Contemporary Clinical Trials 81 (2019) 11–18

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

# Repeated ketamine infusions for antidepressant-resistant PTSD: Methods of a multicenter, randomized, placebo-controlled clinical trial

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ARTICLE INFO

*Keywords:*
Ketamine
Rapid-acting antidepressant
PTSD
Veterans

ABSTRACT

Posttraumatic stress disorder (PTSD) is a debilitating disorder with limited medication treatment options. Recent reports have described the dearth of research on new drug development as a crisis in the pharmacotherapy of PTSD. There are only two PTSD medications approved by the U.S. Food and Drug Administration, and both are serotonergic antidepressants. Therefore, there is a tremendous need to identify more effective and more rapidly

*Abbreviations:* AE, Adverse event; ARAC, Assessment of Rapid Affect Changes; AUDIT, Alcohol Use Disorders Identification Test; B-IPF, Brief Inventory of Psychosocial Function; CADSS, Clinician-Administered Dissociative States Scale; CAP, Consortium to Alleviate PTSD; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; CGI, Clinical Global Impression Scales; DNA, Deoxyribonucleic acid; DRRI-2, Deployment Risk and Resilience Inventory-2; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorder 4th Edition*; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*; DSI-SS, Depressive Symptom Index – Suicidality Subscale; ECG, Electrocardiogram; EDTA, Ethylenediaminetetraacetic acid; FDA, US Food and Drug Administration; FTND, Fagerstrom Test for Nicotine Dependence; FTND-ST, Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco; GAD-7, Generalized Anxiety Disorder 7-item scale; MADRS, Montgomery-Asberg Depression Rating Scale; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment History Questionnaire; MINI, Mini-International Neuropsychiatric Interview; PANSS, Positive and Negative Symptom Scale; NMDAR, *N*-methyl-d-aspartate receptor; PCL-5, PTSD Checklist for *DSM-5*; PGI, Patient Global Impression; PHQ-9, Patient Health Questionnaire-9; PTSD, posttraumatic stress disorder; PROMIS, Patient-Reported Outcomes Measurement Information System; QDS, Quick Drinking Screen; QIDS-SR, Quick Inventory of Depressive Symptoms – Self-Report; RNA, Ribonucleic acid; SAFTEE, Systematic Assessment for Treatment Emergent Effects; SITBI, Self-Injurious Thoughts and Behaviors Interview; SSRI, Serotonin reuptake inhibitor; STOP, Snoring, Tired, Observed, Blood Pressure; VA, US Department of Veterans Affairs; VR-12, Veterans RAND 12-item Health Survey; WHYMP, West Haven-Yale Multidimensional Pain Inventory.

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https://doi.org/10.1016/j.cct.2019.04.009
Received 14 December 2018; Received in revised form 4 April 2019; Accepted 13 April 2019
Available online 15 April 2019
1551-7144/ Published by Elsevier Inc.

Active duty military
Combat
Treatment resistant

acting pharmacotherapies for PTSD that work through novel neural mechanisms. Pilot evidence and case reports provided preliminary evidence supporting the safety and utility of investigating the therapeutic effects of ketamine in PTSD. However, the efficacy of this drug for PTSD has not yet been tested in active duty military or veteran populations. Here, we report the design and methods of a study funded under the Consortium to Alleviate PTSD. The study is a multisite, placebo-controlled, double–blind, randomized clinical trial to examine the dose-related efficacy of ketamine, as compared to placebo, in producing a rapid and sustained reduction in PTSD symptomatology in veterans and active duty military populations with antidepressant-resistant PTSD. Approximately 198 eligible participants who meet criteria for PTSD will be randomized to the study drug (i.e., ketamine 0.5 mg/kg, ketamine 0.2 mg/kg, or placebo). The study drug will be administered intravenously twice per week for 4 weeks, followed by a 4-week follow-up period. This ongoing study is the only trial of therapeutic effects of ketamine for PTSD and the first placebo-controlled trial to determine the dose-related effects of repeated ketamine on PTSD.

