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RESEARCH ARTICLE

High-dose ketamine infusion for the treatment of posttraumatic stress disorder in combat veterans

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INTRODUCTION: Combat veterans are at high risk for the development of posttraumatic stress disorder (PTSD) and substance use disorders. Ketamine has been shown to be an effective treatment for numerous mental health disorders, although research on its efficacy in combat-related PTSD in veterans is very limited.

METHODS: The study population consisted of 30 US military veterans with combat-related PTSD. Participants underwent a standard induction series of six 1-hour ketamine infusions with the goal of obtaining a transpersonal dissociative experience. Participants were given a series of self-report questionnaires to assess for changes in symptoms of depression, PTSD, and substance use prior to the first and sixth infusions.

RESULTS: Symptoms of depression as measured by change in score on the Patient Health Questionnaire decreased significantly from an average of 18.9 to 9.5 ($P < .001$). Similarly, symptoms of PTSD as measured by change in score on the PSTD Checklist for DSM-5 dropped significantly from an average of 56.2 to 31.3 ($P < .001$). Self-reported levels of substance use did not significantly decrease during the study period, although the level of use trended down.

CONCLUSIONS: This observational study suggests that high-dose ketamine infusion therapy, which induced a transpersonal dissociative experience, could be a valuable tool in the treatment of combat-related PTSD. Further study is needed to better elucidate ketamine's mechanism of action with regards to the treatment of PTSD.

INTRODUCTION

Combat veterans are at high risk for the development of posttraumatic stress disorder (PTSD) as well as comorbid mental health and substance use disorders that can lead to significant functional impairment and morbidity.[1] The estimated prevalence of PTSD ranges from 27% to 37% in Vietnam armed forces veterans,[2] 10.1% for Gulf War veterans,[3] 11.5% for veterans deployed to Afghanistan,[4] and 18% for those deployed to Iraq.[4] It is estimated that less than half of returning veterans receive mental health treatment, and of those who do seek treatment, only half receive quality care.[5]

Ketamine, a widely used anesthetic, recently has been found to effectively treat mental health disorders, including treatment-refractory major depressive disorder, bipolar depression, suicidality, and PTSD.[6-17] This study sought to better characterize the role that ketamine could play in the treatment of PTSD.

METHODS

Study participants

The study population consisted of 30 US military veterans. Inclusion criteria included participants who previously served in a designated combat zone and who had been diagnosed with combat-related PTSD by clinicians at the Department of Veterans Affairs. Participants were men and women age 18 to 75 who passed medical screening, were not receiving lamotrigine or any monoamine oxidase inhibitors, and did not have psychosis. The Institutional Review Board at IntegReview (Austin, Texas) approved the study (Protocol KRP001), and written informed consent was obtained from all study participants.

Procedures

Eligible participants were identified by the clinical staff. After consenting to participate in the study, each participant underwent a psychosocial evaluation by a trained mental health professional. Medical records from the Department of Veterans Affairs were reviewed. Military service records from the Department of Defense were also reviewed to ensure that the participants had served in a combat zone.

Participants underwent a standard induction series of six 1-hour ketamine infusions. The first infusion began with a dose of 1 mg/kg of the participant's body weight, with a maximum of 60 mg on the first 1-hour infusion. There were no boluses given. After the first infusion, the dose was adjusted up or down, with the goal of attaining what the investigators referred to as the psychotropic therapeutic response (PTR). The treatment center defined the PTR as the dose at which the patient experiences the optimum transpersonal and transformative experience. The major assumption that underlies this treatment strategy is that the experiential (or "psychedelic") aspect of ketamine infusion therapy is not a "side effect" to be eliminated, but rather an essential component of the treatment. The PTR is an individualized dose specific to each patient.

TABLE 1
Final ketamine dose calculation and ketamine dosage

	Mean	SD	Median	Range
Dose calculation (mg/kg)	1.94	0.73	1.80	0.83 to 4.13
Final dose (mg)	163.83	52.50	150.00	60.00 to 300.00

SD: standard deviation.

For each infusion, the patient sat in a recliner in a private room with one staff member in attendance for the entire 1-hour infusion and for at least 30 minutes afterwards. The 6 infusions were performed over a 2- to 3-week period depending on each patient's availability. Patients had IV access established and were monitored using continuous pulse oximetry and 3-lead cardiac monitoring. Blood pressure was recorded prior to infusion and at regular intervals during and after each infusion. Most patients watched videos of nature scenes with a relaxing soundtrack. Some patients chose to listen to their own music with or without the video playing. Each infusion room was decorated to create a relaxing ambiance. Although historically used as an anesthetic agent, the use of ketamine in this context would be more appropriately referred to as ketamine for non-anesthetic indications (KNAI).

