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ARTICLE

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Dose-related effects of ketamine for antidepressant-resistant symptoms of posttraumatic stress disorder in veterans and active duty military: a double-blind, randomized, placebo-controlled multi-center clinical trial

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This study tested the efficacy of repeated intravenous ketamine doses to reduce symptoms of posttraumatic stress disorder (PTSD). Veterans and service members with PTSD ($n = 158$) who failed previous antidepressant treatment were randomized to 8 infusions administered twice weekly of intravenous placebo ($n = 54$), low dose (0.2 mg/kg; $n = 53$) or standard dose (0.5 mg/kg; $n = 51$) ketamine. Participants were assessed at baseline, during treatment, and for 4 weeks after their last infusion. Primary analyses used mixed effects models. The primary outcome measure was the self-report PTSD Checklist for *DSM-5* (PCL-5), and secondary outcome measures were the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) and the Montgomery Åsberg Depression Rating Scale (MADRS). There were no significant group-by-time interactions for PTSD symptoms measured by the PCL-5 or CAPS-5. The standard ketamine dose ameliorated depression measured by the MADRS significantly more than placebo. Ketamine produced dose-related dissociative and psychotomimetic effects, which returned to baseline within 2 h and were less pronounced with repeated administration. There was no evidence of differential treatment discontinuation by ketamine dose, consistent with good tolerability. This clinical trial failed to find a significant dose-related effect of ketamine on PTSD symptoms. Secondary analyses suggested that the standard dose exerted rapid antidepressant effects. Further studies are needed to determine the role of ketamine in PTSD treatment. ClinicalTrials.gov identifier: NCT02655692.

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a debilitating illness with limited pharmacotherapy options [1–3]. Patients are often treated with monoaminergic antidepressants and off-label combinations of other pharmacotherapies, most of which have inadequate evidence for efficacy in PTSD treatment [4, 5]. Moreover, meta-analytic studies show only small differences between pharmacotherapy and placebo [6], particularly in Veterans suffering from PTSD [7].

Ketamine, an antagonist of N-methyl-D-aspartate (NMDA) glutamate receptors, is a rapid-acting antidepressant with a novel mechanism of action [8, 9]. In a primarily civilian sample, a pioneering proof-of-concept study ($n = 41$) showed rapid reduction in PTSD and depression symptoms 24 h post a single standard ketamine dose (0.5 mg/kg intravenously over 40 min) compared to midazolam [10]. The standard ketamine dose administered 3 times per week for 2 weeks also was recently reported to significantly

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reduce PTSD symptoms compared to midazolam in a randomized controlled pilot study ($n = 30$) [11]. In addition, an uncontrolled, open label study ($n = 15$) in subjects with comorbid PTSD and major depressive disorder (MDD) reported reductions in both PTSD and MDD symptoms following treatment with 6 standard ketamine intravenous infusions over a 2-week period [12]. But another open-label study ($n = 10$) in individuals with comorbid PTSD and MDD found no significant effects on PTSD symptoms 24 h following single standard ketamine infusion [13]. Moreover, a randomized controlled clinical trial ($n = 40$) found no significant effects of a single standard infusion of ketamine compared to midazolam in 4 groups of individuals with comorbid PTSD and/or chronic pain [14]. Together, previous studies suggest the potential utility of ketamine in treating PTSD symptoms. However, the evidence is mixed and, to date, only the standard dose (0.5 mg/kg) ketamine has been tested. These findings underscore the need for larger, and more definitive, placebo-controlled trials to determine the efficacy of ketamine in treating PTSD symptoms.

This study investigated the efficacy of ketamine in a double-blind, randomized, 3-arm, controlled clinical trial in Veterans and active duty service members with PTSD symptoms [15]. Though previous studies had used midazolam as an "active" control comparison [10, 11], benzodiazepines may actually worsen PTSD outcomes [16] and thus, we used placebo as the control condition. Our design used 0.5 mg/kg as the "standard" dose of ketamine, but we also explored the use of a low dose of ketamine (0.2 mg/kg), knowing that it could serve as an "active control" if it was not efficacious itself [17, 18]. Considering that the effects of ketamine are short-lived following a single infusion [10], secondary hypotheses tested the efficacy and durability of repeated ketamine dosing. At the time the study was designed, the evidence suggested that the rapid acting antidepressant ketamine administered twice per week is comparable to 3 times per week [19]. Hence, participants received study drug twice weekly for a total of 8 infusions. Considering that the dissociative symptoms of ketamine are dose dependent, we anticipated that the low dose ketamine will enhance the functional blinding. Although our primary hypotheses focused on PTSD symptoms, we also evaluated the efficacy of ketamine against the depressive symptoms that are highly comorbid in the study population [20]. Finally, we evaluated possible dissociative and psychotomimetic effects of ketamine as well as other adverse events to determine the safety of repeated ketamine dosing in patients with PTSD whose illness itself may be characterized by dissociative pathology [21].