## 1. Introduction

There is tremendous need for testing novel pharmacotherapeutic approaches to posttraumatic stress disorder (PTSD) [1,2]. PTSD is a leading cause of disability among trauma-exposed military and civilians alike. The National Comorbidity Survey Replication estimates the lifetime prevalence of PTSD among adult Americans to be 6.8% [3]. The US Department of Veterans Affairs (VA) estimates that PTSD afflicts 11% of veterans of the war in Afghanistan and 20% of Iraqi war veterans. While antidepressant medications are currently available, their efficacy is limited [4,5]. Currently, only two medications, both selective serotonin reuptake inhibitors (SSRIs), have US Food and Drug Administration (FDA) approval for PTSD treatment. These medications take weeks to months to reach full clinical effects. In civilian treatment seeking populations, fewer than half of the patients achieve full remission on SSRIs [5]. Rates of nonresponse or partial response to these medications among combat-exposed military, particularly those with chronic PTSD, are comparable to or worse than those of the civilian patient population [6,7]. Currently, no pharmacotherapies for antidepressant-resistant PTSD symptoms have efficacy supported by a definitive, multicenter, placebo-controlled trial [2,5]. For example, a second-generation antipsychotic medication did not show efficacy for antidepressant-resistant PTSD symptoms in a recent VA multicenter trial [8]. Hence, there is an urgent need for a novel class of medications that can (1) offer rapid-acting effects, (2) show efficacy in patients not achieving adequate benefit from existing medications, and (3) work for militarily-relevant PTSD. Over the last two decades, accumulating evidence has shown that a low dose of ketamine, a *N*-methyl-d-aspartate receptor (NMDAR) antagonist, may possess these properties.

Ketamine is a rapidly acting antidepressant and is effective in treatment-resistant depression [9]. Twenty years ago, we first reported the antidepressant effects of ketamine [10,11]. Published reports from our group and others indicate that ketamine produces reductions in antidepressant-resistant depression symptoms within 4 h and full clinical response in 50–60% of patients within 24 h [12,13]. More recently, pilot evidence showed a significant improvement in PTSD symptoms 24 h after a single ketamine infusion in a mostly civilian population [14]. Mechanistically, ketamine is believed to reverse trauma-related synaptic abnormalities that are critical to PTSD pathology and treatment [15–17]. In the current report, we describe the study protocol of an ongoing, multicenter, randomized, placebo-controlled clinical trial examining the effects of two doses (0.2 mg/kg and 0.5 mg/kg) of repeated ketamine infusions on PTSD symptoms in veterans and active duty personnel. This study is being conducted as part of the Consortium to Alleviate PTSD (CAP), a multi-institutional and multidisciplinary research consortium funded by the VA and Department of Defense and focused on developing and evaluating effective interventions for the prevention and treatment of combat-related PTSD and comorbid conditions. The primary efficacy measure will be the PTSD Checklist for *DSM-5* (PCL-5), and the primary analysis will use mixed effects regression models [18]. Types and rates of adverse events will be summarized and compared across the study groups. The durability of benefit and the clinical significance of changes in PCL-5 scores will be explored.

## 2. Methods

All study procedures are approved and monitored by an Institutional Review Board at each study site as well as the US Army Medical Research and Materiel Command (USAMRMC) Human Research Protection Office (HRPO). In addition, all study participants complete a written informed consent prior to participation and are eligible to receive other standard of care treatment within their respective VA and military treatment facilities.

### 2.1. Study population

We anticipate recruiting and screening approximately 240 male and female veterans and active duty military participants, between the ages of 18–70 years, in order to meet the target enrollment goals. In order to account for participant dropouts and retain a sample of 159 participants completing the double-blind treatment phase (53 per treatment group), 198 eligible participants (66 in each group) who meet criteria for PTSD as determined by the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) and the study inclusion criteria outlined below will be randomized to the study drug.

### 2.2. Study criteria

#### 2.2.1. Inclusion criteria:

1. Male or female veterans and active duty military personnel between the ages of 18–70 years seeking treatment for PTSD.
2. Diagnosis of PTSD with a score of 23 or higher (i.e., severe PTSD) on the CAPS-5 at screening.
3. Treatment resistance to at least one adequate trial of an antidepressant as determined by the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ).
4. Participants on FDA-approved antidepressant, trazodone, atypical neuroleptic, prazosin, or clonidine may enter the study if they have been on an overall stable treatment, as determined by the study clinician, for at least 4 weeks prior to randomization. Following randomization, changes to doses may be allowable at the investigator's discretion.
5. Participants in PTSD-focused psychotherapy may be enrolled if they have been in therapy for 6 weeks prior to randomization.
6. Able to provide written informed consent.
7. Able to read and write English.

