2023

Is Intravenous Ketamine Efficacious for Symptom Reduction in Adults Diagnosed With Chronic Posttraumatic Stress Disorder?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2022

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not intravenous ketamine is efficacious for symptom reduction in adults diagnosed with chronic posttraumatic stress disorder.

Study Design: A systematic review of two randomized controlled trials (RCT) and one case series published between 2014 and 2021.

Data Sources: All three studies were discovered using PubMed. The articles were published in English, in peer-reviewed journals, and selected based on their relevance to the clinical question, inclusion of patient-oriented outcomes, and recency.

Outcome Measured: The outcome of reduction in posttraumatic stress disorder (PTSD) symptom severity was measured in each study using either the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5), PTSD Checklist for *DSM-5* (PCL-5), or Impact of Event Scale-Revised (IES-R) scores. The mean change from baseline was calculated to demonstrate the treatment effect.

Results: In the crossover RCT led by Feder A, Parides MK et al., intravenous (IV) ketamine resulted in PTSD symptom reduction measured by a mean total IES-R score 12.70 points lower than the midazolam control group ($p = 0.02$). In the RCT conducted by Feder A, Costi S et al., IV ketamine administration demonstrated a mean total CAPS-5 score 11.88 points lower than the midazolam control group ($p = 0.004$). Lastly, in the case series led by Albott CS et al. a 33.27-point mean change from baseline PCL-5 scores ($p < 0.0005$) and an 80% remission rate were recorded after administration of intravenous ketamine.

Conclusion: All three studies in this review demonstrated that intravenous ketamine led to significantly reduced PTSD symptom severity as measured by IES-R, CAPS-5, and PCL-5 scores. This suggests that IV ketamine is an effective method of treatment for chronic PTSD. Further studies should expand the number of participants in the sample populations and explore treatment dosages and duration as well as maintenance therapy regimens.

Key Words: Posttraumatic stress disorder, PTSD, ketamine.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a psychiatric condition that arises after exposure to a severe traumatic event and is characterized by at least 1 month of intrusive symptoms, avoidance, negative alterations in cognition and mood, and increased arousal and reactivity that cause significant distress or impairment in functioning.[1] The prevalence of PTSD in the general population is estimated to be 7.8%, and even higher in trauma-exposed populations, with the highest burden among survivors of interpersonal violence and military veterans.[2,3,4] The Census Bureau, Veterans Affairs, and Department of Defense estimated that over 2.6 million male and 7.5 million female adult US civilians were suffering from PTSD in 2018.[4]

Although there is not an exact estimate available regarding health care utilization, it has been established that when compared to the general population, those with PTSD have increased psychiatric treatment needs, require greater healthcare utilization attributed to co-morbid medical conditions, and have increased rates of surgery and physician visits.[5] The diagnosis and treatment plan for PTSD often includes general practitioner care, trauma-focused psychotherapy, and psychiatry. Trauma-focused cognitive behavioral therapy commonly involves at least 8 to 12 weekly sessions lasting 60 to 90 minutes each and pharmacotherapy is usually continued for a minimum of 12 months.[5] PTSD is also associated with an increased risk of substance use disorder, disability, unemployment, and premature mortality. [4] Based on these combined factors, the total excess economic burden of PTSD in the US was estimated at $232.2 billion, corresponding to approximately $19,630 annually per individual.[4]

PTSD can occur at any age and is often directly attributed to experiencing a significant trauma. The reason why some individuals develop PTSD while others do not under similar conditions, however, is complex and not yet fully understood. Scientists hypothesize that a

multitude of factors including temperament, environment, genetics, and physiological profile may all play a role in an individual's risk and prognosis.[1] Despite the enormous impact of PTSD, the current lack of understanding behind the pathophysiology of its development has failed to provide effective therapeutic targets and few treatment methods to date have demonstrated sufficient efficacy in symptom reduction. [2,4] Current treatment involves both trauma-focused psychotherapy and pharmacotherapy. Strongly recommended treatment interventions include cognitive behavioral therapy, cognitive processing therapy, and prolonged exposure therapy. Conditionally recommended treatments include brief eclectic psychotherapy, eye movement desensitization and reprocessing therapy, narrative exposure therapy, and antidepressant pharmacotherapy.[6] Trauma-focused psychotherapies have the most empirical support but are limited by significant rates of nonresponse in this population.[3] Antidepressant agents sertraline and paroxetine are the only 2 medications currently FDA approved for the treatment of PTSD and are similarly associated with high rates of nonresponse and residual symptoms among responders.[2]