We hypothesized that a standard dose of ketamine would exert a rapid reduction in PTSD symptoms, and that repeated dosing would: (1) maintain this therapeutic benefit through the end of treatment; and (2) during the 4-week follow-up period.

METHODS

Study design

Full details of the study methods were previously reported [15]. Briefly, this double-blind, randomized, controlled trial enrolled Veterans and active duty service members with PTSD symptoms from three centers. It was supported jointly by the US Department of Defense and the US Department of Veterans Affairs as part of the Consortium to Alleviate PTSD (CAP). All study procedures were approved and monitored by an Institutional Review Board at each study site as well as the CAP Data and Safety Monitoring Board and the US Army Medical Research and Development Command Human Research Protection Office. All participants provided written informed consent prior to enrollment. ClinicalTrials.gov identifier: NCT02655692.

Between September 2016 and March 2020, participants were randomized to three parallel study arms: (1) Placebo (normal saline); (2) Low dose (ketamine 0.2 mg/kg); and (3) Standard dose (ketamine 0.5 mg/kg). Eight 40-min intravenous infusions of the study drug were administered twice weekly. Participants were followed weekly for 4 weeks after the last infusion. Self-reported PTSD Checklist for *DSM-5* (PCL-5) assessed PTSD symptoms as the primary outcome and clinician-administered Montgomery-Åsberg Depression Rating Scale (MADRS) assessed depressive symptoms as a secondary outcome prior to each infusion, at 24 h post-first and post-last infusions, and weekly during follow-up. PCL-5 was used as primary outcome to capture the rapid effects of ketamine post each infusion [15]. The Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) was used to confirm the PTSD diagnosis and to assess baseline symptom severity, and as a secondary outcome at the end of treatment and the end of follow-up. At 30 and 120 min after beginning each study drug infusion, secondary analyses assessed dissociative and psychotomimetic effects of ketamine with the Clinician-Administered Dissociative State Scale (CADSS) and the Positive and Negative Syndrome Scale (PANSS), respectively. Finally, at the end of treatment, participants were asked to guess which study drug they received and how confident they were in their guess.

To mitigate against expectations of possible denial of care for a placebo-controlled trial, participants who did not respond to double-blind medication were offered a single administration of open label, standard dose ketamine, but their follow-up data were not included in the durability of effect analyses. Response was defined as at least 25% improvement in CAPS-5 scores following treatment as compared to baseline [15]. We targeted $n = 198$ subjects randomized, but COVID-19 pandemic-related restrictions forced the study to close prematurely.

Study criteria

The study enrolled Veterans and service members between the age of 18 and 70 years [15]. Participants met the following criteria: (1) were diagnosed with PTSD based on the structured CAPS-5 interview; (2) had CAPS-5 score of 23 or higher (i.e., moderate to severe); (3) had a history of nonresponse to at least 1 adequate trial of FDA approved (for PTSD or depression) antidepressant, as determined by the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ); (4) were unmedicated or were stable on an antidepressant for at least 4 weeks or PTSD-focused psychotherapy for at least 6 weeks; (5) if female, were not pregnant or breastfeeding and were on a medically acceptable contraceptive method; (6) were able to read, write, and provide written informed consent in English; (7) did not have psychotic disorder or features, or manic or mixed episodes; (8) did not have an unstable medical condition; (9) had no suicidal or homicidal risk meriting crisis intervention; (10) had no severe brain injury; (11) had no moderate or severe substance use disorder within 3 months – except for mild-moderate alcohol use disorder with negative breathalyzer; (12) were not currently using monoamine oxidase inhibitors, memantine, or long-acting benzodiazepines and had no known sensitivity to ketamine; and (13) had resting blood pressure higher than 90/60 and lower than 150/90 mmHg, and heart rate higher than 45/min and lower than 100/min.

Statistics

Power calculation and analysis plans were previously reported [15] and are further detailed in the online Supplementary Information. Briefly, the PCL-5 was considered the primary outcome, while CAPS-5 and MADRS were considered secondary measures. The primary analysis used mixed effects models, with dose (3-levels), time (8 infusions), and dose-by-time interactions with efficacy determination evidenced as a dose-by-time interaction. The secondary analyses examined the rapid and sustained effects of ketamine compared to placebo, at 24 h post-first and post-last infusion, respectively, by focused contrasts in the mixed models adjusted for multiple comparison. Sustainability of the effects of ketamine on PTSD symptoms was assessed with similar mixed models for PCL-5 and CAPS-5 during the follow-up period; considering that this analysis included only the responders (non-responders received open label ketamine). However, there was no difference in pretreatment severity and the results are similar without covarying for severity. The dissociative and psychotomimetic effects were examined using comparable mixed models for CADSS and PANSS, while adding interval (30 min vs. 120 min) and appropriate interactions to the models.