Study design and outcome measures

This was an observational case series of US veterans who received ketamine infusion therapy for the treatment of PTSD. Each participant was given a series of self-report questionnaires prior to the first and sixth

TABLE 2
Pre- and post-infusion comparison of self-report measures

Instrument	N	Pre-infusion	SD	Post-infusion	SD	*F*	*P*	Chi-squared
PHQ-9	30	18.9	6.2	9.5	7.3	90.9	<.0001	37.0
PCL-5	30	56.2	14.5	31.3	20.0	55.6	<.0001	19.7
AUDIT	23	5.3	6.8	4.4	6.7	1.0	.3	37.6
DAST-10	24	1.7	1.3	1.6	1.4	0.7	.4	62.0

AUDIT: Alcohol Use Disorders Identification Test; DAST-10: Drug Abuse Screen Test; PCL-5: PTSD Checklist for DSM-5; PHQ-9: Patient Health Questionnaire; SD: standard deviation.

ketamine infusions. The PTSD Checklist for DSM-5 (PCL-5), a 20-item self-report measure, was administered to monitor change in PTSD symptoms.[18] The Patient Health Questionnaire (PHQ-9) was used to screen for symptoms of depression.[19] Alcohol consumption, behaviors associated with alcohol consumption, and alcohol-related problems were screened for using the Alcohol Use Disorders Identification Test (AUDIT).[20] The Drug Abuse Screen Test (DAST-10) was administered to screen for drug abuse and negative consequences of drug use.[21] In addition, participants were asked about current marijuana use and history of recreational ketamine use. Participants were also asked to describe their experience regarding the dissociative and psychomimetic effect of the ketamine and their perceptions of the value of PTR as part of their therapy.

RESULTS

Although the ketamine doses administered in this study were generally higher than those in previously reported research, the participants were responsive to verbal stimuli at all times during the infusion. The doses were gradually increased on each infusion based on a given participant's response during the previous infusion. Ketamine dose calculations and final doses are presented in **TABLE 1**. Other than some occasional nausea, none of the participants experienced any significant adverse events or significant vital sign abnormalities.

Comparisons of self-report questionnaires pre- and post-infusion are demonstrated in **TABLE 2**. Individual responses on the PHQ-9 and PCL-5 for pre- and post-infusions are outlined in **TABLE 3**. No participants endorsed increased symptoms on the PHQ-9, and 2 participants (7%) reported no change in symptoms. On the PCL-5, 3 participants (10%) endorsed increased symptoms. On measures of substance abuse (DAST-10 and AUDIT), 6 and 7 participants had missing data, respectively. While self-reported levels of substance abuse did not significantly decrease during the study period, it appeared that ketamine infusion did not predispose patients to increased substance use, and the level of use trended down. Anecdotally, some participants reported a decreased desire to drink alcohol after receiving the ketamine infusions. On a measure of depression (PHQ-9), symptoms of depression dropped significantly, from an average score of 18.9 to 9.5, a 50% reduction, with a Cohen's *d* effect size of 1.38 ($F = 90.0$, $P < .001$). Finally, symptoms of PTSD as measured by PCL-5 also dropped significantly, from an average score of 56.2 to 31.3, a 44% reduction, with a Cohen's *d* effect size of 1.42 ($F = 55.6$, $P < .001$).

DISCUSSION

This observational study suggests that ketamine infusion therapy could be a valuable tool in the treatment of combat-related PTSD. Case reports have indicated that ketamine or ketamine analogues may be an effective treatment for veterans with PTSD.[22] McGhee et al[23] reported the somewhat serendipitous finding that PTSD in Operation Iraqi Freedom/Operation Enduring Freedom veterans who received ketamine during surgeries was 27% compared with 46% in those who did not receive ketamine. In a recent study by Albott et al,[24] veterans with comorbid treatment-resistant depression (TRD) and PTSD were administered 6 ketamine infusions of 0.5 mg/kg over a 12-day period. The researchers found a significant decrease and remission of both symptoms of depression and PTSD over the study

TABLE 3
Individual responses on the PHQ-9 and PCL-5 pre- and post-infusion

Instrument	PHQ-9 score		PCL-5 score	
	Pre-infusion	Post-infusion	Pre-infusion	Post-infusion
Veteran 1	26	19	53	58
Veteran 2	27	14	80	42
Veteran 3	19	1	55	14
Veteran 4	11	1	37	5
Veteran 5	14	3	51	16
Veteran 6	18	11	50	32
Veteran 7	24	8	24	20
Veteran 8	15	9	60	19
Veteran 9	5	0	68	8
Veteran 10	7	2	29	11
Veteran 11	14	2	63	13
Veteran 12	25	12	60	21
Veteran 13	23	11	62	38
Veteran 14	26	18	75	62
Veteran 15	24	8	64	32
Veteran 16	19	2	60	10
Veteran 17	16	10	65	36
Veteran 18	15	5	59	26
Veteran 19	10	0	42	5
Veteran 20	24	21	64	77
Veteran 21	17	14	74	50
Veteran 22	25	13	65	44
Veteran 23	16	0	37	7
Veteran 24	23	23	79	64
Veteran 25	24	13	43	36
Veteran 26	11	1	49	13
Veteran 27	22	22	35	44
Veteran 28	17	16	51	48
Veteran 29	23	18	60	56
Veteran 30	27	7	72	32

PCL-5: PTSD Checklist for DSM-5; PHQ-9: Patient Health Questionnaire.

period, with a median length of symptom relapse of 20 days for depression and 41 days for PTSD.[24] As such, ketamine infusions appear to be a promising treatment for veterans with TRD and/or PTSD, and further research is needed to understand ketamine's safety and efficacy in this population. To our knowledge, this is the first study to investigate the efficacy of high-dose ketamine infusion treatment of PTSD in combat veterans.

