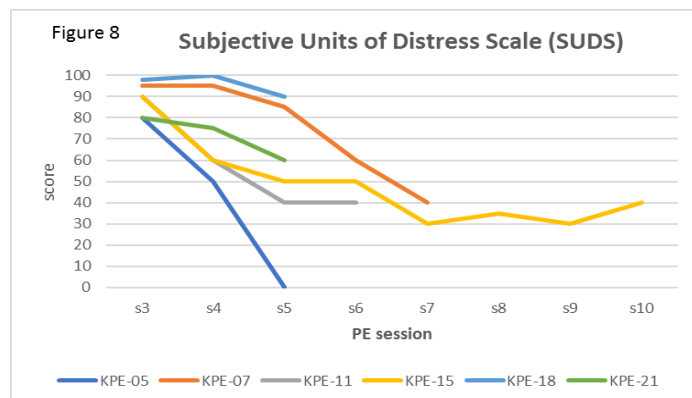
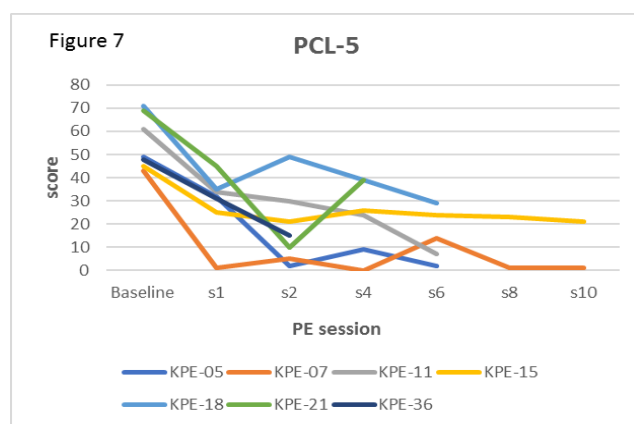
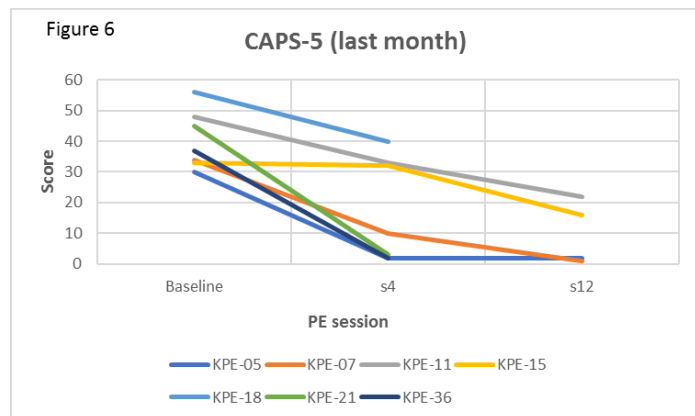


scores over time. SUDS, a proxy for extinction, were recorded starting after IE (session 3). Overall, scores in all rating scales demonstrated substantial improvement during treatment. For o3 subjects (KPE-05, KPE-07, and KPE-11), PE therapy ended after 7 sessions instead of 10 after therapists and subjects agreed that clinical goals were already achieved and no further sessions were needed.

Table 1. Demographics and Clinical Characteristics

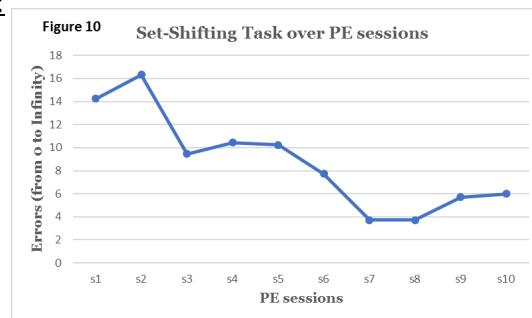
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
	KPE07	KPE15	KPE11	KPE05	KPE21	KPE18	KPE36	KPE02§	KPE14§	KPE12§	KPE08*	KPE34*
Age	38	34	42	54	38	72	24	39	52	38	32	48
Gender	Male	Male	Female	Male	Male	Male	Female	Male	Male	Male	Male	Male
Trauma	Sexual	Combat	Sexual	Combat	Combat	Combat	Sexual	Sexual	Combat	Combat	Combat	Combat
Duration of PTSD, years	23	14	6	15	15	52	2	11	9	14	7	24
Psychiatric hospitalization	No	No	No	No	No	Yes	No	Yes	Yes	Yes	No	No
Past SUD/AUD¶	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No
Suicidal attempts	No	Yes	No	No	No	Yes	No	Yes	No	Yes	No	No
Psychiatric medications	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MDD	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes
Anxiety disorder	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
CAPS-5 score	34	33	48	30	45	46	37	64	33	<23	38	<23
PCL-5 score	43	44	60	49	69	71	48	74	64	51	37	48
MADRS score	18	18	18	30	27	34	21	39	15	26	N/A	N/A
CGI score	5	4	5	4	5	5	5	6	5	6	4	4

*KPE08 and KPE34 were excluded due to below CAPS-5 score for moderate-severe PTSD symptoms. Remaining baseline assessment not completed. § KPE02, KPE12 and KPE14 are enrolled but have not received treatment yet. KPE¶SUD/AUD: Substance Use Disorder/Alcohol Use Disorder



2.4.2. Pilot data suggests cognitive improvement during treatment:

CogState, a computerized software with utility for within-subjects experimental designs, for the parametric properties of their outcome measures, and their use in psychopharmacology trials^{43,44} was used to capture changes in cognitive performance. Our group has previously used CogState in several ketamine studies^{7,40}. Here, we present the average set-shifting (SETS) task performance (Figure 10) on 07 Veterans for the pilot study. SETS identifies whether a card is the target stimulus dimension (a color or a number) with total number of errors across five rounds (lower score=better performance). SETS, an executive function, is a measure of cognitive flexibility which is deficient in PTSD patients (i.e., an inability to modify previously learned thoughts and behaviors based on changes in the environment) and related to glutamate hypoactivity in the prefrontal cortex⁴⁵. These preliminary findings is in line with our *Exploratory Aims 1*, where ketamine may work as cognitive enhancer of PE. We intent to measure neuropsychological changes during ketamine-PE treatment by administering CogState tests at several time points.