The limitations of current treatment methods and lack of progress in discovering alternative options have made it imperative to investigate novel pharmacologic interventions. Evidence for the role of glutamate in mediating stress responsivity and forming traumatic memories suggests a potential benefit for pharmacotherapeutic interventions including intravenous (IV) ketamine, an antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor.[2] This systematic review evaluates two randomized controlled trials (RCTs) and one case series to assess the efficacy of IV ketamine as a treatment option for chronic PTSD.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not intravenous ketamine is efficacious for symptom severity reduction in adults diagnosed with chronic posttraumatic stress disorder.

METHODS

Studies were searched for and selected by this author based on their relevance to the clinical question, inclusion of patient-oriented outcomes, recency, and fulfillment of criteria based on population, intervention, and outcomes measured. The population of the studies targeted were adults diagnosed with chronic PTSD, the intervention searched for was IV ketamine, and the outcome investigated was reduction in PTSD symptom severity. The studies referenced in this review were found on PubMed using the keywords "posttraumatic stress disorder or PTSD" and "ketamine." Inclusion criteria for the search included RCTs, case series', studies published in/after 2011, and adult populations (18 years and older). Exclusion criteria for the search were studies involving children and those published before 2011. It was required that all studies were published in peer-reviewed journals and written in the English language. The search resulted in the selection of two RCTs and one case series that include the intervention of IV ketamine and assessed for a reduction in PTSD symptoms. Outcomes were measured by the mean change from baseline or mean difference between treatment groups using the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5), PTSD Checklist for *DSM-5* (PCL-5), or Impact of Event Scale-Revised (IES-R) scores. The RCTs compare IV ketamine with midazolam as a control. The case series has no control group but relates treatment results to pre-treatment baseline measurements. Statistical analyses and significance measurements utilized include p-values, confidence intervals, number needed to treat (NNT), and event rates. The demographics and characteristics of these studies can be found in Table 1.

Table 1. Demographics & Characteristics of Included Studies

Study	**Feder A, Parides MK, Murrough JW, et al.[2]**	**Feder A, Costi S, Rutter SB, et al.[3]**	**Albott CS, Lim KO, Forbes MK, et al.[10]**
Type	RCT	RCT	Case series
# of Patients	41	30	17
Age (years)	18-55	18-70	18-75
Inclusion Criteria	Patients 18-55 years old who have a primary diagnosis of chronic PTSD as defined by DSM-IV-TR clinical interview criteria or a score of >50 on CAPS-5.	Patients 18-70 years old who have a primary diagnosis of chronic PTSD as defined by DSM-IV-TR clinical interview criteria (for at least 3 months), SCID-5, and a score of >30 on CAPS-5.	Veterans 18-75 years old with diagnoses of treatment resistant depression (TRD) and chronic PTSD as defined by CAPS-5, DSM-IV-TR clinical interview, and a failure to achieve depression remission from at least 2 antidepressant medications.
Exclusion Criteria	Lifetime history of psychotic or bipolar disorder, current bulimia or anorexia nervosa, alcohol abuse or dependence in previous 3 months, serious unstable medical illness, sleep apnea, active suicidal or homicidal ideation, or current use of any psychotropic medications.	Any serious unstable medical condition, active suicidal or homicidal ideation, lifetime history of psychotic disorder or bipolar disorder, current anorexia or bulimia nervosa, alcohol or substance use disorder within 3 months, history or recreational ketamine or phencyclidine use on more than one occasion or any use within previous 2 years, or current treatment with a long-acting benzodiazepine or opioid medication.	Any unstable medical condition, moderate-to-severe traumatic brain injury, active substance use disorder in the previous 6 months, lifetime history of psychosis or bipolar disorder, or active suicidal ideation. Women of childbearing potential were required to have a negative pregnancy test prior to study initiation and remain on reliable contraception for the study duration.
W/D	6	1	2
Interventions	IV ketamine hydrochloride vs. IV midazolam	IV ketamine hydrochloride vs. IV midazolam	IV ketamine hydrochloride

OUTCOME MEASURED

All three studies measure the outcome of reduction in PTSD symptom severity. The methods of measurement are similar but vary slightly between studies.

