Development of Ketamine Administration as a Treatment for Chronic PTSD

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a highly prevalent, chronic, and disabling condition for which currently available pharmacotherapies are insufficiently effective. Ketamine, which is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising and rapid-acting novel treatment intervention for this disorder. Findings from a proof-of-concept, randomized, controlled crossover study of single-dose intravenous ketamine administration (compared to single-dose midazolam) in patients with chronic PTSD suggest that ketamine is associated with rapid improvement in core PTSD symptoms and comorbid depressive symptoms, and is generally well tolerated. Additional research is needed to confirm its efficacy and safety for patients with PTSD. Results from ongoing trials of repeated intravenous administration for PTSD are expected to yield more definitive evidence. Potential mechanisms of action as well as future research directions are discussed. **[*Psychiatr Ann*. 2020;50(2):68-76.]**

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Posttraumatic stress disorder (PTSD) is a chronic and disabling condition that can develop after a traumatic event (eg, exposure to actual or threatened death, serious injury, or violence) and has an estimated lifetime prevalence of 7.8% in the general population.[1] The disorder is characterized by four symptom clusters: (1) intrusion symptoms, (2) avoidance, (3) negative alterations in cognition and mood, and (4) alterations in arousal and reactivity. Currently available pharmacotherapies for PTSD are insufficiently effective, with only two medications, the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine, approved by the US Food and Drug Administration. SSRIs and other off-label treatments (eg, venlafaxine) are frequently ineffective or only partially effective, often necessitating treatment with combinations of medications with insufficient empirical guidance. Thus, there is an imperative need for novel pharmacotherapeutic interventions for this disabling disorder.

DEVELOPMENT OF A NOVEL TREATMENT INTERVENTION FOR PTSD

Ketamine, a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist,

had been in use as an anesthetic agent for several decades before the idea first surfaced that it might help alleviate PTSD symptoms. In the year 2000, a single intravenous (IV) infusion of a subanesthetic dose of ketamine was first reported to rapidly reduce depressive symptoms in patients with major depression,[2] and subsequent research on IV ketamine administration has shown significant promise for treatment-resistant depression (TRD).[3] These initial findings led to the conduct of the first proof-of-concept, randomized controlled trial (RCT) of IV ketamine for PTSD, which was funded by the US Army Research and Materiel Command and led by author AF in collaboration with the principal investigator (Dennis Charney, MD, Icahn School of Medicine at Mount Sinai).[4]

At the time, there was concern in the field that ketamine, a dissociative anesthetic, might potentially worsen PTSD symptoms, including dissociation. Published chart review and observational studies involving ketamine administration to patients in the aftermath of trauma exposure but not to patients with chronic PTSD had yielded mixed results. A retrospective chart review study of 56 moderately injured accident survivors found significantly higher PTSD symptoms 1 year after injury in patients who had received esketamine during ambulance transport than in those treated with racemic ketamine or opioid medication.[5] Acute stress symptomatology was also strongly elevated in the esketamine group but only mildly elevated in the racemic ketamine group, suggesting that peritraumatic ketamine administration might increase the risk of PTSD symptom development.[5] The same research group subsequently conducted a prospective, naturalistic study of 50 moderately injured accident victims who received a single infusion of racemic ketamine, opioids, or non-opioid analgesics.[6] When subsequently screened within 3 days of hospital admission, patients treated with ketamine exhibited significantly higher acute stress disorder symptoms compared to the other groups.[6] Both esketamine and racemic ketamine were co-administered with midazolam.