*2.2.2. Exclusion criteria:*

1. Participants with a diagnostic history of schizophrenia or schizoaffective disorder as confirmed by the Mini-International Neuropsychiatric Interview (MINI) 7.0 for *DSM-5*.
2. Participants with a history of antidepressant-induced hypomania or mania.
3. Participants currently exhibiting psychotic features or meeting criteria for current manic, hypomanic, or mixed episode as confirmed by the MINI 7.0 for *DSM-5*.
4. Current, ongoing serious suicidal risk as assessed by evaluating investigator.
5. Moderate severity or greater substance use disorder (excepting alcohol use disorder) during the 3 months prior to randomization, as determined by the MINI 7.0 for *DSM-5*. Alcohol Use Disorder may be allowed based on the judgment of study clinician that patients can remain sober for all study visits.
6. Participants on monoamine oxidase inhibitor, memantine, or long acting benzodiazepines.
7. Any history or signs of serious medical or neurological illness. A participant with a clinical abnormality may be included only if the study clinician considers the abnormality will not introduce additional risk factors and will not interfere with the study procedure.
8. History of traumatic brain injury with loss of consciousness for > 24 h or posttraumatic amnesia for > 7 days; Participants may be considered if the trauma occurred > 1 year ago, and no more than minimal symptoms have persisted over the past year.
9. Breathalyzer showing an alcohol level > 0% at screening, or at the discretion of the investigator, prior to any study drug infusion.
10. Any history indicating dementia or mental retardation as determined by psychiatric interview.
11. Known sensitivity to ketamine as determined by the study clinician.
12. 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.
13. Females will be excluded if they are pregnant; breastfeeding; or do not agree to utilize a medically accepted birth control method.

*2.3. Study sites*

Participating sites include the Clinical Neurosciences Division of the National Center for PTSD at West Haven, Connecticut VA Medical Center and Brooke Army Medical Center. Each site (West Haven and San Antonio) is currently enrolling to accrue 99 participants over a period of 4 years (i.e., approximately 25 participants per site per year). Both study sites have extensive experience in conducting clinical trials and in the administration of ketamine.

*2.4. Study procedures*

This is a double-blind, placebo-controlled, 4-week clinical trial in which patients will be randomized to one of three treatment groups based on the content of their intravenous infusions throughout the study: 0.9% saline (placebo), ketamine (0.2 mg/kg), or ketamine (0.5 mg/kg). On each infusion day, preinfusion assessment of adverse events and symptom severity will be conducted using a set of clinician- and self-rated scales. Participants will then receive a 40-min intravenous infusion of the study drug based upon randomized treatment assignment. Patients are clinically monitored, and symptoms are assessed repeatedly during and after infusion up to 120 min following the study drug administration. Participants will receive infusions twice per week (e.g., Monday and Thursday) for 4 weeks, and then a 4-week follow-up period will follow. Nonresponders (i.e., < 25% improvement from the baseline CAPS-5 score) at the end of the double-blind treatment period (end of Week 4) will be offered a single infusion of open-label ketamine 0.5 mg/kg to assure participant access to ketamine and as a point of reference for double-blind treatment.

*2.4.1. Blood collection for future biomarker testing*

We will collect blood samples at visits 2 (baseline; prior to first infusion), 3 (24-h post infusion #1), 7 (midtreatment; prior to infusion #5), 11 (end of treatment; 24-h post infusion #8), and 16 (end of follow-up; 4 weeks post infusion #8). Four tube types will be collected at each of these 4 time points: (1) PAXgene DNA, (2) PAXgene RNA, (3) EDTA plasma tube, and (4) serum separator tube. The CAP's standard Consortium operating procedures are followed for the processing, storage, and shipping of sample aliquots. All samples are stored in freezers at the Consortium's Biorepository.