I. Feder A, Parides MK et al. utilizes the Impact of Event Scale-Revised (IES-R), a 22-item self-report measure that assesses subjective distress caused by traumatic events on a 5-point scale from 0 ("not at all") to 4 ("extremely"), for a total score ranging from 0-88.[7]

II. Feder A, Costi S et al. utilizes the Clinician Administered PTSD Scale for *DSM- 5* (CAPS-5), a 30-item professional administered questionnaire that reflects changes in existing PTSD symptoms and the addition of new symptoms on a 5-point scale from 0 ("absent") to 4 ("extreme/incapacitating"), for a total score ranging from 0-120.[8]

III. Albott CS et al. utilizes the PTSD Checklist for *DSM-5* (PCL-5), a 20-item self-reported measure that assesses the subjective distress caused by the 20 *DSM-5* symptoms of PTSD on a 5-point scale from 0 ("not at all") to 4 ("extremely") for a total score ranging from 0-80.[9]

RESULTS

Feder A, Parides MK et al. conducted a crossover RCT comparing ketamine with an active placebo control, midazolam. The authors enrolled 41 participants between the ages of 18 and 55 who had a current diagnosis of moderate to severe chronic PTSD as defined by a score of $\geq$50 on the CAPS-5. Patients were randomly assigned to receive a single IV infusion of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) on their first procedure day. Patients who scored $\geq$50 on the CAPS-5 two weeks after their first infusion received an infusion of the second study drug. 35 participants completed the study, 6 after their first infusion (all of whom had been

randomly assigned to receive ketamine first) and 29 after their second infusion. The primary outcome measured was reduction in PTSD symptom severity 24 hours after infusion, assessed by IES-R scores compared to baseline. In a primary crossover analysis adhering to a modified intention-to-treat principle including all 29 participants who completed both infusions, total IES-R scores after ketamine infusion demonstrated significant improvement compared to midazolam, represented by a difference in mean change from baseline of 12.7 (95% CI, 2.5-22.8; $p = 0.02$).[2] An additional intention-to-treat analysis conducted with all 41 participants using only first infusion data agreed closely with a difference in mean change from baseline of 8.6 (95% CI, 0.94-16.2; $p = 0.03$). [2] Additionally, the authors reported that symptoms in 7 participants randomly assigned to ketamine first (n = 22) remained significantly reduced after infusion, compared to only 1 participant randomly assigned to midazolam first (n = 19). [2] Using this data, I calculated a NNT of 4, indicating that for every 4 patients with chronic PTSD treated with IV ketamine, 1 more patient would achieve significantly reduced symptom severity compared to the control. The results are summarized in Table 2 and 4 below.

Table 2. Clinical Improvement in IES-R Score Comparing Ketamine and Midazolam Groups (Crossover and First Infusion Results)

Crossover (n = 29)		**First Infusion (n = 41)**	
Difference in Mean Change From Baseline IES-R Score (95% CI)	***P*-value**	**Difference in Mean Change From Baseline IES-R Score (95% CI)**	***P*-value**
12.7 (2.5-22.8)	0.02	8.6 (0.9-16.2)	0.03

Similarly, Feder A, Costi S et al. conducted a RCT comparing ketamine with the active placebo control of midazolam, however, the authors investigated the efficacy of repeated infusions as opposed to the single dose used in their original proof-of-concept study. The authors enrolled 30 participants between the ages of 18 and 70 who had a current diagnosis of moderate to severe chronic PTSD as defined by a CAPS-5 score of $\geq$30. Participants were randomly