2.4.3. Pilot suggests acceptability and tolerability of Ketamine-PE: We interviewed participants on the experience of receiving combined intervention. Veterans identified the role of *ketamine as a facilitator* to the emotionally-charged sessions in PE as one female participant stated “I was struggling with the custody of my daughter against my ex-husband and was unemployed before starting PE. I would have never been able to commit into therapy with that level of stress so it ketamine definitely helped”; another male Veteran stated “Ketamine removed the edge... I felt calmer...helped with depression too and prepared me for what was coming”. Two other male Veterans mentioned the potential *pro-cognitive effect of ketamine* specially during IE: “... ketamine definitely helped especially with the imaginal exposure...I don’t think I would have been able to deal with the step-by-step trauma without ketamine first... helped me focusing more in the therapy without much of the negative thoughts”; “I was able to calm down during the imaging part and able and focus to do the PE experience. That was huge”. We also found that the combined intervention was tolerable even when there was no respond to ketamine. As a male Veteran stated: “ketamine did help a little if any with my PTSD or depression...but it was tolerable...I did not feel ketamine and PE was a huge commitment”. This patient completed 10 PE sessions. A special consideration for retention of subject in this study is the risk that early improvement during medication phase may discourage subjects to continue with PE. We piloted an intervention to foster retention, which consists in a simple but clear explanation to participants about the rationale of the study. We highlighted that any rapid relief of PTSD symptoms during infusions is unlikely to last and so completing PE may provide the best chance for long-term improvement. This rationale was reminded throughout the study and seemed well received by subjects.

Summary of preliminary studies: Our research experienced showed that ketamine treatment rapidly decrease PTSD symptoms but for a short-term even with repeated doses. Safe use of ketamine in the long-term is not yet an option. PE therapy has the most robust evidence to sustain PTSD response. Considering potential synergies on the underlying therapeutic mechanism of ketamine (i.e., promoting synaptogenesis in vmPFC) and PE (i.e., formation of extinction memories), an empirical study is reasonable. Our pilot study demonstrated the feasibility and acceptability to conduct the study among Veterans with PTSD.

3. VA SIGNIFICANCE AND INNOVATION

While PE is recommended as the “gold standard” therapy for PTSD, its efficacy in the military and veteran population could be improved as most patients remained with PTSD diagnosis at the end of treatment. If successful, the study would provide significant novel evidence to clinicians caring veterans with PTSD for the use of ketamine as a cognitive enhancer and/or therapy facilitator of PE. It is foreseen that further studies could distinguish and refine the essential components of this approach, enhance the methodology, elucidate the mechanisms involved, and identify sub-PTSD populations (i.e. PTSD clusters and comorbidity) that most likely benefit from this intervention. The project would also serve as an initial platform to expand further studies on the efficacy and safety of MEP model of treatment.

4. RESEARCH DESIGN AND METHODS

4.1. Design Overview.

This is a single site, interventional study designed to determine the efficacy, safety, and tolerability of

Use of active placebo control	Midazolam, a short-acting benzodiazepine and anesthetic agent, has shown to yield smaller antidepressant effect of ketamine than those studies which used saline ⁵¹ . This finding suggests that active placebo control is needed to <u>avoid overestimating ketamine's efficacy</u> . While there is no active placebo control drug that perfectly mimic the dissociative and psychomimetic side effects of ketamine, midazolam has pharmacokinetic characteristics similar to those of ketamine, fast onset of action, short elimination half-life (2.5 hrs.) and has been used in several ketamine studies ^{48,52,53} . For this study, midazolam's infusions would be completed at least 24 hrs. prior to PE session. Based on midazolam's short bioavailability, <u>it would not interfere with exposure training in PE</u> .
Inclusion of comorbid psychiatric conditions	Traumatic experiences have a variety of psychiatric sequelae, often including multiple comorbid psychiatric diagnoses. Depressive disorders have been found to co-occur in most individuals who develop PTSD ³³ and may act as an indicator of a more severe response to trauma exposure. The high rates of comorbidity between PTSD and depression have thus led to suggest that their co-occurrence may be better conceptualized as a general traumatic stress construct, rather than discrete co-occurring disorders ^{54,55} .
Stable treatment prior to randomization	Washout from psychiatric medications would: 1) limit recruitment and result in a sample that is not characteristic of many Veterans seeking treatment; 2) raise ethical concerns as severe conditions (e.g., agitation) require rapid stabilization usually through pharmacological interventions. Keeping stable doses of prior psychotropic regimen will decrease confounding effects.
Ideal body weight to calculate ketamine doses	Ketamine is initially distributed to highly perfused tissues, including the brain, to achieve levels four to five times that in plasma. Ketamine has high lipid solubility and low plasma protein binding, which facilitates rapid transfer across the blood-brain barrier. Since plasma volume is more consistently and directly proportional to ideal body weight but not actual body weight in obese patients, using ideal body weight would help insure that all the study subjects receive the same "brain dose".

4.2. Study Site-Minneapolis VA Medical Center:

4.2.1. Clinical: The clinical facilities for the proposed study at the MVAMC are: 1) The Post-Traumatic Stress Recovery (PTSR) Service Line (Team L; Acting Director: Matthew Kaler, Ph.D.) within the outpatient psychiatry department; and 2) The Mental Health Outpatient (1P Nurse Manager: Deborah Brisch-Cramer, RN) and the Primary & Specialty Medicine Service Line, 3F, Stepdown Unit (3F Nurse Manager: Trudy Harpole, RN). Secure file space for the primary (hard copy) records is available at the VA in Dr. Shiroma's locked office within the outpatient service. There are several private offices in the mental health department available for conducting private clinical assessments and interviews with study participants.

4.2.2. Office and Research Space: The PI has an office within the outpatient service department (Room 1P-121) near by the offices of Drs. Kaler (Acting Director) and Thuras (Biostatistician). Dr. Disner and Polusny have their offices at Building 68 where the Clinical Investigators Team is located. Dr. Kehle-Forbes' office is located at the CCDOR. Clinical room 1P-119 at the outpatient mental health of the main MVAMC hospital building will be used for infusion of study medications. 1P-119 is fully equipped with a mobile desktop PC, pulse oximeter, blood pressure and heart rate monitoring, and infusion drip and pump. A crash cart is located near by the entrance. The outpatient mental health service is staffed by RNs, LPNs, and ancillary personnel. A second infusion in case 1P-119 cannot accommodate more subjects will be provided at 3F backup. Equipment and clinical personnel are similar to 1P-119. Several conference rooms are available at both locations to conduct private clinical assessments and interviews with study participants. To facilitate logistics for study participants, lodging is available during infusion phase at Building 10 located 10-minutes walking from the clinical units.