*2.5. Dependent measures*

Although the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) is the gold-standard measurement for PTSD [19,20], it is not designed to detect rapid changes occurring following each ketamine treatment. Instead, similar to the previous report showing the acute effects of ketamine on PTSD symptoms [21], we have selected the PCL-5 as the primary outcome measure for this study. The PTSD Checklist for DSM-5 (PCL-5) [22] is similar in form to the PCL-4 [23]. The PCL-5 will be obtained at baseline, 24 h post first infusion, prior to each infusion, and 24 h post last infusion (i.e., infusion #8), then weekly for the remainder of the 4-week follow-up period. As a quality-control step for the participant self-rated outcome and for diagnostic purposes, we will obtain CAPS-5 scores at baseline, at the end of treatment and at the end of follow-up to correlate with the PCL-5 findings. The index trauma identified at baseline will be evaluated for symptom changes over the course of the trial using trained and supervised masters- or doctoral-prepared independent evaluators and closely monitored procedures established by the Consortium.

*2.5.1. Secondary outcome measures*

The project will use the CAP Common Data Elements for the assessment of dependent measures to help ensure adequate assessment across multiple construct domains and to help maintain measurement consistency across CAP studies so that outcomes from various studies might be compared [24]. Additional study-specific measures will also be obtained. While a full list of study measures and assessment procedures is outlined in Table 1, secondary outcomes include: The Assessment of Rapid Affect Changes (ARAC), Montgomery-Åsberg Depression Rating Scale (MADRS) [25], Quick Inventory of Depressive Symptoms – Self-Report (QIDS-SR) [26], Patient Health Questionnaire-9 (PHQ-9) [27], the Generalized Anxiety Disorder 7-item scale (GAD-7) [28], Clinical Global Impression Scales (CGI) [29], the Systematic Assessment for Treatment Emergent Effects (SAFTEE) [30], Clinician-Administered Dissociative States Scale (CADSS) [31], Positive and Negative Symptom Scale (PANSS) [32], Insomnia Severity Index (ISI) [33], Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment short forms [34], Snoring, Tired, Observed, Blood Pressure (STOP) Sleep Apnea Screen [35], West Haven-Yale Multidimensional Pain Inventory (WHYMPI), 3-item numeric rating scale of pain severity, the Self-Injurious Thoughts and Behaviors Interview (SITBI) [36], Depressive Symptom Index – Suicidality Subscale (DSI-SS) [37], Veterans RAND 12-item Health Survey (VR-12) [38], Fagerstrorm Test for Nicotine Dependence (FTND) and Fagerstrorm Test for Nicotine Dependence – Smokeless Tobacco (FTND-ST) [39], Cogstate [40], and Quick Drinking Screen (QDS) [41].

*2.6. Clinical assessments*

Following informed consent, participants undergo the initial screening process, which involves a physical examination and health assessment (e.g., medical and psychiatric history), lab work, an electrocardiogram (ECG), and standardized psychiatric assessments. Each