By contrast, a retrospective chart review study of a larger sample of US service members who had suffered burns during deployment, ranging in severity, yielded opposite findings. Of the 147 service members who underwent at least one surgical operation at the burn center, the group that had received intraoperative ketamine showed significantly lower prevalence of PTSD (32 of 119) than the group that had not (13 of 28) despite higher burn severity and number of surgeries in the former group.[7] Although a more recent retrospective chart review study in a larger sample of burned service members who had received intraoperative ketamine (n = 189) or had not (n = 100) did not replicate these findings, PTSD prevalence did not differ statistically between the two groups, suggesting that intraoperative ketamine after trauma does not increase risk of PTSD development.[8] A recent retrospective matched cohort study of US service members injured in combat who received (n = 107) or did not receive (n = 1,051) ketamine for analgesia during hospitalization yielded similar findings, but dosing data were not available.[9]

It is possible that these diverging findings might be due to differences in administered doses of ketamine (subanesthetic vs anesthetic) or co-administered medications (eg, midazolam). Further, given the results from a database review suggesting that opioid administration during acute care after combat injury might protect against the emergence of PTSD,[10] it is difficult to interpret findings from the studies by Schönenberg et al.[5,6] because opioids were used as the comparison condition.

After publication of studies of ketamine administration in the aftermath of trauma, several case reports of single-dose IV ketamine administered to patients with chronic PTSD appeared in the literature. A 23-year-old veteran with chronic treatment-resistant PTSD and major depressive disorder (MDD) experienced rapid PTSD and depressive symptom improvement after IV ketamine administration combined with propofol, lasting for 15 days.[11] A 26-year-old veteran with comorbid MDD and PTSD, who was also receiving midazolam, propofol, and lidocaine, experienced rapid remission of depression and anxiety, followed by relapse 14 days later.[12] In another report, a 7-year-old child with PTSD and severe emotional and aggressive outbursts showed dramatic improvement in all symptoms, and was able to speak during psychotherapy for the first time about his past abuse history after receiving IV ketamine for two procedures (tonsillectomy and neuroimaging) separated by 3 months; symptom improvement lasted 13 and 8 days, respectively.[13] Additionally, a retrospective analysis of oral ketamine augmentation in patients with TRD, and several with comorbid PTSD or severe anxiety, found a 70% reduction in inpatient hospital days and a 65% reduction in hospital admissions **(Table 1)**.[14]

Results of our proof-of-concept, randomized, controlled, double-blind crossover study comparing the effect of a single dose of ketamine (0.5 mg/kg, administered IV over 40 minutes) to single-dose active control midazolam (0.045 mg/kg) in a sample of unmedicated patients with chronic PTSD, were published in 2014.[4] The ketamine and midazolam infusions were administered 2 weeks apart. Forty-one patients (predominantly civilians exposed

Table 1.

Clinical Studies and Case Reports of Ketamine

Use	Author	Study Design	Participant's Condition	Participants, *n*	Ketamine Type and Dose	Assessment Time Points	Results
In the aftermath of trauma	Schönenberg et al.[5]	Retrospective cohort study	Accident victims with moderate injuries	56	Single or fractionated dose of S-ketamine, racemic ketamine, or opioids	1 year post-exposure	Higher PTSD symptoms in patients who had received S-ketamine
	Schönenberg et al.[6]	Naturalistic prospective study	Accident victims with moderate injuries	50	Single or fractionated dose of racemic ketamine, opioids, or non-opioid analgesics Body weight-dependent dosage Ketamine was routinely combined with midazolam	Within 3 days of admission	Higher acute stress disorder symptoms in patients who had received ketamine
	McGhee et al.[7]	Retrospective cohort study	US service members who were burned	147	IV ketamine during surgery	Not specified	Lower PTSD prevalence in patients who had received ketamine
	McGhee et al.[8]	Retrospective cohort study	US service members who were burned	289	IV ketamine during surgery	At least 30 days post-injury	No statistical difference in PTSD prevalence between patients who had received ketamine and those who had not
	Highland et al.[9]	Retrospective matched cohort study	US service members injured in combat	1,158	IV ketamine for analgesia; dosing data not available	30 to 365 days post-injury	No statistical difference in PTSD prevalence between patients who had and had not received ketamine
For chronic PTSD (clinical trials)	Feder et al.[4]	Proof-of-concept, randomized, controlled, double-blind crossover study	Patients with chronic PTSD	41	Single IV dose of ketamine (0.5 mg/kg) and single IV dose of midazolam (0.045 mg/kg)	Primary outcome 24 hours post-infusion Multiple, up to 1 week post-infusion	Rapid reduction in PTSD symptoms 24 hours after ketamine compared to midazolam No significant difference in PTSD symptoms 1 week post-infusion