4.3. Subject Recruitment and Selection.

Referrals will occur from VA clinicians and clinics, and responses from posted fliers and study pamphlets including study ads on approved MVAHCS social media. We will also use direct mailings of opt-out letters to potential participants. For these, we will identify them through approved VA methods including the corporate data warehouse (CDW). To reduce subject burden, a waiver of HIPAA authorization and written informed consent will be obtained for a brief initial phone evaluation or a brief evaluation via Qualtrics and preliminary medical record review prior to scheduling further assessment visits (*see further details in Appendix 5 – Recruitment and Retention*).

4.3.1. Eligibility Criteria: The following eligibility criteria will be used to identify a broad array of participants with PTSD considered suitable for the study.

Table 3: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Male or female Veterans aged 18-75 years old. • Diagnosis of PTSD (Clinician-Administered PTSD Scale for DSM-5 -CAPS-5 score ≥ 23 (i.e., moderate to severe PTSD) at screening. • Voluntarily eligible to participate in PE. • Severity of PTSD symptoms defined by PCL-5 > 33. • Stable doses (no dosing adjustments/changes) for ≥ 4 weeks; ≥ 6 weeks for fluoxetine) of trazodone, FDA-approved antidepressants, atypical neuroleptics, trazodone, prazosin, and clonidine. During study if changes in doses of these medications occur, it is up to the PI to determine continuation. • Willingness/able to sign informed consent. • Able to read and write English.	• Previous or current participation in PE therapy • Mental retardation, pervasive developmental disorder, and/or moderate/severe cognitive impairment (Mini-mental State Examination score ≤ 27). • Any unstable physical (e.g., decompensated heart disease) or non-psychiatric CNS condition. • Lifetime history of psychosis-related disorder, history of antidepressant-induced mania, current mania, hypomania or mixed episode, or any condition other than PTSD judged to be the primary presenting psychiatric diagnosis confirmed by the Mini-International Neuropsychiatric Interview (MINI 7.0 for DSM-V). • Moderate to severe traumatic brain injury (mental status change or loss of consciousness > 30 min; Glasgow Coma Scale < 13; post-traumatic amnesia > 24 hours; visible lesion on CT/MRI brain scan) and no more than minimal symptoms in the last year. • Severe substance and/or alcohol use disorder (DSM-5) within 6 months of recruitment plus breathalyzer > 0 prior to each infusion; presence of illicit drugs by positive urine toxicology except for cannabis • Currently taking memantine, long-acting benzodiazepine, and monoamine oxidase inhibitors (MAOIs), or unable to be free of short-acting sedatives 8hrs prior to infusion. • For women: current pregnancy (confirmed by lab test), initiation of female hormonal treatments within 3 months of screening, or inability/unwillingness to use a medically accepted contraceptive method during the study. Women who are surgically sterile, have been post-menopausal for at least 1 year or whose partner had a vasectomy at least 3 months ago will not be excluded • At screening, resting blood pressure (sitting or supine) lower than 90/60 or higher than 150/90, or resting heart rate lower than 45/min or higher than 100/min. • -Serious and current risk of suicidal/homicidal ideation and/or behavior with intent and/or plan as assessed by study investigator.

4.3.2. Informed Consent: Voluntary informed consent will be obtained in accordance with local IRB approvals. Subjects will have the option to consent electronically through DocuSign, or in person. At the consent session, all assessments, and information on treatment will be explained. Subject comprehension of information will be assessed by the Modified Dysken Screening Tool, an instrument commonly used at MVAMC to determine the decision-making capacity of a potential research subject to provide informed consent. Willingness to participate in assessments and random assignment to 1 of 2 treatments (ketamine+PE vs midazolam+PE) will be confirmed and information about confidentiality and study payments will be provided.

4.4. Assessment Procedures.

Assessments will take place in two contexts: 1) at baseline, throughout treatment, and at follow-up, and 2) during each infusion. These assessments are summarized in Table 4 and Table 5, respectively. Clinical interviews will be conducted by trained independent evaluators who are blind to participant treatment condition. Subject compensation will also be provided to increase participant retention and reduce missed assessments (*see further details below*). To facilitate adherence, self-rated scales/questionnaires (which will NOT contain PHI/IIHI) will be administered through the following options chosen by the participant: 1) administration of assessments through phone or video contact with research staff; 2) mail and return with pre-paid envelop, or in-person when the participant comes to MVA; 3) encrypted e-mail with pdf/word format (Azure RMS is available for emailing outside VA); 4) encrypted Azure email containing direct link to electronic REDCap assessments. 4.4.1. 5) encrypted Azure email containing link to remote cognitive testing (CNS Vital Signs) 6) Link to Qualtrics survey sent by study staff via Qualtrics

Eligibility and Baseline Assessment: The Eligibility and Baseline Assessment (EBA) will be accomplished during 1-2 visits within a 14-day period prior to starting treatment. It will take a total of 4 hours. Life Events Checklist for DSM-5 (LEC-5) will identify life events commonly associated with PTSD symptoms. The DDRI-2 Combat Experiences and Postbattle