**Table 1**
Timeline of study procedures.

| Assessment/procedure | Visit 1 | Visit 2 | Visit 3 | Visits 4–6; 8–10 | Visit 7 | Visit 11 | Visit 12 | Ol fu (post-8th INF/Vst 12.5) | Visits 13–15 | Visit 16 |
|---|---|---|---|---|---|---|---|---|---|---|
| | SCR | Infusion 1 | FU 1 | INF 2,3,4,6,7,8 | Infusion 5 | FU 2 | FU 3 - Optional visit open label (post-8th infusion) | OL FU | FUs 4–6 | FU 7 |
| | | Day 0 | Day 1 | Days 3, 7, 10, 17, 21, 24 | Day 14 | Day 25 | 28 | 29 | Day 35, 42, 49 | Day 56 |
| Adverse events | | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| AUDIT | X | | | | | | | | | |
| ARAC | | X (30, 120) | X | X (30, 120) | X (30, 120) | X | X (30, 120) | X | X | X |
| B-IPF | X | | X | | | X | | X | X | X |
| CGI | | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| CADSS | | X (30, 120) | | X (30, 120) | X (30, 120) | | X (30, 120) | | | |
| CAPS-5 | X | | | | | X | | | | X |
| Concom med Log | X | X | X | X | X | X | X | X | X | X |
| Demographics & military service | X | | | | | | | | | |
| DRRI-2 - combat experiences subscale | X | | | | | | | | | |
| DRRI-2 - aftermath of battle subscale | X | | | | | | | | | |
| DSI-SS | X | X | X | X | X | X | X | X | X | X |
| FTND | X | | X | | | X | | X | X | X |
| FTND-ST | X | | X | | | X | | X | X | X |
| GAD-7 | | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| Health interview | X | | | | | | | | | X |
| History of head injury (DVBIC) | X | | | | | | | | | X |
| Informed consent* | X | | | | | | | | | |
| Insomnia Severity Index | | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| Life Events Checklist for *DSM-5* | X | | | | | | | | | X |
| MGH-ATRQ | X | | | | | | | | | |
| MINI-7 | X | | | | | | | | | |
| MADRS - Full Scale | | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| MADRS - Item 10 Only | X | | | | | | | | | |
| Numerical rating scale for pain intensity | X | | X | | | X | | X | X | X |
| PHQ-9 | X | | | | | X | | | | X |
| PROMIS (Sleep) | X | | X | | | X | | X | X | X |
| PANSS | | X (30, 120) | | X (30, 120) | X (30, 120) | | X (30, 120) | | | |
| PCL-5 | X | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| PGI | | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| QDS | X | X | | | X | X | | | X (14 only) | X |
| QIDS-SR | X | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| SITBI | X | | | | | X | | | | X |
| STOP | X | | | | | | | | | |
| SAFTEE | X | X | X | X | X | X | X | X | X | X |
| VR-12 | X | | X | | | X | | X | X | X |
| WHYMPI | X | | X | | | X | | X | X | X |
| Cogstate | X | | X | | | X | | X | | X |
| Physical exam | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Routine lab tests | X | | | | | | | | | |
| Breathalyzer | X | X (PRE INF) | X | X (PRE INF) | X (PRE INF) | X | X (PRE INF) | X | X | X |
| Electrocardiogram (ECG) | X | | | | | | | | | |
| Serum pregnancy test | X | | | | | | | | | |
| Urine pregnancy test | | X (PRE INF) | | X (PRE INF) | X (PRE INF) | | X (PRE INF) | | | |

(*continued on next page*)

**Table 1** (*continued*)

| Assessment/procedure | Visit 1 | Visit 2 | Visit 3 | Visits 4-6; 8–10 | Visit 7 | Visit 11 | Visit 12 | Ol fu (post-8th INF/Vst 12.5) | Visits 13–15 | Visit 16 |
|---|---|---|---|---|---|---|---|---|---|---|
| | SCR | Infusion 1 | FU 1 | INF 2,3,4,6,7,8 | Infusion 5 | FU 2 | FU 3 - Optional visit open label (post-8th infusion) | OL FU | FUs 4–6 | FU 7 |
| | | Day 0 | Day 1 | Days 3, 7, 10, 17, 21, 24 | Day 14 | Day 25 | 28 | 29 | Day 35, 42, 49 | Day 56 |
| Blood collection/Banking (e.g., DNA, RNA, plasma, serum) | | X | X | | X | X | | | | X |
| Vital signs | X | X (PRE,10, 20, 40) | X | X (PRE,10, 20, 40) | X (PRE,10, 20, 40) | X | X (PRE,10, 20, 40) | X | X | X |
| Infusion | | X | | | X | | | | | |
| Open-label infusion | | | | | | | X | | | |
| Blinding form | | | | | | X | | | | |

