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REVIEW

# Ketamine as treatment for post-traumatic stress disorder: a review

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## Abstract

Post-traumatic stress disorder (PTSD) continues to make headlines given multiple military engagements across the world and civilian traumas, and resultant PTSD development continues at an even pace. Currently, antidepressant and cognitive-behavioral therapy have the greatest evidence base but still do not yield a remission of PTSD symptoms in many patients. Off-label and novel treatments continue to be considered for more refractory and disabling cases of PTSD. Ketamine is one such treatment that has been discussed and utilized more often for treatment-resistant major depressive disorder (MDD). Its mechanism is controversial regarding its potential to create anxiety, but the perceived benefit of a rapid reduction of symptoms makes it worthy for study in animal models of, and possibly human studies in, PTSD. The current literature and theoretical mechanism of action is discussed in this manuscript.

**Keywords:** acute stress, brain-derived neurotropic factor, ketamine, N-methyl-D-aspartate, off-label use, post-traumatic stress disorders, psychological substance-related disorders, receptors, stress disorders, traumatic.

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## Introduction

Post-traumatic stress disorder (PTSD) is the presence of recurrent, intrusive distressing memories, dreams, dissociative reactions such as flashbacks, and reactions to internal or external cues that symbolize or resemble an aspect of a traumatic event experienced by an individual.[1] The traumatic event can be an actual or threatened case of death, serious injury, or sexual assault that affected an individual, close friend, or family member.[1] In response to these symptoms, individuals often attempt to avoid situations where they may be reminded about the trauma internally by controlling thoughts, memories, and emotions or externally by avoiding people, places, conversations, and situations that can trigger memories regarding the traumatic event.[1] They may also exhibit changes in memory formation. For example, they may display selective amnesia – that is, inability to remember specific details surrounding the trauma that are not related to external causes such as substance use and physical trauma.[1] They may also develop a constellation of symptoms that mirrors major depressive disorder (MDD) including negative beliefs and expectations, negative emotional states, anhedonia, and social withdrawal.[1] In addition to these symptoms, patients may experience changes in emotional reactivity including irritability, self-destructive behavior, hypervigilance, sleep disturbance, and lack of concentration.[1]

PTSD has a prevalence of 8.7% in the United States, with a prevalence of 3.5% during any given 12-month period.[1] According to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), PTSD has a higher prevalence among military veterans, as well as firefighters, police officers, and emergency medical personnel. Globally, the greatest prevalence is found among survivors of rape, military combat and captivity, and politically motivated genocide.[1] Children and adolescents usually show a lower prevalence of PTSD following a traumatic event, although according to the DSM-5 this could reflect inadequate measurement tools. PTSD is more common among Latinos and African Americans as well as American Indians and less common in Asian Americans.[1]

PTSD is associated with high degrees of disability, making it difficult for an individual to maintain employment and social wellness.[1] According to DSM-5, in both community and veteran populations, PTSD is associated with poor social and family relationships, excessive absence from work, and lower income, educational, and occupational success. In addition to the disabilities caused by PTSD alone, there are several

comorbidities associated with the disorder. Individuals with PTSD are 80% more likely than those without PTSD to meet the diagnostic criteria for at least one other mental disorder.[1] In males, conduct disorder and substance use disorder are common. Other disorders that commonly co-occur include MDD, alcohol use disorder, and anxiety disorders.

The Veteran's Administration/Department of Defense currently includes the use of selective serotonin reuptake inhibitors (SSRIs) for use as pharmacotherapy for PTSD.[2] The SSRIs included in this recommendation are sertraline and paroxetine. Although SSRIs are one of the primary modes of pharmacotherapy for PTSD, there are many drugs that may also be used. For example, serotonin–norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, are also listed as a recommendation for monotherapy in PTSD.[2] Other classes of drugs that may be used include imipramine and phenelzine – a tricyclic antidepressant (TCA) and monoamine oxidase inhibitor, respectively.[2] These medications are listed with caution though, as they may have potentially serious side effects. One novel treatment not typically included in guidelines is ketamine.