Experiences self-assessments will help narrow multiple traumas down to the one creating most distress for veteran to ensure consistency throughout research assessments and PE therapy. The CAPS-5 Selection of Index Event will specify the individual event that will be focused on during therapy and research sessions. Provisional diagnosis of PTSD would be obtained by PCL-5 score >33. The CAPS-5 score >23 will establish moderate to severe PTSD diagnosis. The Mini International Neuropsychiatric Interview (M.I.N.I.) 7.0⁵⁶ will confirm the absence of exclusionary diagnoses. Lack of moderate/severe cognitive impairment will be ascertained by MMSE score ≥28. The Defense and Veterans Brain Injury Center (DVBIC) 3-Item Screening Tool for brief TBI screen will evaluate for head injury and related symptomatology. The Alcohol Use Disorders Identification Test (AUDIT) score <8 will exclude harmful drinking behavior plus breathalyzer to assure alcohol level = 0%. Lack of unstable medical illnesses will be confirmed by review of medical records by study M.D. and/or RN, physical examination, basic metabolic laboratory tests, ECG, and if needed, consultation with study anesthesiologist or primary care. Further clinical studies could be ordered if deemed necessary. A serum pregnancy, if applicable, and drug screen will ensure no one is pregnant and to document possible illicit substance use. Secondary outcomes also assessed at EBA will include cognitive function (CNS Vital Signs), recent PTSD symptoms by The Impact of Event Scale-Revised (IES-R), severity of depressive symptoms (MADRS), level of anxiety (Beck Anxiety Inventory-BAI), suicide risk (Columbia-Suicide Severity Rating Scale-C-SSRS screener version), pain intensity (Numeric Rating Scale-NSR for pain), clinical impression of illness severity (Clinical Global Impression-CGI) quality of life (World Health Organization Quality of Life-Brief-WHOQOL-BREF), and expectation of treatment (CEQ).

4.4.2. Treatment Assessment: The research staff will ascertain PTSD symptoms severity by administering the CAPS-5 at weeks 4, and 10. Several secondary outcomes at EBA (IES-R, PCL-5, MADRS, BAI, C-SSRS, NSR, MEQ30) plus general side effects (Patient Rated Inventory of Side Effects- PRISE/ Frequency, Intensity, and Burden of Side Effects Rating-FIBSER) will be obtained 24 hrs. post-ketamine and prior to PE session at week 1, 2, and 3 (medication-PE phase). During the medication-free phase, rating scales again will be administered at week 4, 6, 8, and 10. Cognitive performance by CNS Vital Signs will be done at weeks 1, 2, 3, 4, and 10. Therapeutic alliance measure by the working alliance inventory-short revised version for clients (WAI-SR) will be administered before session 3 and 6, and after the final session. Fear activation and extinction during PE sessions would be measured by the Subjective Units of Distress Scale (SUDS). PE therapists will collect (PHQ-9) every-other session as part of routine clinical care. To reduce subject burden, and decrease missing data, several repeated measures will be conducted via telephone interviews which are comparable to interviews conducted by face-to-face administration. Urine toxicology will be repeated before each infusion for a total of 4 times during the treatment phase.

4.4.3. Follow-up Assessment: Following completion of PE, participants will attend a 3-month Post-Treatment Assessment at monthly intervals (total of 03 follow-up visits). Each visit will take about 2 hours. Follow-up assessments will involve secondary outcomes (except for CNS Vital Signs). The CAPS-5 will be administered at 1 and 3-month follow-up.

Table 5: General Assessment Schedule

Construct	Measure	Eligibility and Baseline Assessment	Treatment Assessments	Follow-Up Assessments
		2 weeks	Week 1 to 10	3 months
Primary Outcome Measure				
PTSD symptoms	CAPS-5	X	X	X
Screening Assessments				
Decision-making capacity	Dysken Screening Tool	X		
Diagnostic interview for comorbid conditions	M.I.N.I.7.0	X		
Index Trauma	LEC-5	X		
	DDRI-2 Combat Experiences	X		
	DDRI-2 Postbattle Experiences	X		
	CAPS-5 Selection of Index Event	X		
AUDIT	Alcohol consumption			
DVBIC	TBI/Head trauma			

Moderate/severe cognitive impairment	MMSE	X		
Infusion Safety Measures				
Physical Exam/ECG/Labs/Breathalyzer		X	X	
Urine toxicology/Pregnancy test		X	X	
Recovery from infusion	mAldrete		X	
Side Effects (dissociative, psychotogenic, and manic symptoms)	CADSS, BPRS+, YMRS, MEQ30		X	
Secondary Outcome Measures				
Cognitive performance	CNS Vital Signs	X	X	
Subjective units of distress (a proxy for extinction)	SUDS		X	
General Stress	PHQ-9		X	
PTSD severity, last month	PCL-5	X	X	X
PTSD severity, last week	IES-R	X	X	X
Depressive Symptoms	MADRS	X	X	X
Suicide Risk	C-SSRS	X	X	X
Anxiety Symptoms	BAI	X	X	X
Pain Intensity	NRS	X	X	X
Quality of Life	WHOQOL-BREF	X	X	X
Therapeutic Alliance	WAI-SR		X	
General Adverse Events	PRISE/FIBSER		X	X
Global Rating of Illness Severity and Improvement	CGI	X	X	X
Credibility/Expectation of Outcome Treatment	CEQ	X		

5.4.4. Independent Evaluation Integrity: The PI will oversee assessment core to ensure that independent evaluators will 1) undergo standardized training in all assessment instruments, 2) demonstrate reliability of assessment at the beginning of the protocol; and 3) receive reliability checks on their evaluations throughout the protocol. Initial competency will be established by on-site didactic training for all clinical assessments and data collection procedures followed by the establishment of inter-rater reliability. Inter-rater reliability will be accomplished using a train-to-criterion protocol with recorded patient interviews (for symptom scales all total scores will be required to be within 2 points of the standardized score and all individual item scores were required to be within 1 point of the standardized score; for diagnostic assessments 100% agreement will be required for the primary diagnosis). To maintain competency and reduce “drift,” in-person didactic re-training sessions will be conducted annually, and inter-rater reliability established at 6-month intervals to ensure that they meet at least 80% reliability of their measurement. Remediation and additional training will be provided as needed until competency was achieved.

4.5. Experimental Treatment Conditions.

4.5.1. Randomization Procedures: Our planned enrollment includes 40 veterans in each treatment condition, for a total of 80 Veterans completing primary outcome (20% attrition rate) (see Sample Size Determination below). Participants will be randomly assigned to weekly 1) single ketamine infusions+PE vs 2) single midazolam infusions+PE for the first 3 weeks of treatment. Randomization will be conducted using SAS PROC PLAN by the research pharmacist. Research pharmacist is not listed as co-investigator for the study. Randomization will use permuted blocks of 4. Research pharmacist will keep the original random allocation sequences in an inaccessible third place and record what these codes mean to avoid further confusion.