Table 1. (continued)

Clinical Studies and Case Reports of Ketamine

Use	Author	Study Design	Participant's Condition	Participants, *n*	Ketamine Type and Dose	Assessment Time Points	Results
For chronic PTSD (clinical trials)	Albott et al.[26]	Open-label trial	Patients with TRD and comorbid PTSD	15	Six IV doses of ketamine (0.5 mg/kg) over 12 days	24 hours after each infusion Weekly for 8 weeks following the last infusion	Rapid and sustained improvement in depressive and PTSD symptoms Median time to relapse in PTSD remitters 41 days post-infusion
For chronic PTSD (case reports)	D'Andrea and Andrew Sewell[11]	Case report	23-year-old veteran with chronic treatment-resistant PTSD and MDD	1	Single IV dose of ketamine (35 mg) combined with propofol	Not specified	Immediate and dramatic improvement, including euthymic mood, complete resolution of anxiety and hyperarousal, and normalized sleep lasting for 15 days
	Womble[12]	Case report	26-year-old veteran with comorbid MDD and PTSD	1	Single IV dose of ketamine (0.5 mg/kg = 35 mg) combined with other agents	Not specified	Complete resolution of anxiety and depression, normalized sleep, and disappearance of nightmares for 14 days post-infusion
	Donoghue et al.[13]	Case report	7-year-old with PTSD and severe emotional and aggressive outbursts	1	Single IV dose of ketamine (10 mg) administered for two procedures, 3 months apart (in the first procedure ketamine was combined with other agents)	Not specified	Patient demonstrated less physical aggression and increase in emotional regulation lasting for 13 and 8 days post-procedure, respectively
Retrospective study	Hartberg et al.[14]	Retrospective study	Patients with TRD, several with comorbid PTSD or severe anxiety	37	Repeated sublingual doses of ketamine, initial dose of 0.5 mg/kg titrated up by 20% to 50% at each subsequent treatment, frequency ranging from twice weekly to every other week Final doses ranged from 0.5 to 7 mg/kg per treatment	Through the end of ketamine treatment, median of 31 months	70% reduction in inpatient hospital days and 65% in hospital admissions

Abbreviations: IV, intravenous; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; TRD, treatment-resistant depression.

Table 2.

Sample Comments from Patients 4 Hours After a Single Ketamine Infusion During a Randomized Controlled Trial for Patients with Chronic PTSD

Patient	Response
A patient with chronic PTSD after a sexual assault	"I feel good, I want to get out and do things, like get a haircut. I haven't felt like this in a year. I tried to think about (the assault) but couldn't. That was strange… I feel more connected to others, less afraid."
A rescue and recovery worker with chronic PTSD since the 9/11 attacks on the World Trade Center	"I feel much better; the [ambulance] sirens outside on the street no longer bother me. I called several friends that I hadn't spoken with in a while. I feel calm, not so jumpy."
A patient with chronic PTSD after a sexual assault	"I feel energetic, not stressed out or anxious; I feel good, refreshed. I enjoyed going outdoors for a smoke. I haven't dwelled on my thoughts about (the assault), I let it go. I feel happy, upbeat, my mind is clear. Interacting with others no longer takes so much effort, I don't feel like I have to fake."

Abbreviation: PTSD, posttraumatic stress disorder.

to different types of trauma), randomized to receive ketamine or midazolam as their first infusion, completed at least one infusion; 29 patients received both infusions. In crossover analyses, core PTSD symptoms assessed 24 hours post-infusion with the Impact of Event Scale–Revised were significantly improved with ketamine compared to midazolam. Analyses including all 41 participants 24 hours after the first infusion also showed superiority of ketamine over midazolam (see **Table 2** for sample participant comments). Ketamine's effect on PTSD symptoms did not differ across symptom clusters and remained significant after adjusting for baseline and 24-hour depressive symptoms. Although at 7 days post-infusion treatment effects no longer differed significantly (assessed with the Clinician-Administered PTSD Scale for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition), seven patients randomized to receive ketamine as the first drug remained improved 2 weeks post-infusion compared to only one patient randomized to receive midazolam first. Comorbid depressive symptoms also improved after ketamine administration.