RESULTS

A total of 262 individuals were consented and assessed for eligibility. Of these individuals, 158 were found eligible, randomized, began

Table 1. Demographics and Clinical Characteristics.

	Standard Dose $n = 51$ 0.5 mg/kg	Low Dose $n = 53$ 0.2 mg/kg	Placebo $n = 54$ placebo	*p* value
Sex – male (%)	38 (74.5)	43 (81.1)	40 (74.1)	0.63
Mean age (SD)	43.2 (12.7)	45.2 (11.2)	42.0 (10.8)	0.37
White - Non-Hispanic	29 (56.9)	28 (52.8)	37 (68.5)	0.57
Black	7 (13.7)	7 (13.2)	6 (11.1)	
Hispanic	12 (23.5)	11 (20.8)	8 (14.8)	
Other	3 (5.9)	7 (13.2)	3 (5.6)	
<12th grade, high school	6 (11.8)	5 (9.4)	7 (13.0)	0.66
Some college	20 (39.2)	17 (32.1)	15 (27.8)	
College degree	21 (41.2)	25 (47.2)	22 (40.7)	
Some graduate	4 (7.8)	6 (11.3)	10 (18.5)	
Duty Status - Veteran	34 (66.7)	36 (67.9)	37 (68.5)	0.98
Active duty	17 (33.3)	17 (32.1)	17 (31.5)	
Army	29 (56.9)	32 (60.4)	33 (61.1)	0.59
Navy	8 (15.7)	10 (18.9)	10 (18.5)	
Air Force	4 (7.8)	6 (11.3)	7 (13.0)	
Marine	10 (19.6)	5 (9.4)	4 (7.4)	
# Deployments				
0	19 (37.3)	20 (37.7)	17 (31.5)	0.12
1	15 (29.4)	7 (13.2)	11 (20.4)	
2	14 (27.5)	13 (24.5)	13 (24.1)	
3+	3 (5.9)	13 (24.5)	13 (24.1)	
Years military service	11.2 (7.5)	12.0 (8.6)	10.9 (8.3)	0.77
PCL-5	47.5 (14.5)	46.6 (17.7)	48.6 (12.8)	0.80
CAPS-5	38.5 (8.4)	40.4 (9.1)	38.8 (8.0)	0.38
MADRS	27.8 (9.3)	27.8 (10.3)	28.2 (8.4)	0.97

PCL-5 PTSD checklist for *DSM-5*, *CAPS-5* clinician-administered PTSD scale for *DSM-5*, *MADRS* Montgomery-Åsberg depression rating scale.

treatment, and included in the study analysis. The CONSORT flow diagram is provided in the Supplement. Among the randomized groups, discontinuation rates were similar (placebo: 19%, low: 15%, standard: 16%; $\chi^2(2) = 0.3$, $p = 0.88$). Demographics of the randomized participants are provided in Table 1 and there were no group differences. Participants had moderate to severe symptoms of PTSD and depression. The majority of participants (156/158; 99%) met criteria of current major depressive episode.

Effects of ketamine on primary outcome

The primary analysis on the PCL-5 scores (Fig. 1A) found no significant effect of treatment ($F_{(2,148)} = 1.8$, $p = 0.17$). There was a significant time effect ($F_{(9,133)} = 37.1$, $p < 0.0001$) but no treatment-by-time interaction ($F_{(18,137)} = 1.1$, $p = 0.38$), indicating that PCL-5 scores improved over time for all treatment groups (Table 2). A priori planned between groups secondary analyses found no significant reduction in PCL-5 score 24 h after the first standard dose [mean difference (±SEM) from placebo = 6.6 (±3.1), t(149) = 2.1, $p = 0.04$, adj. $p = 0.11$] and at the end of treatment [mean difference (±SEM) = 5.0 (±3.4), t(147) = 1.5, $p = 0.14$, adj. $p = 0.28$] compared to placebo. Similarly, the low dose compared to placebo was not significantly different after the first infusion [mean difference (±SEM) = 3.3 (±3.1), t(149) = 0.3, $p = 0.29$, adj. $p = 0.57$] and at the end of treatment [mean difference (±SEM) = 6.4 (±3.3), t(147) = 2.0, $p = 0.05$, adj. $p = 0.16$]. There were no differences between standard and low doses of ketamine ($p > 0.2$, adj. $p > 0.5$). Additional exploratory analyses and assessment of blinding can be found in the Supplements.