4.5.2. Study Medication Phase: Over the course of the study, infusions from both treatment conditions (ketamine and midazolam) will be administered individually in a private room. The procedures for both treatment conditions are similar and described as follows:

Procedures during infusion: Table 6 describes the schedule of assessments on the day of infusion. Veterans will arrive in the morning after an overnight fast of at least 8 hours. Firstly, participants will be asked “After the last infusion, did you: a. Have to go to the emergency room? If so, what was the reason?; b. have to be

hospitalized even for a day? If so, what was the reason?; c. Get sick or have a medical event that we should know about?; and d. Change or discontinue any of your regular medications, or add a new one? Any affirmative response will be communicated to PI who will determine whether study procedures should continue as planned, postponed or cancelled. Lack of breath alcohol level (breathalyzer=0) and will be evaluated prior to each infusion and randomly up to 4 times throughout the trial. A urine pregnancy (urine dipstick test) will also done prior to infusions. An indwelling catheter will be placed in the non- dominant arm for medication administration. Digital pulse oximetry, respiratory rate, pulse rate, and blood pressure will be recorded every 10 min for 1 hour beginning 10 min before infusion. Resting-state EEG will be collected while participants sit quietly with their eyes open. EEG will be collected using a 64 channel Biosemi ActiveTwo system (<https://www.biosemi.com/products.htm>). The Biosemi system uses active electrodes to reduce input impedance at the scalp, allowing low-noise measurements free of interference without any skin preparation. Biosemi ActiView software will be used to acquire EEG data. We will measure EEG before (t-15), during (t+25 min) and after (t+145 min) each of the three weekly infusions. Electroencephalogram data will be collected in a laptop computer. An electroencephalogram (EEG) measures the electrical activity in the brain (brain waves) using electrodes (small metal discs or sensors) placed on the scalp with gel. Resting-state EEG is a measure of ongoing brain activity. The oscillatory nature of resting-state EEG, as well as the functional connectivity between brain areas, is related to various cognitive functions (Rogala et al., 2020). Ketamine induced widespread changes in low and high resting EEG frequency bands, which were predictive of decreases in depressive symptoms and suicidal ideation. We propose to add EEG to inform potential early and sustained response to ketamine during prolonged exposure therapy in PTSD. Based on the dose, rate of infusion, and endpoint/purpose of the study, the infusions do not fall into the category of “moderate sedation” and therefore no cardiac monitoring will be required. Subjects will then receive IV infusion of either 0.5 mg/Kg of ketamine hydrochloride solution or midazolam 0.045 mg/kg over 40 minutes. The dose of ketamine will be calculated by ideal body weight based on sex, age, height, and body frame in the Metropolitan Life Insurance tables. Psychotogenic effects will be measured with the four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+) consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization; dissociative effects and manic symptoms will be measured with the Clinician-Administered Dissociative States Scale (CADSS) and Young Mania Rating Scale (YMRS), respectively. Additionally, the patients will be regularly questioned during the infusions about any dysphoric emotions or altered sensory experiences. There will be no psychological intervention or directive to the subjects during the immediate effect of study medications. Potential side effects related to ketamine (CADSS, YMRS, and BPRS+) will be measured within 60 minutes prior to and immediately upon completion of each infusion and then hourly during the post-infusion monitoring period (up to 2 hrs.). The Revised Mystical Experience Questionnaire (MEQ30), a self-rating scale that assess the effects of acute psychedelic experience will be completed before they leave the unit.

Guidelines established for clinically significant changes in vital signs and mental status during the ketamine infusions will be as follows: systolic blood pressure (BP) >161 or <89, diastolic BP >110; heart rate <40 or >130 beats/min; respiratory rate <10 or >30 per minute; pulse oximetry <90%; severe hallucinations, confusion, delusions, irrational behavior, or agitation. Dr. Tolly, study anesthesiologist, will assist during infusions if necessary. Medications such as labetalol or hydralazine (hypertensive episode), ondansetron (nausea, vomiting), and flumazenil (oversedation) as well as a crash cart will be available to manage unanticipated side effects. The infusion will be discontinued if adverse events do not respond to interventions. If baseline vital signs are not back to baseline readings and/or side effects persist beyond the 2-hour post-infusion period, we will continue monitoring on a 30 minutes interval or as clinically indicated, consult with Dr. Tolly (study anesthesiologist), and provide treatment accordingly including possibility of hospitalization. Before leaving the infusion unit, subjects must demonstrate that all clinically significant side effects are resolved by obtaining a score ≥ 9 in the modified Aldrete (mAldrete) scoring system. Written instructions about rare but serious side effects and measures to improve recovery at home will be provided at discharge.

Table 6: Assessment Schedule on Infusion Day

	Measure	t ₀ -60 min	Baseline (t ₀)	t ₀ +40 min	t ₀ +100 min	t ₀ +160 min	t ₀ +24 hrs.
Outcome Measures							
PTSD symptoms	PCL-5						X
Depression	MADRS						X

Anxiety	BAI						X
Pain intensity	NRS						X
Cognition	CNS Vital Signs						X
Suicide risk	C-SSRS						X
Psychedelic Effects	MEQ30					X	
Hemodynamic Measures							
BP, pulse, RR, SatO ₂		X	X	X	X	X	
Safety Measures							
Pregnancy	Urine dipstick	X					
Alcohol level	Breathalyzer	X					
Side Effects	PRISE/FIBSER						X
Dissociation	CADSS	X	X	X	X	X	
Psychomimetic	BPRS+	X	X	X	X	X	
Mania/hypomania	YMRS	X	X	X	X	X	
Recovery	mAldrete					X	