Notes: *No study procedures will be completed prior to completion of the Informed Consent. The "Day" number is an approximation and the actual day may vary depending on delays in prior visits. *Abbreviations:* ARAC, Assessment of Rapid Affect Changes; AUDIT, Alcohol Use Disorders Identification Test; B-IPF, Brief Inventory of Psychosocial Function; CADSS, Clinician-Administered Dissociative States Scale; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; CGI, Clinical Global Impression Scales; CGI, Clinical Global Impression Scales; DNA, deoxyribonucleic acid; DRRI-2, Deployment Risk and Resilience Inventory-2; DSI-SS, Depressive Symptom Index – Suicidality Subscale; FTND, Fagerstrom Test for Nicotine Dependence; FTND-ST, Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco; FU, follow-up; GAD-7, Generalized Anxiety Disorder 7-item scale; INF, during infusion; MADRS, Montgomery-Asberg Depression Rating Scale; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment History Questionnaire; MINI, Mini-International Neuropsychiatric Interview; OL, open label; PANSS, Positive and Negative Symptom Scale; PCL-5, PTSD Checklist for *DSM-5*; PGI, Patient Global Impression; PHQ-9, Patient Health Questionnaire-9; PRE, pre-infusion; PROMIS, Patient-Reported Outcomes Measurement Information System; QDS, Quick Drinking Screen; QIDS-SR, Quick Inventory of Depressive Symptoms – Self-Report; RNA, ribonucleic acid; SAFTEE, Systematic Assessment for Treatment Emergent Effects; SCR, screening; SITBI, Self-Injurious Thoughts and Behaviors Interview; STOP, Snoring, Tired, Observed, Blood Pressure; VR-12, Veterans RAND 12-item Health Survey; WHYMP, West Haven-Yale Multidimensional Pain Inventory.

participant will complete a demographics form to elicit information about the participant's characteristics, such as education level, socio-economic status, race and ethnicity, military grade, deployment history and combat exposure. Participants undergo structured diagnostic interviews – the CAPS-5 and the Mini-international Neuropsychiatric Interview (MINI) 7.0 [42] by trained research personnel. Baseline and follow-up ratings are performed by trained masters- or doctorally prepared independent evaluators, who undergo a multi-step training process of both didactics and supervised interviews and whose performance is evaluated routinely in inter-rater reliability sessions. CAPS-5 interviews are audio-recorded, and these recordings are reviewed and assessed by the CAP Assessment Core. All study raters undergo extensive training; certification and regular calibration exercises under the direction of the CAP Assessment Core. Raters at each site must initially conduct interviews under observation by a trained diagnostician in a live interview session and meet agreement. All interviews are audiotaped to confirm ongoing inter-rater reliability and to correct for the potential of rater drift. Consensus discussions regarding difficult cases will be presented for consideration during scheduled conference calls attended by all CAP study independent evaluators. The primary investigator at each site supervises the administration of clinical measures at the site with oversight from the CAP Assessment Core.

### 2.7. Group assignment

Stratified block randomization is used to balance assignment by infusion center and comorbid alcohol use disorder and to decrease the chance of accidental unblinding. Blinded dose codes are sent to each of the site pharmacists, who will prepare the infusions so as to maintain the double blinding. Both ketamine and saline are odorless and colorless, and research staff and participants are not be able to discern between the placebo and active medication. Ketamine is be stored in the pharmacy according to the procedures for controlled substances, and any opened vials are discarded according to hospital policy. The study drug is prepared and dispensed by the research pharmacy. The participants are asked whether they have deduced their treatment arm at the end of treatment. Blinding is maintained throughout the study. The CAP Data Management and Biostatistics Core maintains the list of unblinded assignments for both sites. The research pharmacists will also each have a list of unblinded assignments for their site. Unblinded randomization codes are kept in a secure and locked area within each research pharmacy, where only pharmacy personnel have access. In the case of medical emergency, the blind may be broken by site-designated study personnel by calling the research pharmacist and following standard procedure for caller identification and research study identification.

### 2.8. Analysis plan

Descriptive statistics will be calculated prior to statistical analysis. Distributions of quantitative variables will be assessed for normality using normal probability plots, and Kolmogorov-Smirnov statistics and transformations or nonparametric methods will be used as necessary. All statistical tests will be two-sided. Uncorrected alpha level of 0.05 will be used for testing the primary hypothesis as described below. Pairwise post-hoc comparisons and tests of secondary outcome measures will be adjusted using Holm-Bonferroni procedure. All analyses will be intent-to-treat.