Responder analysis

The percentage of responders showing ≥25% improvement in PCL-5 [15] (Fig. 2) at 24 h post-first infusion is higher in the two active groups (47% on ketamine standard dose, 47% on ketamine low dose) than in the placebo group (33% on placebo), but the difference in proportions was not significant (Chi-sq(2) = 5.0, $p = 0.08$) (Fig. 2). The odds of reaching responder status with this first dose were more than 80% higher on active treatment than on placebo [OR = 1.88, 95% CI: (0.84, 4.22) for standard dose vs. placebo, OR = 1.82, 95% CI: (0.82, 4.05) for low dose vs. placebo], though the odds did not achieve statistical significance. Examining the 4 sub-scores of the PCL-5 (i.e., reexperiencing, etc.) yielded comparable results to total PCL-5 scores and treatment-by-time interaction $p > 0.05$).

Effects of ketamine on secondary outcomes

The CAPS-5 scores showed a time effect ($F_{(1,124)} = 103.4$, $p < 0.0001$) but no treatment main effect ($F_{(2,145)} = 0.8$, $p = 0.46$) and no treatment-by-time interaction ($F_{(2,124)} = 2.7$, $p = 0.07$; Fig. 1B). Compared to placebo, individual contrasts showed no significant reductions for the CAPS-5 in the ketamine low dose [mean difference (±SEM) = 6.0 (±2.7), t(124) = 2.2, $p = 0.03$, adj. $p = 0.09$], or the ketamine standard dose group [mean difference (±SEM) = 4.7 (±2.8), t(124) = 1.7, $p = 0.09$, adj. $p = 0.18$]. There were no differences between standard and low doses of ketamine ($p = 0.65$, adj. $p = 0.65$).

In contrast, ketamine had significant dose-related effects on depression symptoms. In the analysis of MADRS data, the mixed

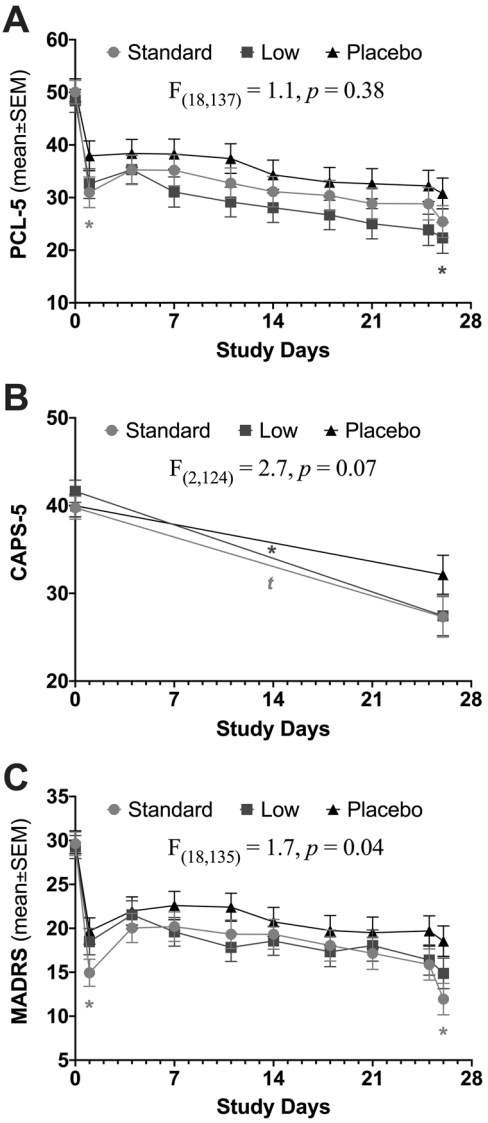

Fig. 1 The effects of ketamine on posttraumatic stress disorder (PTSD) and depression symptoms. A The PTSD Checklist for *DSM-5* (PCL-5) scores were significantly reduced over the treatment period but did not differ between the treatment groups. Secondary analysis showed reduction in PCL-5 following standard dose ketamine compared to placebo at 24 h post first infusion (red * on Day 1, $p = 0.04$, adj. $p = 0.11$). There was also significant reduction in PCL-5 at 24 h post last infusion in low dose ketamine compared to placebo (blue * on Day 26, $p = 0.05$, adj. $p = 0.16$). **B** There was a non-significant effect of ketamine on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), reflecting reduction in CAPS-5 in the low dose (blue *, $p = 0.03$, adj. $p = 0.09$) and in the standard dose (red t, $p = 0.09$, adj. $p = 0.18$) over the treatment period compared to placebo. **C** The Montgomery-Åsberg Depression Rating Scale (MADRS) scores were significantly reduced over the treatment period. This MADRS reduction differed between the treatment groups. There was significant improvement in depression symptoms at 24 h and end of treatment in the standard dose ketamine compared to placebo (red * on Day 1 and 26, $p \leq 0.05$, adj. $p \leq 0.05$). There was no significant improvement in depression symptoms following low dose ketamine compared to placebo. Notes: Assessments collected prior to each study drug infusion, except on Day 1 and Day 25, which were collected 24 h post-first and post-last infusions, respectively.