4.5.3. PE therapy: PE is an evidence-based psychotherapy for PTSD that is based on the Emotional Processing Theory of PTSD; the four components of PE are: 1) exposure to safe situations, objects, or people that cause distress and are avoided because they are trauma reminders (in vivo exposure), 2) revisiting and processing of the trauma memory (imaginal exposure), 3) psychoeducation about trauma-related symptoms, and 4) breathing retraining⁵⁷. Session 1 includes the presentation of treatment rationale and program overview, information gathering, and breathing retraining. Session 2 includes education about common reactions to trauma, rationale for in vivo exposure, and construction of an in vivo exposure hierarchy. The hierarchy includes safe or low-risk activities and situations that were avoided because of their association with the trauma. Throughout the treatment, participants will be assigned homework to confront items on the hierarchy in a gradual fashion, working up to the most anxiety-arousing situations. During Session 3, the rationale for confronting the trauma memory in imagination is presented and initiation of imaginal exposure and processing is conducted. In this procedure, participants will be asked to close their eyes, visualize the trauma, and recount it aloud in the present tense for 45–60 min. The memory recounting will be repeated if necessary to allow total reliving of 45–60 min. The exposure will be audiotaped; participants will be instructed to listen daily to the tape. Sessions 4–10 will be conducted in a similar fashion: therapists review homework, conduct imaginal exposure to trauma memory for 30–45 min, discuss the imaginal exposure, and assigned in vivo and imaginal exposure homework. In the final session, participants summarize learning in treatment, discuss their progress, future plans, and relapse prevention. PE therapy will be delivered by video conference using a VA-approved platform (e.g., VA video connect, WebEx, Microsoft Teams), face-to-face, or by phone to provide flexibility to subjects.

PE Training, fidelity and supervision: Licensed doctoral-level and masters-level clinical psychologists will deliver the PE treatment. Besides two VA clinicians who have been approved to donate time to the study and treat participants as part of their regular caseload, a study psychologist with training in PE (Yelena Vorobyov) will dedicate most of her time to provide PE therapy Training and supervision of PE will include regular review of session video or audio to determine presence or absence of essential PE component, and monitor for protocol violations (Dr. Polusny). PE sessions will be video or audio recorded and 10% (~100 sessions) will be randomly selected and reviewed by Dr. Kehle-Forbes to ensure fidelity to the treatment manual (25 sessions will be selected from sessions 1–2, session 4, sessions 6–9, and sessions 10 and above).

4.6. Outcome Measures.

4.6.1. Primary Outcome Measure: The primary outcome is the difference in PTSD symptom severity from baseline to week 10 measured by the 30-item **CAPS-5** past month version (for current PTSD) total score.

4.6.2. Interview based Assessments: We will collect demographic data using the **PhenX Measures** for Mental Health. History of psychiatric risk factors will be obtained by initial interview. Comorbidity and potential exclusionary diagnosis will be determined by **M.I.N.I.** We will exclude individuals with psychosis related disorders, bipolar I and II disorder, and alcohol/illicit substance use disorder within 6 months of initial assessment as the use of ketamine will be contraindicated⁶¹. A widely used brief screening test, the **MMSE** will quantitatively assesses for exclusion of moderate-to-severe cognitive impairment cognitive.

4.6.3. Secondary Outcome Measures: **CNS Vital Signs** consists of several tests that will examine several

cognitive domains. Neurocognitive batteries are brief, previously used in pharmacological trials, and overall, it can be administered repeatedly using many alternate forms and still provide acceptable test–retest reliability without generating significant practice effects. Severity of depression would be measured by the **MADRS**, a semi-structured 10-item scale designed to be particularly sensitive to change over time in patients treated with antidepressant medication. The **PCL-5** is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. For the study, the PCL-5 will serve to screen potential candidates for PTSD and to monitor symptom changes during and after treatment. A PCL-5 cut-point score of 33 has been advised as a reasonable value until further psychometric work is available. The **IES-R** is a short, easily administered self-report questionnaire of 22 questions to measure the subjective response to a specific traumatic event within the specific time frame of the past seven days and can be used repeatedly to assess progress. The **BAI** will serve as the gold standard self-report measure of general anxiety symptoms to distinguish anxiety from comorbid conditions such as depressive symptoms. The **C-SSRS-screener last visit version** will be used to count prospective or treatment emergent suicidal behaviors. The C-SSRS has been used in many treatment trials to measure treatment emergent suicidal events during pharmacotherapy⁵⁸. **SUDS** is a self-rating measure of distress ranging from 0 (complete relaxation) to 100 (maximum distress) and will measure activation of fear structure, decrease in fear during exposure sessions (within-session extinction); and decrease in initial reactions to the feared stimuli across sessions (between-session extinction). SUDS ratings correspond well with other indices of fear expression, including physiological indicators. Based on the PE protocol, the therapist will initially generate with the patient anchor examples at 0, 25, 50, 75, and 100 (e.g., 25: riding a roller coaster). SUDS will then be recorded every 5 min during the imaginal exposure. Peak SUDS scores, highest reported distress during first (Session 3) and last imaginal exposure session (Session 10-12), and mean SUDS scores, average reported distress during first (Session 3) and last imaginal exposure (Session 10-12), will be calculated. **PHQ-9** is a 19 item self-rated measure of general stress ranging from 0 (not at all) to 3 (nearly every day). **NRS** is a one-dimensional measure of pain intensity in adults. The NRS is a segmented numeric version of the visual analog scale in which a whole number (0–10 integers) is selected to reflect the intensity of their pain anchored at 0 representing “no pain” and at 10 representing “worst pain imaginable”. The **CGI** is a brief assessment consisting of a 3-item observer-rated scale that measures illness severity, global improvement or change, and therapeutic response. The CGI has been widely used in clinical trials concerning psychotropic treatments. The **WHOQOL-BREF** is a 26-item brief assessment of quality of life in four factor-analytically confirmed dimensions: Physical, Psychological, Social, and Environmental. The **Credibility/Expectancy Questionnaire (CEQ)** is an 8-item scale of belief in the rationale and logic of a treatment (credibility) and belief in a likely positive outcome from a treatment (expectancy). The CEQ has been shown to predict treatment reactions in expected ways. The CEQ was modified slightly for this protocol to include questions about expectancy regarding changes in PTSD symptoms. The **WAI-SR** is a 12-item self-report measure designed to assess three dimensions of the working alliance: (a) the personal bond between therapist and client (Bond subscale), (b) the agreement between therapist and client on goals (Goals subscale), and (c) the agreement between therapist and client on how to achieve those goals (Tasks subscale). Respondents rated how frequently alliance-related statements applied to them on a Likert scale ranging from 1 (never) to 7 (always), yielding a total score that ranges from 12 to 84. **MEQ30** is a self-rated, 30-item, questionnaire that captures the frequency of acute psychedelic experience during infusion. Participants will complete MEQ30 before they leave the infusion unit.