SAFETY CONSIDERATIONS

Results from our RCT showed that ketamine was generally well tolerated, with only transient dissociative symptoms peaking during infusion.[4] No significant psychotic or manic symptoms were observed. One patient dropped out due to feeling uncomfortable during ketamine infusion, likely due to dissociative side effects. Three patients were administered beta-blockers to treat blood pressure elevation during ketamine administration; however, once more stringent parameters were employed for pre-infusion blood pressure (ie, participants with blood pressure readings above 140/90 mm Hg on two measurements prior to infusion would not receive an infusion), this intervention was no longer necessary. The most common side effects of ketamine emerging during infusion were short lived (blurred vision, dry mouth, restlessness, and fatigue) or responded to treatment (nausea/vomiting and headache).[4] Secondary analyses of combined data from three RCTs of ketamine for TRD and bipolar disorder I and II that included patients with comorbid PTSD and/or a history of abuse also found no clinically significant increase in positive psychotic, dissociative, or anxiety symptoms in these patients 1 week after a single ketamine infusion.[15] Although published studies to date have found no evidence of PTSD symptom worsening after ketamine administration, safety considerations remain central in research studies of ketamine for PTSD.

MECHANISMS OF ACTION

Glutamate is the primary excitatory neurotransmitter in the central nervous system, and it is known to modulate stress responses and memory formation, including trauma memories. In animal models, chronic stress induces dendritic atrophy in the hippocampus and medial prefrontal cortex, impairing connectivity in glutamatergic synapses. Ketamine, a glutamate NMDA receptor antagonist, rapidly reverses these effects of chronic stress on synaptic plasticity.[16] Abnormalities in glutamatergic function are also thought to play a key role in the pathophysiology of PTSD;[17] ketamine might reduce PTSD symptoms through regulating glutamate release. In animal studies, subanesthetic ketamine doses have been shown to increase glutamate release, likely through blockade of NMDA receptors located on gamma-aminobutyric acid interneurons, with resulting disinhibition of glutamatergic cells in the prefrontal cortex through AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) glutamate receptor activation and via increase in brain-derived neurotrophic factor and mammalian target of rapamycin complex 1 signaling, which are key mediators of synaptic plasticity.[18]

Krystal et al.,[18] in their review of the pathophysiology of PTSD, propose that the disorder might result from "synaptic disconnection." Although PTSD might initially develop through failure of fear extinction (in which harmless stimuli are perceived as threatening) via trauma-induced plasticity in the amygdala, hippocampus, and other regions, simpler models based on abnormal fear conditioning and deficits in fear extinction do not explain the full range of PTSD symptomatology. Some PTSD symptoms (eg, anhedonia, cognitive impairment) might instead develop from impaired connectivity in predominantly glutamatergic synapses in corticolimbic circuits, resulting from dysregulated glutamatergic signaling, inflammation, and hypothalamic-pituitary-adrenal axis dysfunction. Repeated exposure to trauma-related cues and recurrent intrusions of trauma memories further perpetuate the chronic stress experienced by people with PTSD, creating a vicious cycle leading to further biological dysregulation.[18] In patients with chronic PTSD, ketamine might restore synaptic connectivity, resulting in rapid symptom improvement. This potential mechanism of action is being investigated with functional neuroimaging studies before and after ketamine administration in patients with PTSD.

Other animal studies **(Table 3)** of relevance to PTSD include models based on fear conditioning, which examine the effects of ketamine on fear reconsolidation and extinction. The range of mechanisms through which ketamine might improve PTSD symptomatology is far from being fully understood, as ketamine has a complex pharmacological profile with affinity for many other receptors beyond the glutamate system. Of note, findings from recent studies in animals additionally suggest that ketamine might have prophylactic effects when given 1 week prior to stress exposure.[19]

Table 3.

