Title: Repeated Sub-anesthetic Ketamine to Enhance Prolonged Exposure Therapy in Post-traumatic Stress Disorder: A Proof-of-concept Study

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A. BACKGROUND

A.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 (https://www.healthquality.va.gov/guidelines/mh/ptsd/) added fluoxetine and venlafaxine as monotherapy. Unfortunately, even after an adequate medication trial, response and remission rates are approximately 60% and 30%, respectively(Stein, Ipser, & Seedat, 2006). 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 benefit(Berger et al., 2009), 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.

A.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 list(Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). A multi-center study(Schnurr et al., 2007) 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 in PTSD severity scores on the CAPS at 6-month follow-up with rates of PTSD remission at 40% in PE and 33% in PCT. A recent review of clinical trials of trauma-based therapies for PTSD (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)(Steenkamp, Litz, Hoge, & Marmar, 2015). 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%)(Steenkamp et al., 2015). *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.*

A.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 of the biology of fear learning and memory into human clinical trials (i.e., d-cycloserine, propranolol, MDMA, yohimbine, methylene blue, rapamycin, hydrocortisone). Cumulative research(Dunlop, Mansson, & Gerardi, 2012) indicates that PE may be improved by administration of 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"*). Ketamine, an FDA-approved anesthetic that blocks glutamate neurotransmission at high anesthetic doses(Moghaddam, Adams, Verma, & Daly, 1997) but that at subanesthetic doses, induces a paradoxical increase in glutamate neurotransmission(Abdallah et al., 2016) has shown to enhance neuroplasticity in mood disorders(Li et al., 2011) and PTSD(Girgenti, Ghosal, LoPresto, Taylor, & Duman, 2017) . Ketamine's putative mechanism (e.g., sustained increase in prefrontal synaptic connectivity) persists beyond its bioavailability(Duman & Aghajanian, 2012) which is translated into a clinical durability that ranges between 7-14 days by a single infusion through 16-26 days by repeated infusions in PTSD (Feder et al., 2014) (Albott et al., 2018) and mood disorders (Murrough et al., 2013) (Shiroma, Johns, et al., 2014). The therapeutic window created by ketamine's lasting brain effects was recently examined in a MEP study for OCD patients. A single IV ketamine followed by a brief course of CBT (e.g., 10 one-hour exposure sessions) resulted in a 63% response rate(Rodriguez et al., 2016).

A.4. Glutamate Dysregulation in PTSD.

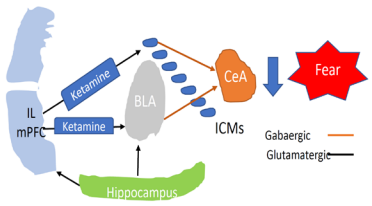
The neurobiological model of PTSD has shifted from monoaminergic to a more complex neuroplasticity hypothesis. Glutamate is heavily implicated in learning, memory, experience-dependent forms of synaptic plasticity, such as long-term potentiation (LTP)(Malenka & Nicoll, 1999), and ultimately in the formation of

traumatic memories and their treatment(Myers, Carlezon, & Davis, 2011). A cascade of neural events that alter both structural and functional glutamatergic connectivity is triggered when the brain's adaptive neuroplasticity response to stress is surpassed by severe trauma. Based primarily on preclinical data, it is proposed that trauma triggers pro-inflammatory processes and dysregulation of HPA-axis that leads to paradoxical extra-synaptic glutamate spillover secondary to reduce astrocyte function and astrocyte loss. Excessive glutamate input causes excitotoxicity and reduction of synaptic connectivity in corticolimbic circuits that regulate response to stress and emotion (i.e., medial prefrontal cortex and hippocampus) which ultimately translate into PTSD symptomatology(Averill et al., 2017).

A.5. Neurocircuit of Fear Extinction in PTSD and glutamatergic receptors.

Trauma-exposed patients suffering from PTSD experience deficits in the extinction of learned fear associations when compared to those who do not develop PTSD(Lommen, Engelhard, Sijbrandij, van den Hout, & Hermans, 2013). During extinction, repeated exposure to a cue previously associated with a fear-provoking event results in the gradual formation of a new memory that is thought to suppress fear expression by establishing an inhibitory memory rather than erase the conditioned stimulus. While extinction is procedurally simple, it involves multiple extinction mechanisms.