#### 2.8.1. Primary specific aim

The study's primary aim is to test the dose-related effects of ketamine on PTSD symptoms in veterans and active duty military population. We will follow our prior PTSD clinical trial [8] using mixed effects regression models, with group, time, and group by time effects for the primary outcome variable (PCL-5). We will stratify on study site and alcohol use comorbidity. Though the two study sites include different populations (i.e., primarily veterans at West Haven, and primarily

active duty service members in San Antonio), we do not expect to observe significant differences in treatment effects by study site. Nonetheless, we will test the interaction of treatment group and infusion center and perform follow-up analyses by site as necessary. Similarly, we do not expect significant moderating effects of alcohol use comorbidity but will assess the interaction between treatment and alcohol use comorbidity and perform follow-up tests as necessary. This approach will be applied to most secondary outcome measures as well. Mixed effects regression models use all available data on each participant, are flexible in modeling the correlation structure of the data, and give unbiased results under missing data at random assumptions. We will select the best-fitting correlation structure for the primary and each secondary outcome based on Schwartz-Bayesian Information Criterion. Time will be considered as a categorical predictor and post-hoc tests between groups will be conducted for the change from baseline to end-point, which is of primary interest. To assess the trajectory of ketamine effects over time, we will test for linear, quadratic and higher order time trend differences. Post-hoc tests will also be performed to assess whether dose effects are linear. Change in PTSD symptoms is expected to be the largest for the higher-dose ketamine group. However, it is possible that the change in the higher-dose ketamine group is not significantly different from the change in the lower-dose ketamine group. Thus, we will also estimate effect sizes with confidence intervals for the change from baseline to end-point in each group and use this information together with safety data to inform dose selection for potential future studies of ketamine efficacy and evaluation of mechanism of action in PTSD.

In addition to testing the potential moderating effect of comorbid alcohol use described above, we will also perform exploratory analyses to assess moderating effects of depression, medication status, substance abuse, age, and gender by adding these factors one at a time to the models above and testing interactions between each potential moderator and treatment group. We will follow the approach of Kraemer et al. for testing moderator effects [43]. Dropout rates will be compared across groups, and sensitivity analyses using pattern-mixture models will be performed if there are disproportionate dropout rates in the treatment arms of this trial or concerns that the data are not missing at random. Effects of intermittent missing data due to noncompliance with treatment schedule can also be assessed using these models.

#### 2.8.2. Exploratory aim 2

Our second aim is to evaluate the safety of repeated ketamine exposure. Changes in psychotic (PANSS), dissociative (CADSS) and cognitive symptoms (Cogstate) across time between groups will be assessed using mixed effects regression models, with group as between-participant factor and time as a within-participant factor as described in the primary specific aim. We anticipate significant differences between ketamine and placebo during infusions but no significant between-group differences at discharge and at the 2-week and 1-month follow-up. Descriptive statistics will be calculated to summarize types and rates of reported Adverse Events between groups. Rates of adverse events will be compared using Fisher's exact tests since numbers of adverse events per arm may be small. Exact logistic regression analyses will be used to assess effects of additional, potentially confounding covariates on adverse events if possible (i.e., if sufficient numbers of adverse events are present in the sample to allow for such analysis).

#### 2.8.3. Exploratory aim 3

To assess the durability of ketamine effects on PCL-5, we will use mixed effects regression models in the participants who responded to the study drug by the end of the double-blind treatment. Week post-treatment will be a within-participant factor and the treatment group a between-participant factor in this analysis, and we will covary for severity at the end of treatment. We will perform pairwise comparisons over time to determine if participants maintain improvements on ketamine during the 4-week follow-up.

#### 2.8.4. Exploratory aim 4

To test the clinical significance of PCL-5 changes, we will perform secondary mixed model analyses on CAPS-5, CGI, VR-12, PROMIS, WHYMPI, and the Numerical Rating Scale for Pain Intensity [44], using the same approach as described in Aim 1.

#### 2.8.5. Exploratory aim 5

To test the integrity of the blind, we will use chi-square tests and ANOVA models to compare the accuracy and level of confidence in the guessed treatment assignment between groups.