model showed a significant treatment-by-time interaction ($F_{(18,135)} = 1.7$, $p = 0.04$, Fig. 1C) and a time effect ($F_{(9,133)} = 35.0$, $p < 0.0001$) but no treatment main effect ($F_{(2,150)} = 1.3$, $p = 0.28$). Individual contrasts showed rapid reduction in MADRS at 24 h post-first infusion for the standard ketamine dose group [standard vs. placebo mean difference (±SEM) = 4.6 (±1.9), t(148) = 2.5, $p = 0.02$, adj. $p = 0.05$] but not for the low ketamine dose ($p > 0.1$, adj. $p > 0.2$). The standard dose was different from the low dose [mean difference (±SEM) = 3.9 (±1.9), t(149) = 2.1, $p = 0.04$, adj. $p = 0.08$], however, this finding did not survive correction for multiple comparisons. At the end of treatment, ketamine effects were significantly superior to placebo for MADRS reduction by the standard dose [mean difference from placebo (±SEM) = 6.4 (±2.2), t(140) = 2.9, $p = 0.004$, adj. $p = 0.01$)], but not for the low ketamine dose ($p = 0.15$, adj. $p = 0.27$) or compared to the low dose group [mean difference (±SEM) = 3.3 (±2.2), t(141) = 1.5, $p = 0.14$, adj. $p = 0.27$].

Durability of the ketamine effects

After the end of the 4-week treatment period, participants in the standard dose ($n = 13$; 25%), low dose ($n = 18$; 34%), and placebo groups ($n = 25$; 46%) with <25% improvement on the CAPS-5 were considered nonresponders [15] and were offered open-label, standard dose ketamine. Excluding those with open-label dosing, mixed model analysis for durability of effects (data not shown) in participants over the 4 weeks posttreatment also showed significant time effects ($F_{(3,68)} = 6.5$, $p < 0.001$) but no treatment main effect ($F_{(2,68)} = 2.3$, $p = 0.11$) or treatment-by-time interactive effect on the PCL-5 scores ($F_{(6,68)} = 2.0$, $p = 0.08$). At the end of 4 weeks of follow-up, PCL-5 scores were significantly lower in the ketamine low dose compared to placebo [mean difference (±SEM) = 15.3 (±5.8), t(68) = 2.6, $p = 0.01$, adj. $p = 0.03$] but not compared to the standard dose group [mean difference (±SEM) = 9.8 (±4.8), t(68) = 2.0, $p = 0.05$, adj. $p = 0.09$]. There were no differences between placebo and ketamine standard dose ($p = 0.34$, adj. $p = 0.34$).

Examining the durability of ketamine effects on CAPS-5 scores, the mixed model showed a time effect ($F_{(2,71)} = 54.7$, $p < 0.0001$) but no treatment ($F_{(2,127)} = 1.4$, $p = 0.26$) or treatment*time effects ($F_{(4,70)} = 1.9$, $p = 0.13$). At 4 weeks posttreatment, CAPS-5 scores were non-significantly reduced in the ketamine low dose compared to the placebo [mean difference (±SEM) = 8.4 (±3.7), t(65) = 2.2, $p = 0.03$, adj. $p = 0.09$] and the standard dose group [mean difference (±SEM) = 2.7 (±3.4), t(63.7) = 0.8, $p = 0.43$, adj. $p = 0.43$]. The CAPS-5 reduction in the ketamine standard dose was not significant compared to placebo [mean difference (±SEM) = 5.7 (±3.7), t(64.9) = 1.6, $p = 0.13$, adj. $p = 0.25$]. Similarly, there was a main effect of time on MADRS ($F_{(3,70)} = 5.8$, $p = 0.001$), but no treatment ($F_{(2,70)} = 1.3$, $p = 0.29$) or treatment*time effects ($F_{(6,70)} = 0.8$, $p = 0.55$). Individual contrasts at 4 weeks posttreatment, found non-significant lower MADRS scores in the ketamine low dose compared to placebo [mean difference (±SEM) = 7.9 (±3.5), t(70) = 2.3, $p = 0.03$, adj. $p = 0.08$], and no differences between other groups ($p = 0.48$, adj. $p = 0.48$).