Figure 1

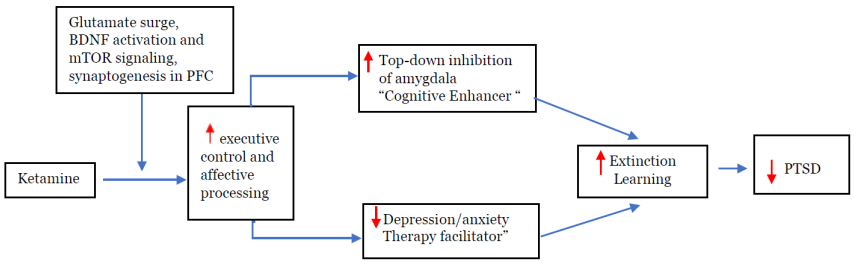


The neural circuitry of extinction (*Figure 1*) is based on a model composed by interactions among 3 structures: the amygdala, medial prefrontal cortex (mPFC), and hippocampus(Milad et al., 2007) (Pitman et al., 2012). The amygdala is a central locus underlying the encoding, consolidation, and expression of extinction memory. In the amygdala, the basolateral complex (BLA), GABAergic intercalated cell masses (ICMs) and the central nucleus (CeA), are critical structures that modulate within-session extinction and extinction retention process(Milad & Quirk, 2002). The hippocampus is responsible for encoding contextual information during extinction training and subsequently using that information to promote or block expression of extinction memory by its interactions with the amygdala and mPFC(Corcoran & Maren, 2001). Within the mPFC, afferents from glutamatergic pyramidal neurons in the infralimbic (IL) sub region activate glutamatergic neurons in the BLA that synapse onto inhibitory GABAergic interneurons which gate signaling from the BLA to the CeA(Rosenkranz, Moore, & Grace, 2003) (Bloodgood, Sugam, Holmes, & Kash, 2018). The IL-mPFC specifically modulates the consolidation and/or expression of extinction memory(Hsu & Packard, 2008) while having little to no effect on within-session extinction(Quirk, Russo, Barron, & Lebron, 2000; Sierra-Mercado, Corcoran, Lebron-Milad, & Quirk, 2006). Neural activation in the IL shortly following extinction training correlated with success of long-term extinction retention and recalling of extinction memories(Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2007).

A.6. Proposed Mechanisms of Ketamine-enhanced PE Therapy.

A.6.1. Ketamine as a Cognitive Enhancer of Extinction Learning: Based on the information described above, we propose that repeated ketamine treatment will increase the synaptic connectivity and neural activation in the mPFC (*Figure 2*). These cellular and molecular changes will **augment the top-down mPFC's inhibitory drive over the excitatory responses of amygdala during extinction learning**. Given that ketamine preferentially activates mPFC, we also hypothesize that ketamine will exert its therapeutic effect on the expression/consolidation of extinction memory(Santini, Ge, Ren, Pena de Ortiz, & Quirk, 2004) without interference of within-session extinction. As extinction memories are labile and fragile, ketamine could bolster the formation, persistence, and possibly context independence of extinction memories and thus, preventing relapse. This proposed mechanism received support from a recent study using a rodent paradigm for preclinical assessments of PTSD. Girgenti[7] and colleagues demonstrated that a single dose of ketamine followed by extinction training for three consecutive days enhances the recall of extinction learning (i.e., reduced freezing behavior to cue) and decreases fear renewal 8 days later. This study also showed that ketamine plus extinction exposure increased synaptic proteins promoter (mTORC1) and neuronal activation (cFos) in the mPFC. Moreover, AMPA receptor inhibitor (NBQX) partially but significantly blockaded the effects of ketamine supporting previous findings that the rapid ketamine effect

Figure 2



requires activation of AMPA receptors(Zarate & Machado-Vieira, 2017) and that AMPA receptor agonist infused systematically or directly into the mPFC facilitate contextual fear extinction (Milad & Quirk, 2002) (Zushida, Sakurai, Wada, & Sekiguchi, 2007) (Zarate & Machado-Vieira, 2017). While this study did not specifically elucidate the role of IL-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 ketamine(Fuchikami et al., 2015). Other mouse studies (Ju et al., 2017) 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 increased in the levels of BDNF in the mPFC and hippocampus.

A.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 (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) (Zayfert, Becker, Unger, & Shearer, 2002) (Rytwinski, Scur, Feeny, & Youngstrom, 2013). 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) (Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002) (Larsen, Wiltsey Stirman, Smith, & Resick, 2016) in PE session 3. 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)(Keller, Feeny, & Zoellner, 2014).