## 3. Discussion

To date, only one randomized study evaluating the effectiveness of a single infusion of ketamine (one dose, 0.5 mg/kg) has been studied in 22 PTSD patients in comparison to 19 PTSD patients who received midazolam [14]. Recently, a small open label study reported reduced PTSD symptoms for repeated infusion of 0.5 mg/kg ketamine in 15 veterans with comorbid depression and PTSD [45]. The present study builds upon the pilot data from prior studies to provide more definitive results in a larger sample and to address some of their limitations, including: (1) *Sample size* – The proposed study is much larger and likely to yield definitive results; (2) *Dose* – The proposed study would compare two doses of ketamine (0.2 mg/kg, 0.5 mg/kg); (3) *Inactive comparator* – This study would incorporate the FDA standard placebo as a reference for evaluating ketamine effect; (4) *Study population* – The prior study was conducted in a civilian population or veterans, while this study will recruit both veterans and active duty personnel; and (5) *Number of ketamine infusions* –This study involves 8 ketamine infusions over 4 weeks followed by a 4-week follow-up, making this trial the length of many standard PTSD studies. Thus, the success of this ongoing study should be a critical bridge between the initial observation in PTSD and the development of NMDA receptor antagonist administration as a treatment for PTSD. A significant result ($p \leq 0.05$, two-tailed) for the primary analysis would serve as the basis for a “go decision” and continued research and development of ketamine as a viable treatment alternative for PTSD. It would also justify the exploration of more highly experimental subtypes and selective NMDA receptor antagonists (e.g., ifenprodil, Glyx-13, AZD-6765, CP101, 606, etc.) for the treatment of PTSD.

## Funding

This research was supported by Consortium to Alleviate PTSD (CAP) award numbers W81XWH-13-2-0065 from the U.S. Department of Defense, Defense Health Program, Psychological Health and Traumatic Brain Injury Research Program (PH/TBI RP), and I01CX001136–01 from the U.S. Department of Veterans Affairs, Office of Research & Development, Clinical Science Research & Development Service. Additional support funding was provided by the VA National Center for PTSD.

## Role of the funding source

The funding sources have had no involvement in the study design, the collection, analysis and interpretation of data, the writing of this report, or the decision to submit this article for publication.

## Disclaimer

The views expressed herein are solely those of the authors and do not reflect an endorsement by or the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, the Department of Defense, the Department of Veterans Affairs, the National Institutes of Health, or the U.S. Government.

## Additional contributions

The authors would like to thank the individuals who are participating in this study for their invaluable contribution. The West Haven site would also like to thank the Emerge Research Program staff and the nurses and lab staff of the Biostudies Unit for the invaluable expertise in conducting this trial and support for its ongoing success.

## Conflict of interest

CGA has served as a consultant and/or on advisory boards for Genentech and Janssen, and editor of *Chronic Stress* for Sage Publications, Inc.; Filed a patent for using mTOR inhibitors to augment the effects of antidepressants (filed on Aug 20, 2018). JHK is a consultant for AbbVie, Inc., Amgen, Astellas Pharma Global Development, Inc., AstraZeneca Pharmaceuticals, Biomedisyn Corporation, Bristol-Myers Squibb, Eli Lilly and Company, Euthymics Bioscience, Inc., Neurovance, Inc., FORUM Pharmaceuticals, Janssen Research & Development, Lundbeck Research USA, Novartis Pharma AG, Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Inc., Sunovion Pharmaceuticals, Inc., and Takeda Industries; is on the Scientific Advisory Board for Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Inc., Naurex, Inc., and Pfizer; is a stockholder in Biohaven Pharmaceuticals; holds stock options in Mnemosyne Pharmaceuticals, Inc.; holds patents for Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia, U.S. Patent No. 5,447,948 (issued Sep 5, 1995), and Glutamate Modulating Agents in the Treatment of Mental Disorders, U.S. Patent No. 8,778,979 (issued Jul 15, 2014); and filed a patent for Intranasal Administration of Ketamine to Treat Depression. U.S. Application No. 14/197,767 (filed on Mar 5, 2014); U.S. application or Patent Cooperation Treaty international application No. 14/306,382 (filed on Jun 17, 2014). Filed a patent for using mTOR inhibitors to augment the effects of antidepressants (filed on Aug 20, 2018). All other co-authors declare no conflict of interest.

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