Adverse effects of ketamine

Examining dissociative effects of ketamine as measured by CADSS, the mixed model analysis showed significant effect of treatment ($F_{(2,147)} = 20.2$, $p < 0.0001$), with dose-dependent ketamine-induced dissociative symptoms (Fig. 3A). As expected, there was a significant treatment by interval (i.e., during vs. post) interaction ($F_{(2,803)} = 102.1$, $p < 0.0001$), with the ketamine-induced dissociative symptoms observed during treatment dissipating 80 minutes after the 40-min infusion was complete (Fig. 3A). We also found time effects on CADSS ($F_{(7,133)} = 8.6$, $p < 0.0001$), with a reduction of dissociative symptoms observed over the 8-infusion treatment period (Fig. 3B).

Table 2. Treatment effect sizes (Cohen d').

	Rapid 24 h post first infusion	End of Treatment 24 h post last infusion	Follow-up 4 weeks post last infusion
PCL-5			
Placebo	0.75	1.13	1.01
Ketamine 0.2 mg/kg	0.93	1.53	1.31
Ketamine 0.5 mg/kg	0.96	1.61	0.89
CAPS-5			
Placebo		0.66	1.01
Ketamine 0.2 mg/kg		1.01	1.68
Ketamine 0.5 mg/kg		1.15	1.41
MADRS			
Placebo	1.25	1.14	0.89
Ketamine 0.2 mg/kg	1.06	1.35	1.06
Ketamine 0.5 mg/kg	1.53	1.81	0.82

PCL-5 PTSD checklist for *DSM-5*, *CAPS-5* clinician-administered PTSD Scale for *DSM-5*, *MADRS* Montgomery Åsberg depression rating scale.

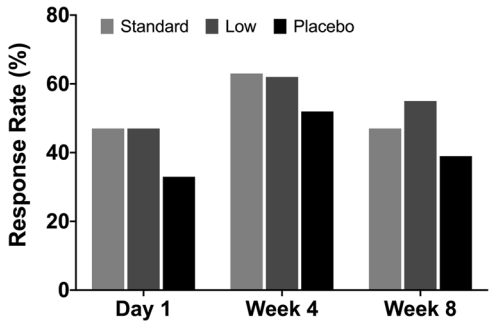

Fig. 2 The response rate during and following treatment. There was no significant difference in response rate (i.e., 25% or more improvement in the PTSD Checklist for *DSM-5* (PCL-5) scores) at 24 h post first infusion (Day 1), 24 h post last infusion (Week 4), and at the end of 4 weeks of follow-ups (Week 8).

Examination of the psychotomimetic effects using the PANSS showed results comparable to the CADSS findings, with significant treatment*interval interactive effects ($F_{(2,148)} = 13.9$, $p < 0.0001$; Fig. 3C). There was also significant time effect ($F_{(7,128)} = 5.1$, $p < 0.0001$; Fig. 3D), but no effect of treatment ($F_{(2,148)} = 1.2$, $p = 0.3$). Follow-up analyses showed ketamine-induced psychotomimetic symptoms observed during infusion significantly improved by 120 min.

The majority of participants ($n = 137$, 87%) reported at least one adverse event (AE), with a total of 402 AEs during the study. Of the 402 AEs, 273 occurred during the treatment infusion period, and 162 of them were considered at least "possibly" related to treatment. There were 13 treatment-related AEs that occurred in >2 participants, and those are displayed in the Supplementary Table S1. AEs most likely associated with one of the active ketamine doses were agitation, anxiety, irritability, and constipation, which occurred infrequently in the ketamine groups and not at all in the placebo group. Notably, nightmare occurrence was comparable across groups, while headache was more common in the low dose ketamine group. Nausea or other gastrointestinal disturbance occurred equally frequently in all groups including placebo.

DISCUSSION

This randomized, controlled trial was the largest sample and longest treatment duration for ketamine studied to date to treat PTSD symptoms in Veterans, and the only one to treat active duty military. The study found that 4 weeks of twice-weekly ketamine infusions failed to demonstrate significant efficacy on PTSD symptoms in a priori planned comparisons to placebo in this population of Veterans and service members. This was true despite observing significant antidepressant effects of ketamine in these patients who had considerable depressive symptoms at baseline. To address comorbid depression in PTSD, our secondary analyses showed significant superiority of the standard Ketamine dose over placebo to reduce depressive symptoms measured by the MADRS. Beneficial effects of the standard dose were seen acutely after the first standard dose and at the end of treatment, but these effects were not sustained during the 4 weeks of post-treatment follow-up.