Some researchers suggest that the symptoms experienced in PTSD may be caused by a loss of synaptic connectivity. The stress experienced in PTSD may impair the functioning of synaptic connectivity, which is mostly mediated by glutamate.[3] As glutamate synapses play a crucial role in these neuronal circuits, it is possible that the use of ketamine may enhance synaptic connectivity in these circuits, ultimately reversing the effects of stress.[4] Other researchers have examined how prophylactic use of ketamine may have a protective effect against the development of stress-related disorders.[5]

The clinical background to PTSD and potential use of ketamine is summarized in Box 1. There is a relative paucity of literature regarding the use of ketamine to treat PTSD compared to that emerging for use in refractory MDD management. However, some data exist, and they will be reviewed next.

## Ketamine pharmacotherapy and mechanism of action

Ketamine has been traditionally used as an alternative to general anesthesia. It produces 'dissociation' between the thalamaco-neocortical and limbic systems.[6] This dissociation is thought to be both functional and electrophysiological in nature. Clinically, individuals given ketamine exhibit a state of catalepsy in which the eyes remain open and have a slow nystagmus.[6] During this state, the individuals maintain corneal and light reflexes.[6] Patients become flaccid, but are awake. Ketamine doses here tend to be higher than those used in the MDD management. Minor central nervous system (CNS) changes have been reported and include disruption of an individual's ability to understand the environment and organize thoughts leading to emergence delirium or psychosis.[7]

Ketamine activity occurs at the N-methyl-D-aspartate-type glutamate (NMDA) receptor as an antagonist.[8,9] It has been studied in greater detail recently due to its potential use as an antidepressant agent.[10] NMDA receptor activation has been shown to increase formation of spontaneous intrusive memories (depressive or anxious), and high activity of the NMDA receptor may be a risk factor for actually developing PTSD.[11] As ketamine functions as an antagonist to the NMDA receptor, it may be a promising drug target to lower PTSD symptoms as such.

## Rationale for use of ketamine

PTSD has been described as a state of hyperarousal plagued by intrusive thoughts, flashbacks, and nightmares. Given that these intrusive thoughts have been linked to NMDA over activity, animal studies have shown some of the potential anxiolytic properties of NMDA antagonism by using ketamine. Zhang and colleagues conducted an animal study in which mice and rats were subjected to contextual fear to simulate PTSD.[10] In this study, rats were subjected to inescapable foot shocks and were subjected to a time-dependent sensitization (TDS).

**Box 1. Clinical background to PTSD and potential use of ketamine.**

1. PTSD is often a difficult-to-treat psychiatric disorder, and currently there exists only one pharmacological class of medication approved for the treatment of these symptoms. The SSRIs offer a treatment advantage of a low side-effect rate, but unfortunately a full remission of PTSD symptoms is often difficult to obtain.
2. Off-label augmentation options exist (atypical antipsychotics, mood stabilizers, hypnotics, and anxiolytics), but all have limited trials and limited efficacy in regard to PTSD treatment.
3. Ketamine is a controversial controlled medication that is gaining popularity in its off-label use in treatment-resistant MDD where it is noted to have an ultra-rapid onset of efficacy but also is limited by its offset of effect over 1–2 weeks.
4. Ketamine likely is more controversial in the use for anxiety disorder as it dampens NMDA receptor activity, and there are some thoughts that it may theoretically increase anxiety instead of helping. Given the treatment-resistant nature of PTSD for many patients, the potential benefit of developing a safe ketamine protocol may be warranted in a similar manner to that of its use for MDD.

The rats were restrained for 2 hours, then placed in a cylinder filled with water and forced to swim for 20 minutes; then, after a 15-minute rest period, they were given diethyl ether until they lost consciousness.[10] Zhang and colleagues repeated the TDS after a 1-week recovery period. During this period, the mice and rats were treated with daily ketamine dosed in the morning according to weight.[10] The positive controls were treated with sertraline, an SSRI, considered a first-line therapy.