Examples of Ketamine Studies in Animal Models Relevant to Posttraumatic Stress Disorder

Animal Model	Result
Chronic stress	Ketamine administered after 21 days of chronic unpredictable stress rapidly reversed the effects of chronic stress exposure, including synaptic deficits in prefrontal cortex neurons[16]
PTSD	In a PTSD model, rats tested 2 weeks after a single prolonged stress plus foot shock procedure showed PTSD-like effects. Subsequent ketamine administration reversed PTSD-like behaviors and also reversed reduction of brain-derived neurotrophic factor levels in the prefrontal cortex[30]
Fear memory reconsolidation	Rats underwent fear conditioning (foot shock). Ten days after context testing, ketamine administered at the end of fear memory reactivation disrupted reconsolidation of contextual fear. This was associated with down-regulation of a transcription factor (regulating synaptic plasticity) in the hippocampus, and upregulation of brain-derived neurotrophic factor mRNA in the medial prefrontal cortex[31]
Fear extinction	Rats underwent fear conditioning (foot shock) and were administered intraperitoneal (IP) ketamine 24 hours later. Ketamine was found to enhance the effects of fear extinction training, administered for 3 consecutive days starting the day after ketamine administration.[32] In a different study, however, while ketamine administered IP was also found to enhance fear extinction, ketamine administered intravenously had the opposite effect, enhancing fear memory and delaying extinction.[33]
Stress prophylaxis	Ketamine administered 1 week prior to (1) exposure to 2 weeks of social defeat stress or (2) 3 weeks of corticosterone-induced resilience to stress in mice[19]

Abbreviation: PTSD, posttraumatic stress disorder.

NEXT STEPS AND ONGOING CLINICAL TRIALS

In recent years, the efficacy of IV ketamine for TRD has been established in a series of studies,[20] and IV ketamine administration has also been shown to rapidly reduce suicidal ideation.[21] Additional studies demonstrated that repeated administration of ketamine or esketamine (ketamine's S[+] enantiomer) can successfully maintain depressive symptom improvement over time.[22] In 2019, esketamine was approved by the FDA for periodic intranasal administration as an adjunct to oral antidepressant treatment for TRD.[23] RCTs of repeated IV ketamine administration in patients with chronic PTSD are currently in progress, including our ongoing RCT of repeated IV ketamine administration (compared to repeated midazolam infusions) in patients with PTSD from predominantly civilian traumas. With this study, we aim to replicate findings from the initial RCT as well as additionally examine the efficacy of repeated infusions (3 times a week over 2 consecutive weeks, for a total of six infusions) in prolonging the duration of symptom improvement **(Figure 1)**. Participation requires a Diagnostic and Statistical Manual of Mental Disorders, fifth edition (*DSM-5*)[24] diagnosis of chronic PTSD of at least moderate severity on the Structured Clinical Inter-