4.6.4. Adverse Events Reporting and Monitoring Plan: The Adverse Events Reporting and Monitoring Plan will guide ongoing data and safety monitoring in the following ways:

1. Ongoing communications with all regulatory oversight entities to ensure all reporting requirements are met including: protocol deviations, continuing reviews, protocol amendments, summary reports of trial progress, adverse events (AEs), serious adverse events (SAEs), and unanticipated problems involving risk to subjects or others (UPIRSOs).
2. Personnel has been trained in the processes for the assessment of AEs in human subjects and AE monitoring. PI-review, and regulatory reporting will occur with ongoing communications with regulatory oversight agencies.

Further details in the Adverse Events: Reporting and Monitoring SOP.

Moderate Risk Data Safety and Monitoring Plan

1. Personnel responsible for the safety review and its frequency:

The PI is responsible for monitoring adverse event data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the

protocol is sought). During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment.

2. The risks associated with the current study are deemed moderate for the following reasons:

- We do not view the risks associated with study medications as minimal.
- Given the established safety and validity of the use of ketamine and midazolam, we do not view the proposed study as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study on site as follows:

3. Attribution of Adverse Events:

Adverse events (AEs) are defined as any clinically significant deterioration in the physical, psychological, mental, cognitive, or psychosocial health status of the subject, observed during the time-period of the study and representing a change from the baseline condition which existed prior to study. AEs will be monitored for each subject participating in the study. Separate and apart from the determination that an AE has occurred, the site investigators will determine their attribution to the study procedures / design according to the following categories:

- Definitely related to Study
- Probably related to Study
- Possibly related to Study
- Not related to Study

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

- Mild adverse event (does not affect patient activity)
- Moderate adverse event (mild disruption in usual activity)
- Severe (major disruption in usual activity)

5. Plan for Determining Seriousness of Adverse Events:

In addition to grading the adverse event, adverse events are evaluated to determine whether they meet the criteria for a Serious Adverse Event (SAE). An SAE is defined as AE's which are considered "serious" because of the gravity of their effect upon the subject. AE's are SAE's if they meet any one of the following criteria: life-threatening (i.e., life or limb was in danger); results in hospitalization (i.e., actual admission, not an ER visit); results in death (subject deceased).

An adverse event is considered serious if it:

- is life-threatening (i.e., life or limb was in danger);
- results in hospitalization (i.e., actual admission, not an ER visit);
- results in death (subject deceased).

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRBs and the data safety monitoring board is necessary.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRSOs). Every AE is evaluated as a possible UPIRSO so as to support the prompt reporting requirements of UPIRSOs. These events are defined as:

- "Possibly related" or "probably related" or "related" to participating in the research ("possibly" related means there is a reasonable possibility that the AE may have been caused by the procedures or intervention of the study) meaning that you can't say "not related" or "unknown."
- Unexpected (in terms of nature, severity, or frequency) given:
 - The research procedures described in the IRB-approved research protocol and /or informed consent document;
 - or
 - The known characteristics of the subject population or disease condition being studied;
- UPIRSO's involve a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized or approved by the IRB.

6. Plan for reporting AEs, SAEs, and UPIRSOs to the IRBs, and the Data Management Committee (DMC)

The investigator is responsible to monitor safety and record the results of that monitoring in the form of an Adverse Events (AE log). The principal investigator will conduct a review of all AEs upon completion of every study subject and will evaluate the frequency and severity of the adverse events, in order to determine if modifications are required to the protocol or consent forms. The PI will report AE's, SAE's, and UPIRSOs to our local IRB and DMC following definitions and procedures established in MVAHCS SOP 10-004. For serious adverse events or serious problems, unanticipated/unexpected, and related or probably related to research, we will complete and submit the Serious Adverse Event Report forms to our local IRB and VA data monitoring committee (DMC) within 5 and 2 business days, respectively, of any study team member first becoming aware. If the event is unresolved at the time of the initial report, or if new information pertinent to the event is discovered, a follow-up report will be submitted to the IRB and DMC.

The monitoring of adverse events during the study will be conducted in two contexts: 1) throughout treatment, and follow-up, and 2) during each infusion. Safety measures will be obtained by administration of rating scales and phone interview of patients.

Safety Monitoring during Treatment and Follow-up: We will use the Patient Rated Inventory of Side Effects (PRISE) in combination with the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) to track general side effects. The PRISE/FIBSER will be administered 24 hrs. post-ketamine during the medication-PE phase, at week 4,6,8 and 10 during medication-free phase, and at month 1,2, and 3 during follow-up. The PRISE is a self-reported, standardized rating measure of somatic symptoms. Rated for the last 7 days, the PRISE identifies and evaluates the tolerability of symptoms in the following domains: Gastrointestinal, Heart, Skin, Nervous System, Eyes/Ears, Genital/Urinary, Sleep, Sexual Functioning, and Other. The FIBSER is a 3-item scale to assess the burden of side effects from medication treatment. Item rates frequency, severity, and degree of interference in day-to-day activities and functioning due to the side effects. Each item uses a 7-point Likert-type scale rated from 0 (i.e. no side effects) to 6 (i.e. intolerable). In addition, we will inquiry for any spontaneous report of adverse events during unscheduled in-person or phone contact with subjects.

Safety Monitoring during Infusion: During each infusion, breathalyzer showing an alcohol level=0%, urine pregnancy test, rating scales, and physiological monitoring measures potential side effects related to medications will occur.

Breathalyzer and urine pregnancy tests will be done prior to each infusion. Rating scales will be administered within 60 minutes prior to and immediately upon completion of each infusion and then hourly during the post-infusion monitoring period (up to 2 hrs.). The patients will also be regularly questioned during the infusions about any dysphoric emotions or altered sensory experiences. The rating scales to be administered include:

1. Clinician- Administered Dissociative States Scale (CADSS): a validated instrument that assesses a dissociative state.

This scale contains 28 (23 subjective and 5 objective) items followed by 5 anchors. The anchors are rated from 0 (no symptoms) to 4 (extreme symptoms). A total score of >4 on CADSS signifies a dissociative state. CADSS has been used in many studies investigating the psychological effects of ketamine.