assigned to receive a total of 6 infusions of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) approximately 3 times per week over 2 consecutive weeks. 29 participants completed all 6 infusions, with 1 participant withdrawn by the study team due to safety concern. The primary outcome of reduction in PTSD symptom severity was measured with the CAPS-5 at baseline and at week 2, after completion of all 6 infusions. Using an intention-to-treat mixed-effects model analysis, researchers demonstrated that while scores were similar in both treatment groups at baseline (mean difference = 0.87, $p = 0.83$), total CAPS-5 scores were significantly lower in the ketamine group at week 2 when compared to the midazolam group (mean difference = 11.88, $p = 0.004$).[3] Additionally, significantly more participants in the ketamine group (N=10/15, 67%) attained a response, defined as ≥30% reduction in symptom severity, compared to those in the midazolam group (N=3/15, 20%).[3] With a NNT of 3, the results suggest that 3 additional patients with PTSD would need to be treated with ketamine to attain 1 additional response when compared to midazolam.[3] Repeated ketamine infusions were found to attain a statistically significant reduction in PTSD symptoms greater than that of the control as reflected in the results summarized in Table 3 and 4 below.

Table 3. Clinical Improvement in CAPS-5 Score Comparing Ketamine and Midazolam Groups (Baseline and Week 2)

	Mean Difference in CAPS-5 Scores	***p*-value**
Baseline	0.87	0.83
Week 2	11.88	0.004

Table 4. Calculations for NNT in Both Feder A et al. Studies

Study	**CER**	**EER**	**ABI**	**RBI**	**NNT**
Feder A, Parides MK et al.	1/19 = 0.05	7/22 = 0.32	0.27	5.4	4
Feder A, Costi S et al.	3/15 = 0.20	10/15 = 0.67	0.47	2.35	3

Similar to the research done by the Feder A, Costi MK et al., Albott CS et al. led a study to examine the efficacy of repeated ketamine infusions for the treatment of PTSD, however, the authors conducted an observational case series in which there was no control group. Study

participants included 17 veterans, aged 18 to 75, with comorbid diagnoses of treatment-resistant depression and chronic PTSD. Participants completed 6 infusions of ketamine (0.5 mg/kg), 3 times a week over a 12-day period. The primary outcome of reduction in PTSD symptom severity was assessed by the mean change in total PCL-5 scores from baseline. Secondary outcomes included reduction in PTSD symptoms, measured by the mean change in total CAPS-5 scores from baseline, and the proportion of individuals in remission from PTSD, as defined by a PCL-5 score <33. Of the 17 participants enrolled, 15 were included in the analyses after 1 participant withdrew due to personal circumstances and another was excluded due to incomplete outcome data. Changes in outcome measures from baseline to 24 hours after the sixth infusion were recorded using a repeated-measures analyses of variance and the magnitude of change was analyzed using the small sample size bias-adjusted Cohen *d* (*d'*). The results, summarized in Table 5, demonstrated a statistically significant decrease in symptoms represented by a mean change in total PCL-5 score from baseline of 33.27 (95% CI, 23.04-43.50; *P* <0.0005, *d'*=2.17) and a mean change in total CAPS-5 score of 18.93 (95% CI, 12.62-25.24; *P* <0.0005, *d'*=1.85).[10] Additionally, it was calculated that 80% (N=12/15) of the sample population achieved remission after the sixth infusion.[10]

Table 5. Clinical Improvement in PCL-5 and CAPS-5 Score

Measure	Mean Change From Baseline 95% CI	*P* Value	Cohen *d'*
Total PCL-5 Score	33.27 (23.04-43.50)	<0.0005	2.17
Total CAPS-5 Score	18.93 (12.62-25.24)	<0.0005	1.85

DISCUSSION

PTSD is a chronic and disabling condition effecting over 10 million adults in the US.[4] Despite its enormous psychological, physical, and financial impact, few treatment methods have demonstrated sufficient efficacy in the management of the disorder. This review evaluated the efficacy of IV ketamine infusions for reducing symptom severity in those with chronic PTSD. In

two RCTs in which patients, clinicians, and study workers were kept blind to treatment and an intention-to-treat analysis included all patients in the groups to which they were assigned, Feder A, Parides MK et al. and Feder A, Costi S et al. demonstrated a significantly greater improvement in PTSD symptom severity in the groups receiving ketamine injections compared to the groups receiving midazolam. With *p*-values of 0.02 and 0.004, respectively, demonstrating the probability that the data occurred under the null hypothesis was unlikely, and NNTs of 4 and 3, respectively, representing a large effect size, these studies provide significant statistical evidence that ketamine infusions are efficacious in reducing symptom severity in adults suffering with chronic PTSD.