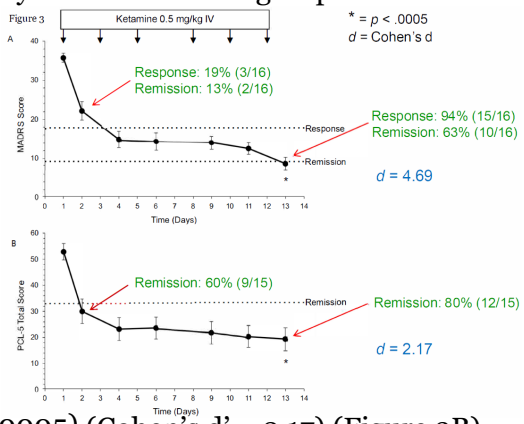
B. PRELIMINARY STUDIES

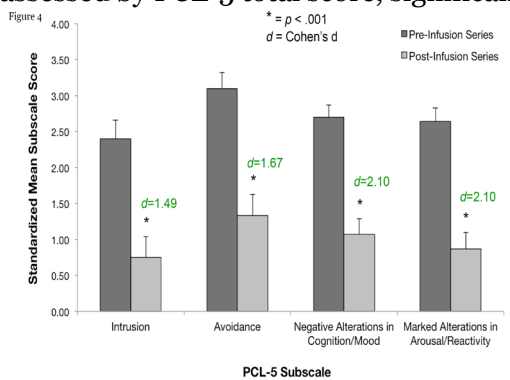
B.1. Research Team is Well Qualified to Undertake this pilot study.

The proposed clinical trial builds directly on the previous experience. **Dr. Shiroma**, PI for this proposal has conducted clinical studies using IV ketamine in depression and PTSD. Dr. Shiroma is currently meeting recruitment benchmarks of a 4-year Merit Review Award aimed to investigate serial ketamine in refractory depression. He was the P.I. (Co-P.I. by Dr. Albott) in the most recent study of serial ketamine and PTSD which provides foundation for this proposal. **Dr. Erbes,** Co-I, is a nationally certified trainer for PE and senior PTSD investigator at the Center for Chronic Disease Outcomes Research (CCDOR) at the Minneapolis VA (MVA). He will oversee PE training and adherence of nationally-certified therapists. **Dr. Thuras**, Co-I, is a biostatistician with more than 20 years of experience at the MVA. 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 VA clinical trials.

B.2. Experience and pilot data on ketamine in PTSD.

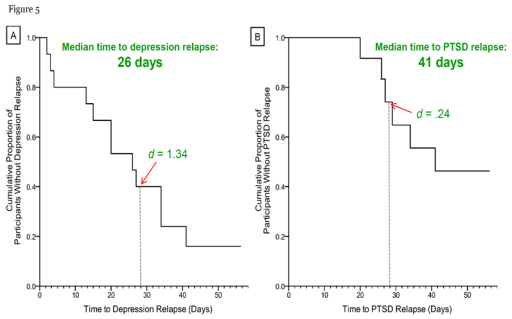
3.3.1. Preliminary data found high efficacy and rapid effect of serial ketamine infusions on the severity of both depressive and PTSD symptoms: Several studies have been published by the P.I. research group on the use of repeated ketamine in TRD(Shiroma, Johns, et al., 2014) (Shiroma, Albott, et al., 2014) (Shiroma et al., 2015) (Albott et al., 2017) (Albott et al., 2018). Expanding previous investigations, a pilot study(Albott et al., 2018) 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 ($F_{6, 90}$= 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.=



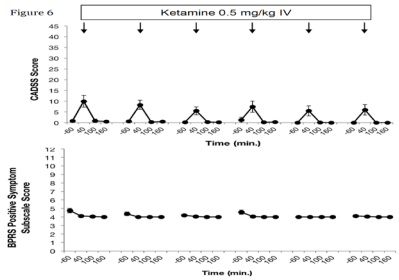


7.2) after treatment (Cohen's d' = 1.85). Figure 4 showed PCL-5 sub-clusters which significantly decreased after completion of treatment. Regarding depression, Montgomery- Åsberg Depression Rating Scale (MADRS) total score decreased over the course of treatment (F2.62, 36.70= 30.17, p < 0.0005), and 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 repeated ketamine sustain response of depression and PTSD for short period: Of the 12 individuals in remission from PTSD after the infusion series, the median time to relapse was 41 days with the 50th and 75th percentiles at 41 and 27 days, respectively (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 four-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 (severity was also significantly higher at follow-up (n = 12), Figure 5A). The mean MDD symptom compared to symptoms 24-hours after the sixth infusion (t= 5.08; df=11, p < 0.0005).



3.3.3. Pilot data suggest repeated ketamine infusion treatment is a tolerable intervention: Side effect were ascertained prior to each infusion, immediately following the infusion (+40 min), and at one (+100 min) and two (+160 min) hours post-infusion (Figure 6). Three participants (18.8%) required beta-blockers to lower blood pressure (systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg). Dissociative symptoms peaked immediately after each ketamine infusion (+40 min) and rapidly resolved during post-infusion monitoring. No significant increase in psychotic or manic symptoms were observed. Of note, no veterans experienced a worsening of PTSD symptoms from baseline at any point during the study, despite the known dissociative effects of ketamine infusions.