Zhang and colleagues ruled out ketamine's effect on locomotor activity in the mice and rats by testing the number of crossing and rearing with lines. Rearing is a measure of activity and exploratory behavior, often used in open fields and mazes. There was no significant difference in the number of rearings or line crossing between the control and experiment groups of the mice and rats. This determined that neither the ketamine nor the exposure to traumatic stimuli affected locomotor activity.[10] In mice, there was a significant increase in contextual freezing in the foot shock group, indicating that a legitimate traumatic response was formed. Zhang and colleagues confirmed that chronic ketamine use next allowed for a significant decrease in the contextual freezing episodes that occurred in the foot drop group. There was also a significant decrease in the contextual freezing when treated with sertraline, the positive control. Freezing time following administration of sertraline was found to be shorter than the freezing time after administration with ketamine.[10]

Zhang and colleagues also found that in the rat group, the locomotor activity was not affected by ketamine (suggesting ketamine was not inducing anxiety or psychosis) use or by the exposure to TDS. Sertraline or ketamine was administered daily starting the first day after the TDS procedure.[10] In post-mortem, it was noted that the hippocampi had significantly decreased levels of brain-derived neurotropic factor (BDNF) in the rats with post-TDS.[10] Chronic administration of ketamine significantly reversed the effect of the traumatic event and increased BDNF levels. This is significant because the hippocampus in particular is associated with control of learning, memory, and also links to the hypothalamus–pituitary–adrenal axis (HPA).[12] There is evidence that antagonizing NMDA receptors can stop consolidation of fear conditioning in the hippocampus[12,13] and theoretically could lower PTSD symptoms. Of note, BDNF is decreased in limbic structures when under stress, and chronic treatment with antidepressants can increase its expression.[10] This is of particular importance because ketamine showed a similar effectiveness to sertraline, one of the current first-line treatments.[10]

Another study examined how ketamine could potentially be used as a prophylactic agent against depressive-like behavior. Using a chronic social defeat (SD) model, learned helplessness, and a chronic corticosterone model, Brachman and colleagues sought to assess whether a ketamine injection could protect against depressive behavior.[5] Mice either received an injection of saline or subanesthetic ketamine. One week later, the mice remained in group housing (control group) or underwent the chronic SD stress model, a model known to reliably create a depressive-like phenotype in mice. Two weeks after SD, the behavior of mice was assessed. One of the measures used was immobility, which is seen as a measure of helplessness or depressed mood in the forced swim test. The mice that received the ketamine injection had significantly decreased immobility, compared to those who received saline, indicating that ketamine may increase resilience to stress.[5] In addition, to assess the effect of ketamine on social interactions, an open field exploration was created, where one area had the scent of female urine and the other did not. The groups of mice were also exposed to a novel mouse, to observe their social avoidance. Ultimately, it was found that the mice that received the ketamine injection were protected from the effects of SD on social behavior.[5]

Additionally, mice that undergo SD are observed to have a dysregulated HPA axis. Using a chronic corticosterone model, Brachman and colleagues sought to examine whether ketamine could protect against the effect of SD on the stress response created by the HPA axis.[5] After being exposed to a brief stressor, researchers found that mice injected with ketamine did not differ from the control saline mice group, suggesting that ketamine is able to partially restore the HPA axis.[5] These findings support the notion that prophylactic use of ketamine may have positive effects when administered before periods of stress. This may be potentially useful in environments where stressful conditions can be predicted, such as those of soldiers in active combat, who are at risk of stress-related disorders such as PTSD.

The use of prophylactic ketamine was also examined in another study that studied the impact of ketamine on the behavioral and neurochemical responses to a stressor. Amat and colleagues injected Sprague Dawley rats with an intraperitoneal ketamine (10 mg/kg) or a saline vehicle. Rats then received treatment with uncontrollable tail shocks (IS) or home-cage control; these treatments were performed for 2 hours, 1 week, or 2 weeks after the injections.[14] The IS rats received shocks of varying intensity, while the home-cage control rats were not bothered. After 24 hours of treatment, juvenile social investigation (JSI) was assessed.[14] The JSIs were examined by timing exploratory behaviors in rats such as sniffing, pinning, and allogrooming, when placed with a juvenile rat in the cage.[14] In addition, extracellular levels of serotonergic (5-HT) in the basolateral amygdala were evaluated, neural structures that work together to increase anxiety following IS.[14]