2. Brief Psychiatric Rating Scale (BPRS+): Psychotogenic effects will be measured with the four-item positive symptom subscale of the BPRS+ consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization. The presence and severity of psychiatric symptoms will be rated on a Likert scale ranging from 1 (not present) to 7 (extremely severe).

3. Young Mania Rating Scale (YMRS): Possible emergence of manic symptoms during infusions will be measured by the Item 1 of the YMRS that ranges from 0 (absent elevated mood) to 4 (euphoric).

Vital signs (blood pressure, pulse, respiratory rate) and oxygen saturation level will be recorded every 10 min for 1 hour beginning 10 min before infusion and then every 30 min. Guidelines established for clinically significant changes in vital signs and mental status during the ketamine infusions will be as follows: systolic blood pressure (BP) >161 or <89, diastolic BP >110; heart rate <40 or >130 beats/min; respiratory rate <10 or >30 per minute; pulse oximetry <90%; severe hallucinations, confusion, delusions, irrational behavior, or agitation. Finally, before leaving the infusion unit, subjects will demonstrate that all clinically significant side effects are resolved by obtaining a score ≥9 in the modified Aldrete (mAldrete) scoring system. The mAldrete consists of 6 discharge factors (consciousness, mobility, breathing, circulation, color and O₂ saturation) each accompanied by three differently weighted answer choices that depict a different patient status. The total modified Aldrete score values range from 0 to 12.

4.8. Criteria for Discontinuation.

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment.
- Clinical deterioration: The following are objective criteria to trigger full assessment, by the study investigator, for possible discontinuation at the investigator discretion: (a) A 25% increase in the PCL-5 or the

CAPS-5 score at any time during the study; (b) Patients with a CGI score ≥ 6 at any post-baseline visit; or (c) increased of baseline suicidality as assessed by the study clinician.

- Evidence of intolerable adverse reaction, or unable to tolerate study drug.
- Safety reasons as judged by the investigator.
- Stopping birth control or a positive pregnancy test during medication phase of study.
- Evidence of problematic alcohol or illicit substance use during the trial.
- Non-compliance to protocol procedures as judged by the investigator.

A subject who discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. Mental Health Treatment Coordinator will be notified of discontinuation. The PI may request removal of blinding to research pharmacist if deemed necessary. Assessment of PTSD severity (PCL-5), depression (MADRS), and suicidal ideations/behavior (C-SSRS) will be followed up 3 months if PI deemed necessary.

4.9. Data Analysis Plan.

4.9.1. Sample Details: A previous study⁵¹ examining the effect of a single dose infusion of ketamine on patients with PTSD reported an effect size of $d=.6$. The dose of ketamine and midazolam, which was used as active placebo control, were similar to our current proposal. The table below shows the effect size detectable at 80% power, $\alpha=.05$, two tailed. As we are using 3

infusions rather than one, we feel that an estimate of .6 would be conservative. With a recruitment goal of 120 patients and an anticipated attrition rate of 25%, we would be powered to observe a difference in effect of $d=.65$ or greater on the CAPS score at 10 weeks with 40 patients per group. We aim for a sample size of **40 subjects per intervention to complete our**

Sample size per group	45	39	34	29	26	23	21
Cohen's d	.60	.65	.70	.75	.80	.85	.90

primary outcome measure (CAPS score at week 10) .

4.9.2. Data Collection: Study data will be collected and managed using VA REDCap (Research Electronic Data Capture) hosted behind the VA firewall on a VINCI server. PHI and IIHI will NOT be collected or stored using REDCap. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

4.9.3. Data Analysis: The data analyses will be performed by Dr. Paul Thuras, Co-I on this project. Each subject will be assessed for the primary outcome variable (CAPS-5 score) at baseline (1-2 weeks prior to starting the intervention), week 4, and at the end of PE treatment (week 10). Important confounding variables such as age, and severity of depression will be included in the model based on previous research^{59,60}. **For Aim 1**, (i.e., the analysis of the efficacy of ketamine infusions vs. active placebo control in change from baseline in CAPS-5 score to the end of treatment), we will use an analysis of covariance to compare both groups on change from baseline to week 10. **For Aim 2** (i.e., the analysis of the efficacy of ketamine infusions vs. active placebo control in change from baseline in anxiety and depression scores to end of treatment), we will employ mixed effects models with age and baseline CAPS severity as covariates. **For Aim 3** (i.e., to examine the safety and tolerability of ketamine as a therapy facilitator of PE therapy), we will use Chi-square tests to compare the frequency of side effects in the ketamine and active placebo control groups. **For the exploratory aims** (i.e., cognitive performance and predictors of dropout/retention), a logistic regression model will be used to examine the effect of change in cognition and PTSD outcomes, and change in PTSD, depression and anxiety symptoms in predicting dropout status.

4.9.4. Missing Data: We will perform intent-to-treat analysis, meaning that all subjects randomized into the two treatment groups will be included in the analysis regardless of the extent of compliance with the treatment or withdrawals during the trial. Once subjects are randomized to midazolam or ketamine, they are considered enrolled in the study and their data will be included in analyses. There is no minimum number of infusions required for inclusion in the analyses. This will create incomplete data because some subjects will withdraw from the study during the treatment with their responses missing after withdrawal. If dropout process is related to the outcome measure (i.e., symptom level), this will present a challenge in the analysis. Most of the currently available statistical methods assume that data is missing at random. However, in this study, it is plausible that the likelihood of dropout is related to the level of or change in symptom level (i.e., those with increase or no reduction in symptom level may be more likely to drop out of the study). When subjects drop out of the study, we will obtain data on reasons for dropout and analyze whether the dropout process is at random with respect to the outcome measures. If the dropout process is related to the outcome measures, we will utilize

models (such as pattern mixture models) that incorporate a nonrandom dropout mechanism. These analyses will be carried out as the secondary analyses for hypothesis-generating purposes.

4.9.5. Test of Blinding: The success of blinding will be tested on a 5-point scale at the end of the infusion period and at week 10 using a 2×5 format. Subjects will be asked to rate the extent of certainty about their treatment (i.e., completely sure, almost sure, tentative guess) and the reason for their choice. We will use a sequentially numbered, opaque, sealed envelopes, pharmacy-controlled allocations, and coded identical containers for adequate concealment allocation. Administration of study drugs and infusion monitoring will be conducted by research nurse keeping blinding from investigators and outcome assessors.