C. STUDY MILESTONES

During Stage I, we will obtain IRB approval. Nationally-certified PE therapists will receive one-time refresher session during quarter 1 with ongoing supervision by Co-I Dr. Erbes. Dr. Erbes will train raters on the CAPS-5 assessment during months 1-3 with ongoing fidelity checks. The study will be conducted during Stage 2 for 12 months including enrollment, interventions and follow-up. Data entry will be an ongoing process but completed by quarter 5 coincident with last data collection. Data analysis/generation of manuscripts and funding application for clinical trial will occur during Q6 (*Table 1*).

Table 1: Timeline

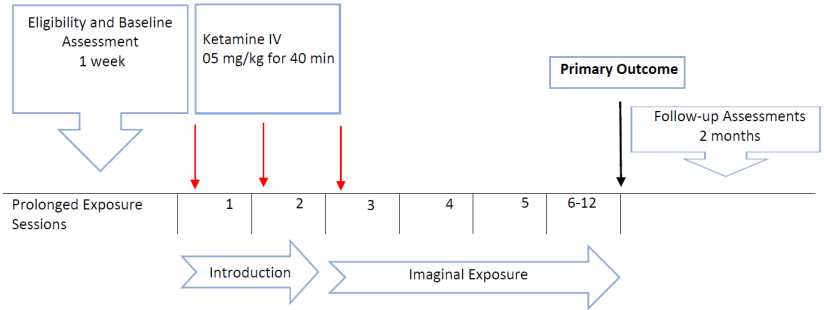
	Stage 1	Stage 2				
	Q1	Q2	Q3	Q4	Q5	Q6
Start-up						
Enrollment						
Intervention						
Outcome assessment						
Data entry/cleaning						
Statistical analysis						
Report writing						
Application for clinical trial (R01 or VA Merit Award)						

D. RESEARCH DESIGN AND METHODS

D.1. Design Overview.

The proposed pilot is an open-label interventional study designed to inform and strengthen the feasibility of protocol

Figure 7



implementation on sub-anesthetic doses of intravenous ketamine as augmenting strategy of standardized, manually-driven PE in PTSD (*Figure 7*). For this purpose, **we aim to: 1) clarify research hypotheses on the efficacy, safety and tolerability of this MEP approach; 2) assess the acceptability of methods and instruments to participants; 3) identify potential barriers to subsequent study completion, and 4) obtain estimates of means, standard deviation and 95% confidence intervals on outcome measures as well as the expected rates of missing data and participant attrition**. We estimate that analysis of data obtained from participation of 10 patients will provide responses to our scientific aims. Participants will be male and female veterans (18 to 75 years old) of any era or military background diagnosed with PTSD. Potential participants will be recruited from Mental Health clinics and screened for eligibility using a two-stage process (phone/chart review, followed by interview). Those who meet eligibility criteria will complete baseline assessment one week prior to starting treatment. Then, treatment will consist of 1) 3-week ketamine-PE phase composed by weekly single intravenous ketamine (0.5 mg/kg for 40 minutes) followed within 24 hrs. by PE session; and 2) ketamine-free PE phase from week 4 through 12. After PE is completed (session 12), patients will be assessed during a 2-month follow-up period at various time points. We estimate that 10 veterans will reach time point for primary outcome measure (CAPS score at week 12) and will be considered for primary analysis. Independent evaluation of PTSD, cognitive function, depression, anxiety and other potential covariates (i.e., pain) will be ascertained at baseline, at several time points during treatment, and at follow- up.

D.1.1. Design Considerations: As with any pilot study, several factors have been considered in the design of this proposal. The goal is to provide a design that is feasible, efficient, and above all, able to answer study aims. Some of the possible alternative designs, and reasons we did not select them, are listed.