The results of this study showed that ketamine administration at intervals before IS were able to block the behavioral effects of IS.[14] Ketamine administration at intervals of 2 hours, 1 week, or 2 weeks before IS prevented increased levels of 5-HT from accumulating in the extracellular space. In addition, IS is known to decrease JSI, but the ketamine injections were able to decrease the effects that IS had on JSI.[14] These findings suggest that ketamine may be beneficial when used prophylactically, as it works to reduce the neural connections that activate a stress

response. The benefits of using ketamine prophylactically were also highlighted in the study conducted by Brachman and colleagues.[5]

A human double-blind, randomized controlled trial by Feder and colleagues of 41 chronic PTSD patients also exists.[15] Participants were washed out from psychotropic drugs for 2 weeks and then were randomized into treatment with IV ketamine or midazolam using a crossover design. The order of infusion was randomized, and the doses were given 2 weeks apart. After administration, pulse oximetry, pulse and blood pressure, and electrocardiography were measured. Response was monitored during infusion and at intervals after infusion. The primary outcome was PTSD symptom severity 24 hours post-infusion and was assessed with the Impact of Event Scale-Revised (IES-R). The researchers found that IES-R scores were significantly improved with ketamine when compared to midazolam. Seven patients who received ketamine first were found to remain significantly improved at 2 weeks as compared to one patient who received midazolam first.[15] Of note, they determined that ketamine was associated with a decrease in comorbid depressive symptoms as well. This is key given that PTSD often presents with patterns of negative thinking and anhedonia. Furthermore, MDD is often comorbid with PTSD.

Several case reports have been published. Womble reported a 26-year-old combat veteran with diagnoses of PTSD and MDD.[16] The patient received ketamine infusion at a rate of 2 L/min. The patient received midazolam as preinduction, and then propofol and lidocaine to establish hypnotic state. Ketamine (35 mg) was next administered. After ketamine, the patient appeared to have acquired a euthymic mood. The patient self-reported a complete reduction of anxiety and depression after infusion from day 1 to day 14. However, at day 14 he began to relapse into a dysphoric state similar to that before infusion.

In another case report, by D'Andrea and colleagues, a 23-year-old veteran with symptoms of PTSD of 6-month duration occurring after a 15-month deployment was treated.[17] According to self-report and information provided by his spouse, the patient's symptoms included sleep terrors and nightmares. He frequently sat 'guarding' his home balcony and crashed his car twice in response to gunshots heard during hunting season. In terms of treatment, the patient had been tried on SSRIs, TCAs, SNRIs, valproate, and atypical antipsychotics at therapeutic doses and treatment durations to no avail. He was also tried on many hypnotics including trazodone, zolpidem, quetiapine, diphenhydramine, and prazosin without improvement. He attempted many forms of psychotherapy including eye movement desensitization and reprocessing, exposure therapy, and meditation among others and refused to continue due to increasing emotional distress. He was also hospitalized three times, including two stays at a facility with treatment programs specific to PTSD. He only achieved short-term, incomplete improvement. He was given a 24-hour medication washout and 30 mg IV propofol followed by 35 mg IV ketamine over 20 minutes.[17] He recovered and experienced only transient nystagmus and visual distortions. He showed an immediate, drastic decrease in dysphoria that led to improved functioning: remission of anxiety and hyperarousal, improved mood to euthymia, normalized sleep without the use of sedatives, and no nightmares. His PTSD Checklist-Military (PCL-M) score decreased from 66 to 29 during this time. His improvement lasted for 15 days, after which he returned to his previous state within the next 24 hours.

A case report by Donoghue and colleagues focused on a pediatric patient: a 7-year-old boy with a history significant of PTSD, reactive attachment disorder, and disruptive behavior disorder who displayed frequent episodes of severe emotional and behavioral outbursts involving destruction of property.[18] He was tried on several medications in the past including sertraline, mirtazapine, lorazepam, trazodone, amphetamine, atomoxetine, guanfacine, clonidine, valproate, and hydroxyzine with no significant improvement. He required many hospitalizations and was living in a long-term residential care facility at the time of the case report. The patient received IV ketamine (10 mg) as part of his anesthesia for tonsillectomy. His caregivers in the residential facility noted a significant improvement in his symptoms: decreased intensity and frequency of aggressive behaviors, and improved ability to control his emotions and behavior. When he did become upset, caregivers noted that his emotions did not escalate to the levels before receiving ketamine. The child also was able to speak about his past trauma for the first time. After 13 days, he returned to his baseline of poor emotional dysregulation. The patient underwent a sedated MRI 3 months later during which he received IV ketamine (10 mg). He again displayed improvements in behavior, which lasted 8 days before symptoms returning.