Depression symptoms, which were substantial in the current cohort, are commonly associated with PTSD, and have been reported to respond relatively poorly to traditional antidepressants. For example, in the VAST-D study, depressed patients with PTSD had poorer overall outcomes than depressed patients without PTSD [22]. In the current study, ketamine showed significant effect in the mixed model and in the secondary analyses, reflecting rapid antidepressant effects on Day 1 and at the end of treatment in the standard dose group. Consistent with the depression literature [17, 18], the low dose ketamine had no rapid antidepressant effect during treatment. However, at the end of the 4-week follow-up, participants in the low dose group were found to have reduced depressive symptoms compared to placebo, suggesting a possible cumulative effect of repeated low doses on depression.

The current study does not support the pilot findings by Feder and colleagues [11], which reported significant effects of standard dose ketamine on PTSD symptoms. Several differences between the trials may have contributed to the differing results. Our study was in military population, while the previous report was primarily in civilians. Notably, previous trials indicated low treatment response in military population suffering from PTSD [7]. Furthermore, our participants were mostly males with only 23% females compared to the previous study with 77% females. The sex differences may have played a role in the differing outcomes. Considering the low number of females per group, we were not able to statistically assess the effect of sex in our cohort. Other differences in the previous study [11] compared to the current trial, include: (1) smaller cohort of 15 subjects per group, (2) using benzodiazepine as control, (3) no low dose arm, (4) administering the study drugs 3 times per week, (5) treatment was for 2 weeks,

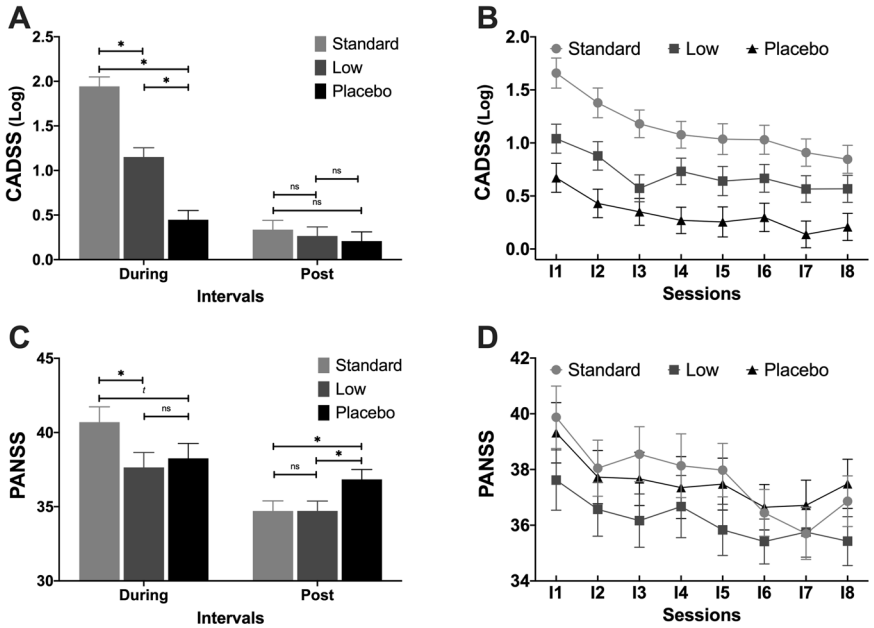

Fig. 3 The dissociative and psychotomimetic effects of ketamine treatment in patients with posttraumatic stress disorder (PTSD). A There was a dose-dependent, ketamine-induced increase in the Clinician-Administered Dissociative State Scale (CADSS) scores at 30 min from the start of the infusion (During). This ketamine-induced dissociation symptoms returned to placebo levels at the 120 min time point (Post). **B** There was a significant time effect on CADSS scores, indicating reduction in the dissociative symptoms with repeated treatment, from the first (I1) to last infusion (I8). **C** The standard dose induced increase in the Positive and Negative Syndrome Scale (PANSS) scores at 30 min from the start of the infusion (During). This ketamine-induced psychotomimetic effect improved at the 120 min time point (Post). **D** There was a significant time effect on PANSS scores, indicating reduction in the psychotomimetic symptoms with repeated treatment, from the first (I1) to last infusion (I8). Abbreviations: ns indicates $p > 0.10$; *t* indicates $p < 0.10$ * indicates $p < 0.05$; Standard = ketamine 0.5 mg/kg; Low = ketamine 0.2 mg/kg.

and (6) the previous study did not require history of nonresponse to an antidepressant. Notably, the previous study found no rapid effects of ketamine on PTSD or depression symptoms at 24 h post first infusion [11]. This could be due to the small sample size but it also underscores the challenges of demonstrating the therapeutic effects of standard dose ketamine in PTSD patients [13, 14].