Table 2. Considerations and Rationale for Choosing the Current Design

Consideration	Rationale
Doses of ketamine	Several studies(Xu et al., 2016) have shown that ketamine doses at 0.5 mg/kg have higher antidepressant and similar adverse effects than lower (e.g., 0.1 mg/kg or 0.2 mg/kg) or higher (e.g., 1.0 mg/kg) doses, respectively. The presence of an inverted U-shaped relationship between dose and response is supported by higher doses of ketamine having no effect inducing mTOR activation(Li et al., 2011). Moreover, a single ketamine at 0.5 mg/kg, and not at 0.2 mg/kg, showed procognitve effects by improving sustained attention and cognitive response control among 71 patients with TRD (Chen et al., 2018). Studies(Feder et al., 2014) (Albott et al., 2018) in PTSD using a single as well as repeated ketamine infusions were dosed at 0.5 mg/kg with rapid, safe but short-lived reduction of PTSD symptom severity.
Interval between ketamine and PE	Ketamine has an elimination half-life is 186 minutes(Clements, Nimmo, & Grant, 1982) with temporary dissociative/psychotomimetic effects observed at doses of 0.5 mg/kg between 40 and 120 minutes posttreatment, which resolve within 240 minutes of administration(Zarate et al., 2006) (Murrough et al., 2013). However, ketamine's putative therapeutic mechanism (e.g., sustained increase in prefrontal synaptic connectivity (Abdallah et al., 2016) (Duman, Aghajanian, Sanacora, & Krystal, 2016)) persists beyond its bioavailability(Duman & Aghajanian, 2012). These lasting physiological brain changes, which is reached within 24 hrs. of treatment, have proved to be a therapeutic window to enhance the outcomes of psychological interventions in pre-clinical and clinical studies (i.e., extinction learning in animal PTSD (Girgenti et al., 2017) model and CBT in OCD(Rodriguez et al., 2016), respectively). Studies in TRD suggested that the peak of antidepressant effects to ketamine occur 24 hours after administration (Zarate et al., 2006)(Zarate et al. 2006a) (Mathew et al., 2010). Moreover, this notion of peak of efficacy following an intravenous ketamine administration is further supported by the temporal overlap of subacute functional network modulation after 24 hours reported by neuroimaging studies (Scheidegger et al., 2012) (Murrough et al., 2015) .
Single vs repeated ketamine infusions.	Our pilot study(Albott et al., 2018) demonstrated that repeated ketamine infusion provides higher efficacy (80% remission) as compared to single infusion (24.1% CAPS-IV score<50)(Feder et al., 2014). Mild transient increases in dissociative symptoms without the emergence of mania or psychotic symptoms were similar in both studies.

Number of ketamine infusions	During PE, session 1 and provide a rationale of PE and understanding of trauma. Imaginal exposure (IE) begins at session 3. Two independent studies(Foa et al., 2002) (Larsen et al., 2016) found post-IE exacerbation of PTSD, anxiety, and depressive symptoms at session 4. We will measure the effect of administering three single ketamine treatments prior to IE aiming to target a key component of PE with the potential to enhance the efficacy PE outcomes.
Inclusion of comorbid condition to PTSD.	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(Rytwinski et al., 2013) 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 (Dekel, Solomon, Horesh, & Ein-Dor, 2014) (Bedard-Gilligan et al., 2015)
Wash-out vs a period of stable doses of current psychotropic medications.	Patient taking psychotropics with potentially serious drug-drug interactions with ketamine (e.g., barbiturates) will be excluded. The therapeutic effect of psychiatric medications is prolonged beyond clearance of active compound or their metabolites from blood and brain so pharmacological "isolation" of ketamine will not likely occur with a brief medication washout. 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. However, keeping stable doses for at least 4 weeks of prior psychotropic regimen will decrease confounding effects on the study of ketamine on PTSD, depression, and anxiety.
Open-label vs use of active placebo.	While the use of active placebo, such as midazolam, would serve to enhance masking intention by mimicking ketamine's side effects profile, the purpose of this pilot is to test the feasibility to conjointly use ketamine and PE rather than to formally assess evidence of efficacy.
Ideal vs actual 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(Clements et al., 1982), 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".

D.2. Study Site.

The clinical facilities for the proposed study 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 Primary & Specialty Medicine Service Line, 3E Stepdown Unit (Nurse Manager: Britta Dass, RN), a 21-bed medical step-down unit is on the located on the 3rd floor of the main MVA hospital building and staffed by RNs, LPNs, and ancillary personnel. 3E clinical rooms are fully equipped with mobile desktop PCs, cardiac and respiratory monitors, infusions pumps, and crash carts. A conference room is available for conducting private clinical assessments and interviews with study participants. 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.

D.3. Subject Recruitment and Selection.

Our planned enrollment includes 10 patients to receive three weekly ketamine-PE treatment followed by ketamine-free PE treatment for 9 additional weeks. Participants will be recruited from veterans receiving mental health treatment. Referrals will occur from VA clinicians and clinics, and responses from posted fliers and study pamphlets. Potential participants will be provided with information about the study and screened through medical records, chart review, and by telephone to determine whether they meet basic inclusion/exclusion criteria. Those who qualify will be scheduled for a more rigorous assessment (*see further details below*).