Another study aimed to examine the efficacy of oral ketamine therapy in an outpatient setting for PTSD and depression. Hartberg and colleagues conducted a retrospective analysis, which analyzed the hospital records of patients who received the oral ketamine, to determine whether there was a change in the number and duration of psychiatric hospital admission before and after treatment.[19] Ultimately, it was found that the use of oral ketamine reduced hospital admissions by approximately 70% per patient. There was a significant decrease in both the number of admission and the length of stay in a psychiatric hospital for patients. This study showed that the use of oral ketamine in an outpatient setting may be beneficial for patients with PTSD.

These case reports provide evidence that in both children and adults, there may be ability for ketamine to facilitate a near recovery symptomatically that may last 1–2 weeks. More studies are needed to determine whether there is a difference between ketamine-naïve patients and those who receive multiple doses and to determine if there is an appropriate dosing protocol for this treatment.

## Safety of ketamine for use in PTSD

As with any novel use of a medication, it is important to investigate the potential harms from side effects. Ketamine's nature is that it can create a transient dissociative state and has been thought to either facilitate or worsen PTSD in the past.[11] It is a controlled and possibly addicting substance.

One study indicated an increased risk of PTSD in patients receiving ketamine. Schoenberg and colleagues investigated whether ketamine administration would affect PTSD symptoms in accident victims. PTSD symptoms were assessed in accident victims by asking them to rate feelings such as dissociation, re-experiencing, avoidance, and hyperarousal. They used a sample of 56 accident victims and screened them retrospectively for acute stress disorder using the Peritraumatic Dissociative Experiences Questionnaire and for PTSD symptoms occurring 1 year after the accident.[20] Patients received single or fractionated doses of racemic ketamine, S-ketamine, or opioids during ambulance transportation. Patients who received S-ketamine were found to have significantly increased acute symptoms including dissociation, re-experiencing, and avoidance. Those who received racemic ketamine were found to have only slightly increased acute symptoms. Of note, they found that patients who received S-ketamine had significantly elevated symptoms of PTSD, whereas there was no difference in patients who received racemic ketamine and opioids. There were no significant long-term effects in those who received racemic ketamine. The authors concluded that ketamine administration in early trauma can lead to excessive stimulation of the stress-induced glutamate receptors and may lead to stronger dissociative symptoms and amalgamation of traumatic memories. Interestingly, there was a difference in symptomatology between S-ketamine and racemic ketamine. This may indicate that S-ketamine and the S-enantiomers are responsible for the negative psychoactive properties of ketamine.

Another study by McGhee and colleagues utilized the PCL-M to determine the diagnosis of PTSD in patients and aimed to determine the prevalence of PTSD in 603 burn patients during their procedure compared to those who did not.[11] Two hundred completed the PCL-M and 147 underwent at least one procedure. They found that patients receiving ketamine displayed a lower prevalence of PTSD. The reported prevalence was 27% for those receiving ketamine as compared to 46% for those who did not. Those who received ketamine often had more significant injuries and a more complicated course of recovery including longer intensive care unit stays and multiple operations and received more morphine. The amount of morphine received did not correlate to PTSD development. They also found that burn size did not predict PTSD development. They concluded that ketamine does not increase the prevalence of PTSD and may even decrease it.