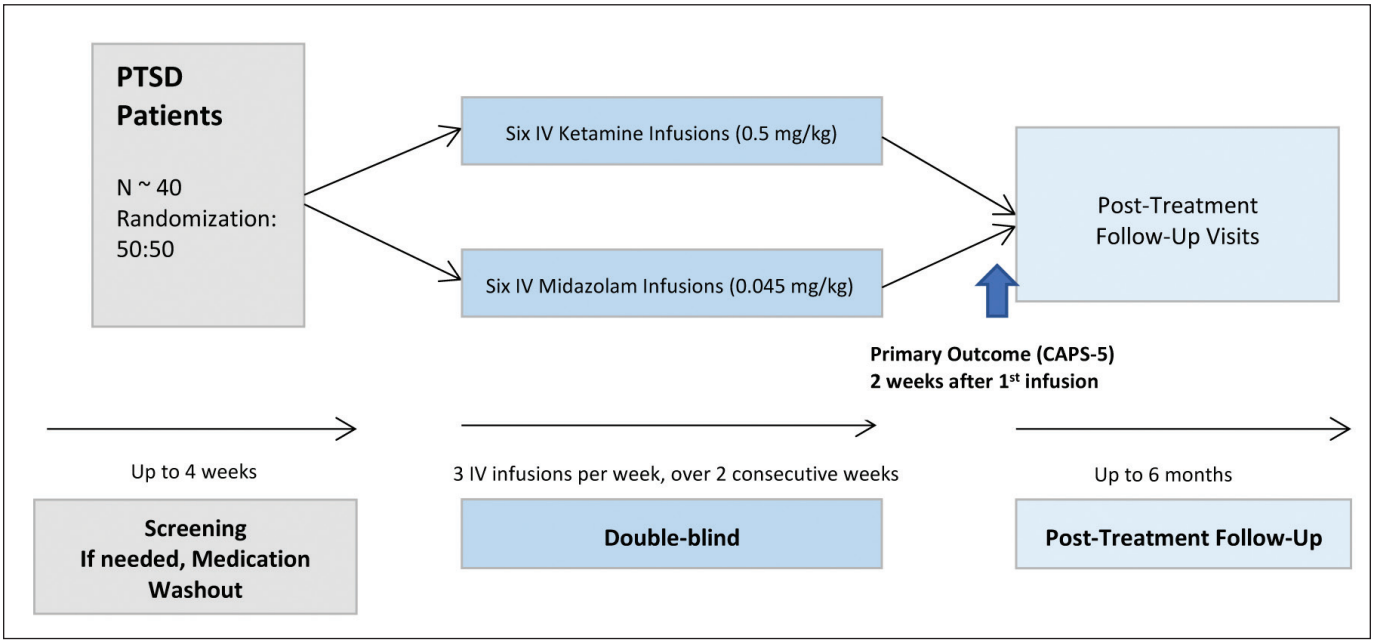

Figure 1. Ongoing randomized controlled trial of repeated intravenous ketamine administration. CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; IV, intravenous; PTSD, posttraumatic stress disorder.

view for DSM-5 (SCID-5), confirmed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Concurrent stable doses of psychotropic medications are allowed, with the exception of standing doses of opioid medication or long-acting benzodiazepines, and treatment-naïve patients are also eligible for the study.

A separate, ongoing, two-site RCT of repeated IV ketamine administration (compared to saline) aims to examine the efficacy of repeated ketamine administration for antidepressant-resistant PTSD in veterans and active-duty soldiers.[25] Findings from a different open-label study (without a control condition) of repeated ketamine infusions in 15 veterans with comorbid TRD and PTSD have recently been published, reporting significant improvement in depressive and PTSD symptoms after treatment, with brief increases in dissociative symptoms but no worsening of PTSD symptoms.[26] In this study, median time to relapse in 12 patients with PTSD that remitted after ketamine infusions was 41 days.

CONCLUSIONS AND FUTURE DIRECTIONS

Although findings published to date are promising, results from ongoing studies of repeated IV ketamine administration for chronic PTSD should yield more definitive evidence. Safety considerations in this population will additionally determine whether ketamine receives approval as a pharmacotherapeutic intervention for PTSD. If its efficacy for PTSD is established, additional studies should examine the efficacy of intranasally administered ketamine for this disorder, which is a delivery method more easily suited to outpatient settings.

Although research studies are still in progress, many ketamine clinical practices that were originally established to treat patients with TRD have added PTSD as a treatment indication. A 2016 to 2017 survey of 57 ketamine clinical providers identified PTSD as the third most common disorder treated at these clinics (5.7%), after MDD (72.7%) and bipolar disorder (15.1%).[27]

Future studies of ketamine for PTSD should additionally take advantage of the window of ketamine-induced neuroplasticity and investigate whether ketamine administration might enhance the effectiveness of psychotherapeutic interventions. Results of an open-label pilot study of ketamine plus cognitive-behavioral therapy in patients with TRD have been published, with promising results.[28] To date, formal studies examining whether ketamine might enhance the effects of psychotherapy in patients with PTSD have not been published. Future studies should investigate whether ketamine can interfere with reconsolidation or enhance extinction of trauma memories, thus potentially improving and prolonging maintenance of treatment response.[29]

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