D.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
1. Male or female Veterans aged 18-75 years old. 2. Diagnosis of chronic (minimum of three months) PTSD (Clinician-Administered PTSD Scale for DSM-5 -CAPS-5 score>33). 3. Voluntarily eligible to participate in PE. 4. Severity of PTSD symptoms defined by PCL-5>33. 5. Psychotropic medications on stable doses (no dosing adjustments/changes for ≥4 weeks; ≥6 weeks for fluoxetine) prior to prior to beginning of the study.	1. Unwillingness/unable to sign informed consent. 2. Previous or current participation in trauma-exposed therapy and/or ketamine treatment. 3. Evidence of mental retardation, pervasive developmental disorder and/or moderate/severe cognitive impairment (MMSE scores ≤27). 4. Any unstable medical or non-psychiatric CNS condition. 5. Lifetime history of psychosis-related disorder, bipolar disorder I or II disorder, or any condition other than PTSD judged to be the primary presenting psychiatric diagnosis. 6. Moderate to severe traumatic brain injury (mental status change or loss of consciousness>30 min; Glasgow Coma Scale <13; post-traumatic amnesia>24hours; visible lesion on CT/MRI brain scan). 7. Active alcohol/illicit substance use disorder within 6 months of initial assessment; presence of illicit drugs by positive urine toxicology. 8. For women: 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. 9. Imminent risk of suicidal/homicidal ideation and/or behavior with intent and/or plan

D.3.2. Feasibility of recruitment: The study will recruit 10 Veterans over 12 months. In the last 12 months, 289 Veterans were diagnosed with PTSD and 114 have received at least 02 PE sessions at the MVA. While we do not anticipate any difficulties, we could expand recruitment to satellite clinics from MVA Health Care System.
D.3.3. Pre-Screening: To reduce subject burden, we will obtain a waiver of HIPAA authorization to allow potential subjects to be pre-screened by chart review followed by an in-person or phone interview prior to scheduling further assessment visits. Potential participants will be provided with information about the study and asked a series of questions to determine if they meet basic inclusion/exclusion criteria (e.g., indicators of current PTSD). They will be informed that the treatment involves multiple infusions of sedatives at subanesthetic doses followed by PE therapy. Those interested will be scheduled for an in-person interview for eligibility.
D.3.4. Informed Consent: Voluntary informed consent will be obtained in accordance with local IRB approvals. 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 MVA to determine the decision-making capacity of a potential research subject to provide informed consent. Willingness to participate in assessments will be confirmed and information about confidentiality and study payments will be provided.

D.4. Study Intervention.

D.4.1. Ketamine infusions: Table 4 describes the schedule of assessments on the day of infusion. Patients will arrive in the morning after an overnight fast of at least 8 hours. 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. 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 0.5 mg/Kg of ketamine hydrochloride solution 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. However, 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 an hour later or until all safety measures (e.g., rating scales and vital signs) return to pre-infusion measures.

Standard Operating Procedures for ketamine infusions is attached. 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. The site study anesthesiologist will assist during infusions if necessary. Medications such as labetalol or hydralazine (hypertensive episode), ondansetron (nausea, vomiting), and flumenazil (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. 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 several measures to improve recovery at home will be provided at discharge.

Table 4: Assessment Schedule on Infusion Day

	Measure	**t_0-60 min**	**Baseline (t_0)**	**t_0+40 min**	**t_0+100 min**	**t_0+x* min**
BP, pulse, RR, $SatO_2$		X	X	X	X	X
Dissociative Symptoms	CADSS	X	X	X	X	X
Psychotogenic Symptoms	BPRS+	X	X	X	X	X
Manic Symptoms	YMRS	X	X	X	X	X
Recovery from ketamine	mAldrete					X

*Patient will be monitored an hour after infusion or hourly until vital signs, side effects from ketamine return to pre-infusion measures and mAldrete score≥9.

D.4.2. 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 retraining(Rothbaum, 2007). 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, plans, and relapse prevention

D.5. 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 5. Clinical interviews will be conducted by trained evaluators. Subject compensation will also be provided to increase participant retention and reduce missed assessments (see further details below).

D.5.1. Eligibility and Baseline Assessment: The Eligibility and Baseline Assessment (EBA) will be accomplished during 1-2 visits over a 7 -day period prior to starting treatment. It will take a total of 3 hours. Provisional diagnosis of PTSD and its severity would be obtained by PCL-5 score>33. The CAPS-5 would be then administered to established PTSD diagnosis. The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I. 6.0)(Sheehan et al., 1998) will be used for psychiatric evaluation to confirm the absence of exclusionary diagnoses. Lack of moderate/severe cognitive impairment will be ascertained with an MMSE score≥28. Evaluation of exclusionary criteria involving unstable medical illnesses will be based on brief physical examination, medical record review by study M.D. in consultation with on-site study

anesthesiologist, basic metabolic laboratory tests, and ECG. A urine pregnancy, if applicable, and drug screen will also be obtained. Secondary outcomes at baseline will include cognitive function (CogState), severity of depressive symptoms (MADRS), levels of anxiety (Beck Anxiety Inventory-BAI), suicide risk (Columbia- Suicide Severity Rating Scale- C-SSRS), 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).