A major challenge in ketamine research is the potential for functional unblinding due to the distinguishing acute dissociative effects of ketamine [23]. Concerns relate to functional unblinding that may lead to negative outcome expectations from placebo exaggerating differences from the study drug. Midazolam, has been used as a putative "active control" in ketamine studies [24]. However, the potential negative effects of benzodiazepine on PTSD are previously documented and may actually exacerbate drug vs. control differences in PTSD treatment studies [16]. Very large pre to post improvements in the current study (even within the placebo group), coupled with no differential dropout, suggest that expectations were not negative in our placebo-treated participants. In the current study, blinding assessment (see Supplements & Table S2) showed the majority of participants supposed they were on low dose ketamine and even within the placebo group, this number was 35%. Only 37% of participants in the standard dose correctly guessed their high dose assignment. The most common reason identified to be the basis for their guess of dose assignment was participant's perception of effects during the infusion – which produced only moderate proportions of participants being "reasonably sure" in that guess. Together, these data suggest that the use of low dose ketamine in a 2:1 design randomization to ketamine may have enhanced participant's expectation of benefit. The effect sizes of both ketamine doses on PCL-5 scores were large and in the predicted range (0.93–1.61), but the effect size of placebo was larger than expected (0.75–1.13), resulting in small ketamine vs. Placebo differences. Unfortunately, failed clinical trials due to high placebo response are not uncommon in this field [25]. Other factors also may have contributed to the high placebo response, including the repeated invasive medical interventions of intravenous infusion twice per week requiring 2–3 weekly visits ~4 h each over 4 weeks in a protocol including comprehensive assessments in a supportive medical milieu of attending to the participant needs during the study period (e.g., booking transportations, meals, etc.).

Finally, the current study demonstrated the feasibility and short-term safety of repeated intravenous ketamine in a large cohort of patients with PTSD. A major concern in the field was whether adverse effects of repeated ketamine doses would exacerbate PTSD symptoms [15]. However, consistent with a recent report [11], the study treatment regimen was found to be well tolerated, showing significant reductions in the dissociative and psychotomimetic symptoms over the treatment period. Moreover, the ketamine-induced dissociative and psychotomimetic effects were transient, returning to normal levels within 2 h of starting the ketamine infusion. These dissociative effects were not so severe as to have an impact on retention in treatment over 8 intravenous infusions. Importantly, as has been reported in depressed patients [18], the ketamine-induced dissociative effects were significantly lower during ketamine 0.2 mg/kg compared to the standard dose (0.5 mg/kg) commonly used to treat depression. The latter finding suggests that using lower doses, if they were found efficacious in PTSD, might offer superior tolerability.

In summary, the current study failed to support the a priori hypothesis test of ketamine efficacy on PTSD symptoms in Veterans and military personnel with symptoms of PTSD. Nonetheless, there were evidence of benefit due to ketamine particularly the rapid antidepressant effects in this population, which has been difficult to treat in other studies. The study provided data supporting the safety and tolerability of repeated ketamine doses in this population. Together, these findings suggest the need to further investigate lower doses of ketamine

in the treatment of PTSD and that ketamine may help to manage the complex array of symptoms associated with PTSD, particularly for patients who have not responded to prior pharmacotherapies.

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 US Army Medical Department, the US 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 US Government.

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AUTHOR CONTRIBUTIONS

Conceptualization: CGA, JDR, JHK. Formal analysis: RG. Investigation/acquisition: all authors. Writing – original draft: CGA, JDR, RG, JHK. Writing – review/edit: all authors. Approval: all authors.

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COMPETING INTERESTS

Dr. Abdallah has served as a consultant, speaker and/or on advisory boards for Aptinyx, Genentech, Janssen, Psilocybin Labs, Lundbeck, Guidepoint, and FSV7, and as editor of Chronic Stress for Sage Publications, Inc. He also filed a patent for using mTORC1 inhibitors to augment the effects of antidepressants (Aug 20, 2018). Dr. Krystal is a consultant for Aptinyx, Inc., Atai Life Sciences, AstraZeneca Pharmaceuticals, Biogen, Idec, MA, Biomedisyn Corporation, Bionomics, Limited (Australia), Boehringer Ingelheim International, Cadent Therapeutics, Inc., Clexio Bioscience, Ltd., COMPASS Pathways, Limited, United Kingdom, Concert Pharmaceuticals, Inc., Epiodyne, Inc., EpiVario, Inc., Greenwich Biosciences, Inc., Heptares Therapeutics, Limited (UK), Janssen Research & Development, Jazz Pharmaceuticals, Inc., Otsuka

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ADDITIONAL INFORMATION

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