The limitations of these studies include the recognition that ketamine was associated with higher rates of dissociative symptoms compared to midazolam, potentially affecting the blind. Additionally, a small sample size of 41 and 30 participants, respectively, and exclusion criteria of comorbid mental health and medical conditions, which are extremely common in this population, minimizes the generalizability and reliability of the research.

The case series led by Albott CS et al. similarly demonstrated a significant and rapid improvement in PTSD symptoms in a group of veterans receiving repeated ketamine injections. The researchers reported that 80% of the sample population achieved PTSD remission with a precise *p*-value <0.0005. The most notable limitation of this study is the observational design without a placebo control, which allows for a multitude of intervening variables, lowers the internal validity, and limits the interpretation of efficacy. Consequently, although this study suggests a relationship between ketamine infusions and PTSD symptom reduction, an experimental study with a control group needs to be conducted before the association can be accepted as valid. Additionally, the study was completed on an extremely small sample

population of 15 that included solely veterans with comorbid diagnoses of chronic PTSD and treatment-resistant depression, resulting in poor generalizability and a weakened ability to draw valid conclusions of the treatment effect.

A drawback to the use of ketamine in this population is that it has been associated with misuse, drug dependence, and withdrawal symptoms upon discontinuation.[11] PTSD is already correlated with an increased risk of substance use disorder[4] which makes this population more susceptible to developing a drug dependence to ketamine. The withdrawal syndrome may include symptoms similar to those of PTSD such as autonomic arousal, anxiety, depression, nightmares, paranoia, delusions, and hallucinations.[11] The risk of drug dependence and presence of withdrawal symptoms may weaken the validity of ketamine's therapeutic effects in the long-term.

CONCLUSION

This systematic review demonstrated that IV ketamine is efficacious in reducing symptom severity in adults with chronic PTSD. Feder A, Parides MK et al. and Feder A, Costi S et al. found that single and repeated ketamine infusions resulted in statistically significant mean changes in symptom severity scores, greater than that of the control. Albott et al. suggested with their case series that repeated ketamine injections significantly reduced PTSD symptoms in a group of veterans, a population noted to be at an increased risk of developing PTSD and to be treatment refractory. In order to further demonstrate the potential that ketamine has, additional experimental trials should be performed with a larger sample size and duration. It would also be beneficial to compare single infusions, repeated infusions, and different doses to determine the ideal average dose and number of treatment sessions required to achieve significant reduction in PTSD symptoms. Longer follow-up in future studies would be useful in assessing the duration of

the treatment effects and to investigate long-term maintenance regimens, if applicable. An ongoing study by Abdallah CG et al. with approximately 198 eligible participants is set to become the first placebo-controlled trial to determine the dose-related effects of repeated ketamine infusions on PTSD symptoms by comparing ketamine 0.5 mg/kg, ketamine 0.2 mg/kg, and a placebo. The participants will be followed for 4 weeks after the trial to examine sustained benefits in PTSD symptomatology.[12] If completed, this study has the potential to further demonstrate the effects of ketamine on PTSD in a larger sample size, as well as investigate ideal dosages and duration of treatment effects.

Currently, ketamine is associated with few drug-drug interactions and no contraindications exist to its use in combination with antidepressants, anxiolytics, or other psychotropic medications commonly used in the treatment of PTSD.[2] While Feder A, Parides MK et al. excluded participants taking other psychotropic medications from their research, Feder A, Costi S et al. and Albott CS et al. permitted the use of concomitant psychotropics and reported no adverse side effects. Although this suggests ketamine's safety and efficacy in combination with other treatment methods for PTSD, a study conducted to specifically investigate its safety with other treatment modalities would be required to establish this relationship.

Intravenous ketamine infusions, as used in the referenced studies, were administered by trained professionals in outpatient research units. This may pose difficulties in regard to access and incorporation into patients' lifestyles, especially for those who have aversions to needles or paranoia. Of note, intranasal esketamine is currently FDA approved as an adjunctive treatment for patients with treatment-resistant depression and major depressive disorder with acute suicidal ideation or behavior.[3] Future research is warranted to determine the efficacy of intranasal ketamine for PTSD treatment.

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