D.5.2. Treatment Assessment: The research staff will measure PTSD symptoms severity by administering the CAPS-5 at weeks 4, 12 and 2-month follow-up. Secondary outcomes that includes cognitive function, anxiety, depression, pain, suicide, and 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 (ketamine-PE phase). We will administer rating scales again at week 4, 6, 8, and 12 (ketamine-free phase), and at 2-month follow-up. Fear activation and extinction during PE sessions would be measured by the Subjective Units of Distress Scale (SUDS).

D.5.3. Follow-up Assessment: Following completion of treatment, participants will attend Post-Treatment Assessment monthly for 2 months (total of 02 follow-up visits). Each visit will take about 2 hours. Follow-up assessments will involve self-report for PTSD symptoms (PCL-5), cognitive assessment (CogState), depressive symptom severity (MADRS), clinical impression of illness severity and improvement (CGI), as well as self-reported measures of pain intensity (NRS for pain), level of anxiety (BAI), suicide risk (C-SSRS), general adverse events (PRISE/FIBSER) and quality of life (WHOQOL-BREF). The CAPS-5 will be administered once at 2-month follow-up.

Table 5: General Assessment Schedule

Construct	Measure	Eligibility and Baseline Assessment	Treatment Assessments	Follow-Up Assessment
		1-2 weeks	Week 1 to 12	2 months
Primary Outcome Measure				
PTSD symptoms	CAPS-5	X	X	X
Interview Based Assessments				
Decision-making capacity	Dysken Screening Tool	X		
PTSD severity	PCL-5	X	X	X
Diagnostic interview for comorbid conditions	M.I.N.I.	X		
Rule-out moderate/severe cognitive impairment	MMSE	X		
Infusion Safety Measures				
Physical Exam/ECG/Pregnancy test/Urine toxicology		X		
Recovery from infusion	mAldrete		X	
Side Effects (dissociative, psychotogenic, and manic symptoms)	CADSS, BPRS+, YMRS		X	
Secondary Outcome Measures				
Subjective units of distress (a proxy for extinction)	SUDS		X	
Cognitive function	CogState	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
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		

D.5.4. 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.

D.5.6. PE Training, fidelity and supervision**:** Licensed doctoral-level psychologists and masters-level clinical social workers will deliver the PE treatment. Therapists will be existing VA clinicians who have been approved to donate time to the study and treat participants as part of their regular caseload. Supervision of PE will include regular review of session video to determine presence or absence of essential PE component, and monitor for protocol violations. Treatment sessions will be videotaped and 12% will be randomly selected and reviewed by PE expert (Dr. Erbes) to ensure fidelity to the treatment manual (15 sessions will be selected from sessions 1–2, session 4, sessions 6–9, and sessions 10 and above).

D.6. Outcome Measures.

D.6.1. Primary Outcome Measure: The primary outcome is the difference in PTSD symptom severity from baseline to week 12 measured by the 30-item **CAPS-5** past month version (for current PTSD) total score(Weathers et al., 2018).

D.6.2. Interview based Assessments: We will collect demographic data using the **PhenX Measures** for Mental Health (https://www.phenxtoolkit.org). History of psychiatric risk factors will be obtained by initial interview. Comorbidity and potential exclusionary diagnosis will be determined by **M.I.N.I.** (Sheehan et al., 1998) 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 contraindicated. A widely used brief screening test, the **MMSE** will quantitatively assesses for exclusion of moderate-to-severe cognitive impairment cognitive. All study-related audio recordings will be maintained in accordance with the Record Control Schedule (i.e., 6 fiscal years after study closure).

D.6.3. Secondary Outcome Measures*:* Severity of depression would be measure 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 MADRS is psychometrically sensitive to assess the rapid onset of antidepressant efficacy (Johnson et al., 2016) . 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 time frame for PCL-5 has been modified to meet research needs as in other studies (e.g., NCT02655692). Moreover, the Mental Illness Research, Education and Clinical Centers (mirecc.va.gov) stated that "The PCL can be easily modified to fit specific time frames or events. For example, instead of asking about 'the past month,' questions may ask about 'the past week' or be modified to focus on events…". 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- last visit version** will be used to count prospective or treatment emergent suicidal behaviors. The C- SSRS has been used in many treatment trials, and to measure treatment emergent suicidal events during pharmacotherapy(Mann et al., 2006). **SUDS**(Jaycox, Foa, & Morral, 1998) 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. **NRS** (Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011) 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** (Busner & Targum, 2007)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 ("The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization," 1995) 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)** (Devilly & Borkovec, 2000) 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.