McGhee and colleagues conducted a follow-up study in 2014.[21] This was a retrospective analysis on data collected from patients at the San Antonio Military Medical Center using a sample size of 289 burn victims who received the PCL-M 30 days after injury. The patients were organized into two groups: those who received ketamine (n=189) and those who did not (n=100). As seen in the previous study in 2008, they found that patients who received ketamine had greater injuries based on the total body surface area burned and injury severity score, longer hospital stays, and greater number of surgeries. However, this study found that there was no statistically significant difference in PTSD rates between those who received ketamine and those who did not (24 compared with 26.98% with $p$=0.582), respectively. As the group who received ketamine had greater baseline injuries than the comparison group, and the effects were similar after treatment, this may suggest that ketamine may still play a role in decreasing the prevalence of PTSD. However, possible reasons for failure to find a statistically significant difference may include lack of statistical power, or failure to control for differences in the severity of baseline injury in the participants. Additionally, it would be prudent to compare military and civilian responses to ketamine in the acute setting to determine if confounding factors are at play that have not been recognized as yet.

It is also important to note ketamine's effects on patients with PTSD who received it for PTSD-specific treatment. The randomized controlled trial by Feder and colleagues in 2014 does note some potential side effects.[15] During this study, one patient dropped out after his infusion of ketamine due to its dissociative effects. Three patients in the study were required to be treated with β-adrenergic antagonists due to increased blood pressure (systolic BP over 180 or diastolic BP over 100). Other than these events, the most common side effects in the first 24 hours were blurred vision, dry mouth, restlessness, fatigue, nausea/vomiting, poor coordination, and headache.

In the case report by D'Andrea and colleagues, the only side effects reported were short-term nystagmus and visual distortions.[17] In the case report by Donoghue and colleagues, no side effects were reported.[18] In the case report by Womble, the patient reported a headache at the completion of infusion.[16]

A retrospective study examined the adverse events of patients receiving long-term oral ketamine for both PTSD and treatment-resistant depression in an outpatient setting.[19] A total of 37 patients were examined in the study. The patients received an initial sublingual dose of 0.5 mg/kg, which was held under the tongue for 2–3 minutes to evaluate for any adverse effects. The dosage was begun at 0.5 mg/kg and then titrated up to 20–50% at each of the following treatments. The final doses ranged from 0.5 to 7.0 mg/kg. The study found that there were no serious adverse events recorded. In addition, there were no medical

emergencies, or psychiatric or psychiatric disturbances noted from ketamine use. There were no reported cases of bladder toxicity, hypertensive, or hypotensive crises. Some mild side effects were lightheadedness, sedation, and dissociative effects, which were often transient and required no further intervention.

Based on the limited data that exist for ketamine as a treatment for PTSD, it appears that there is little risk for routine significant side effects related to its use. Of note, ketamine is associated with few drug interactions such as possible enhancement of the toxic effects of CNS depressants, as well as acting as a strong CYP2C9 inducer and a strong CYP3A4 inhibitor (there are no contraindications to combining it to other psychoactive drugs other than monitoring).[15]

## Summary

PTSD continues to be a problematic psychiatric condition that can be difficult to treat. SSRIs are the first-line treatment, and they are the only pharmaceutical class approved – their use may lead to a reduction in symptoms but, oftentimes, PTSD can be found to be treatment resistant. In addition, there are many patients who have participated in trials of SSRIs as well as many other psychoactive drugs without complete remission. Atypical antipsychotics such as quetiapine and risperidone are sometimes used clinically to control these symptoms. Benzodiazepines are used at times as well, but with caution as individuals suffering from PTSD are at heightened risk for addiction.[22] Prazosin is used regularly now to combat nightmares, which contribute to the insomnia but may not lower other PTSD symptoms. Some are supplemented with psychotherapy and hospitalization but to no avail.

Given this, novel treatments are needed for PTSD. One such treatment could be ketamine. As noted, there exists some hesitation for its use based on the fact that it may cause transient dissociation; however, more recent studies suggest that this may not be as frequent as previously thought. Based on the limited data in the form of animal studies, a randomized controlled trial, and case reports, ketamine has been shown to result in a near complete resolution of symptoms over the short term and seems to have similar findings to the use of ketamine in MDD. These clinical improvements are immediate and last well beyond the half-life of ketamine but unfortunately are transient lasting 1–2 weeks. It is thought that upregulating BDNF and antagonizing NMDA serve to reverse some of the damage caused by chronic stress. With more investigation, ketamine may prove to be a viable tool in treating PTSD for those who fail more conventional treatments.

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