There is a rapidly growing body of literature showing that ketamine is a safe, effective, and novel therapy for TRD.[8,13-16,24] Given the alarming number of veteran suicides in the United States, a more effective means for treating PTSD and TRD is urgently needed. Many of the current theories of how ketamine works to treat TRD center around its action at the *N*-methyl-D-aspartate receptor and the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.[6] Anecdotally, many of the patients treated at our center report that the ability to achieve a change in their cognitive paradigms and the ability to "reset" their thought patterns helps them to radically alter the way in which they contextualize their traumatic experiences. As our results show, this can lead to a significant decrease in symptomatology in this population. While this study was not designed to elucidate the exact role of the experiential component, it does demonstrate successful outcomes with ketamine doses that are higher than the traditional 0.5 mg/kg, which is the dose administered in many previous studies. Some authors have suggested that ketamine therapy may increase the symptoms of PTSD.[25] In our study, 3 of 30 participants endorsed increased symptoms; however, the 2 previous studies that showed an increase in symptoms looked at the administration of ketamine shortly after a traumatic injury, which is a very different context than the patients we were treating in this study.[25,26] It is not entirely clear why 3 veterans endorsed an increase in their PTSD symptoms, especially in light of the fact that 2 of the 3 had a decline in their depressive symptoms. Additionally, none of the participants reported subjectively that the experience worsened their symptoms. We have found that the appropriate "set and setting" makes an enormous difference in how the ketamine experience is perceived. The staff member in attendance plays a very proactive role in helping to guide and ground the patient through his/her ketamine journey. In this regard, our treatment strategy diverges from a more traditional "infusion center" model in that it incorporates elements of shamanistic healing that have historically been absent from Western medicine. Further studies are needed to better characterize the role of the experiential component of ketamine and PTSD symptomatology, as well as if any individuals experience increased PTSD symptomatology from ketamine infusions.

Limitations

There are several limitations to this study. This was an observational study and did not have a placebo arm. Also, because the final set of survey instruments was administered before the sixth infusion, the data demonstrate the effect of ketamine after 5 infusions. We suspect that the effect size would have been greater if the instruments could have been administered several days after the sixth infusion. In our clinical experience, however, we have found that compliance with questionnaires and psychological screening instruments in the veteran population can be quite challenging to obtain after they have finished their induction series of infusions. We felt that it would be better to have a complete data set after 5 infusions rather than to risk losing patients to follow-up after they completed their full series of 6.

Another limitation was the ability to assess the effect of ketamine on veterans' use of alcohol and illicit drugs. A few of the veterans in this study did not fill out the AUDIT and the DAST-10; thus, there was an incomplete data set with regards to those instruments. Several veterans also admitted that they initially underreported their use of alcohol and illicit substances because they had not yet built a sense of trust with the treatment team. Nonetheless, there was a trend towards a decrease in alcohol use. Anecdotally, several participants reported a significant decreased desire to drink alcohol. This element of ketamine therapy deserves further study.

Finally, this study did not look at long-term outcomes but rather the change in PTSD symptomatology over the course of the 2- to 3-week induction series. In our clinical experience, patients will need a "booster" infusion at regular intervals in order to maintain the improvement in symptomatology.

CONCLUSIONS

We feel that this study provides valuable evidence of the role that ketamine can play in the treatment of combat-related PTSD. Specifically, the success we had with significantly higher doses than those used in other studies suggests that the experiential or psychedelic effect of ketamine may be a critical element of how it works therapeutically, rather than an adverse effect to be eliminated. Further study is clearly needed to better elucidate ketamine's mechanism of action with regards to the treatment of PTSD. ■

DISCLOSURES: Dr. Bonnett is the medical director and owner of Klarisana, the ketamine infusion center where this study was conducted. To preserve objectivity, outcome measures and statistical analyses were verified by Cassie Ross, PsyD, who has no financial relationship with Klarisana. Dr. Jain has received research support from or served as a consultant to, speaker for, or on the advisory board of Addrenex, Alkermes, Allergan, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Osmotica, Otsuka, Pamlab, Pfizer, Shire, Sunovion, Supernus, Takeda, Teva, and Tris Pharmaceuticals. Drs. Ross and Wolfson have no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

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