D.6.4. Side Effects Measures: We will monitor side effects during intervention and at follow-up visits. The **PRISE** (Rush et al., 2004)assess for the last 7 days the side effects in the following symptom domains; Gastrointestinal, Heart, Skin, Nervous System, Eyes/Ears, Genital/Urinary, Sleep, Sexual Functioning, and Other. Each domain has multiple symptoms which can be endorsed. The PRISE is use in combination with **FIBSER** (Wisniewski, Rush, Balasubramani, Trivedi, & Nierenberg, 2006) which rates the intensity, frequency and overall burden due to side effects in a 7-point Likert-type scale. During ketamine infusions, we will assess potential side effects by 1) the **CADSS** (Bremner et al., 1998), a clinician-administered tool validated in healthy subjects and patients with PTSD and designed to measure present-state perceptual, behavioral, and attentional alterations occurring during dissociative experiences; 2) the four-item positive symptom subscale of the **BPRS** (Zanello, Berthoud, Ventura, & Merlo, 2013) a clinician-rated tool that assess change in severity of psychopathology consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization; and 3) the **YMRS** (Young, Biggs, Ziegler, & Meyer, 1978), item #1 to evaluate possible manic symptoms. Finally, the **Modified Aldrete score system** (mAldrete)(Aldrete, 1995) is a set of criteria commonly used to assess transition from anesthesia to recovery. Numeric scores of 0, 1, or 2 are assigned to motor activity, respiration, circulation, consciousness, and SpO2 level for a maximal score of 10. A score≥ 9 is required for discharge from post-anesthesia care unit.

6.7. Data Analysis Plan.

6.7.1. Sample Details: ***We propose a sample of 10 patients in this proof-of-concept pilot study***.

6.7.2. 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. 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.

6.7.3. 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 12). ***Statistical analysis for this study will be essentially descriptive in nature. We will assess means, standard deviations, and 95% confidence intervals in symptoms at key assessment points. We will also examine distribution of missing data. In addition to the CAPS-5, we will also examine change in our secondary measures (PCL-5, CogState, MADRS, etc.), again these analyses will be descriptive in nature and will be used to refine our RCT proposal.***

6.7.4. Data Safety.

After the recruitment of 6 subjects, an independent, 3-person panel of physicians and researchers will conduct a reassessment of the risks and benefits to study participants. This panel will review all adverse events for severity and frequency.

6.8. Anticipated potential problems and alternative strategies.

The research infrastructure and SOPs to run ketamine infusions, and a well-established PTSD service are currently in placed at MVA to assure timely start-up within 3 months. However, possible problems and solutions during execution of the study might be: 1) Slow recruitment/enrollment: We cautiously propose recruiting about 10 veterans aim to complete the primary outcome for our study. Nevertheless, if recruitment is slow, we would expand to include recruitment from satellites clinics within the Minneapolis VA Health Care System. In addition, we could reach out the Veteran's population served at the St. Cloud VA Health Care System (SCVAHCS) (see. 6.3.2. Feasibility of recruitment. 2) Dropouts and missing data: In our own sample, out of 16 subjects, only 2 dropped out in agreement with the literature that consistently supports tolerability of serial ketamine infusions. However, if risk of dropping out due to assessment burden occurs, subjects will have the option of completing a minimum core of primary outcome measures and maintain a flexible routine for recurrent appointments. For missing values, we will handle it by data imputation strategies, by last-

observation-carried-forward, and by the exclusion of dropouts (completers-only analyses); 3) Lost of follow-up: We would initiate outreach procedures and safety checks.

E. STUDY COMPENSATION

Participants will be compensated for completing the assessment sessions throughout the study. Assessment sessions involve individual clinical interviews, self-report, and semi-structured questionnaires. Compensation for assessment sessions will be delivered according to the following schedule: $75 for Eligibility Screen and Baseline (1 week prior to starting treatment, approximately 3 hours), $50 for each assessment during medication phase (total of 03 over 3 weeks; +/-02 hrs. each), $30 at post-ketamine PE sessions 4, 6, 8 and 12 (total of 04 over 2 months; +/- 02 hrs. each), and $30 for monthly follow-up post-treatment (twice for+/- 02 hrs.) for a total of up to $405. Participants who prematurely withdraw from study assessments will not be compensated for assessment sessions that have not yet taken place.

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