KETAMINE AND PTSD

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Review

The potential of ketamine for posttraumatic stress disorder: a review of clinical evidence

Anya Ragnhildstveit, Jeremy Roscoe, Lisa C. Bass, Christopher L. Averill, Chadi G. Abdallah and Lynnette A. Averill

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***Abstract*:** Posttraumatic stress disorder (PTSD) is a devastating condition, for which there are few pharmacological agents, often with a delayed onset of action and poor efficacy. Trauma-focused psychotherapies are further limited by few trained providers and low patient engagement. This frequently results in disease chronicity as well as psychiatric and medical comorbidity, with considerable negative impact on quality of life. As such, off-label interventions are commonly used for PTSD, particularly in chronic refractory cases. Ketamine, an *N*-methyl-D-aspartate (NDMA) receptor antagonist, has recently been indicated for major depression, exhibiting rapid and robust antidepressant effects. It also shows transdiagnostic potential for an array of psychiatric disorders. Here, we synthesize clinical evidence on ketamine in PTSD, spanning case reports, chart reviews, open-label studies, and randomized trials. Overall, there is high heterogeneity in clinical presentation and pharmacological approach, yet encouraging signals of therapeutic safety, efficacy, and durability. Avenues for future research are discussed.

Keywords: clinical evidence, esketamine, ketamine, pharmacotherapy, posttraumatic stress disorder (PTSD), rapid-acting antidepressant (RAAD), treatment

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Introduction

of life. Moreover, several pre- and peri-trauma risk

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Is Prehospital Ketamine Associated With a Change in the Prognosis of PTSD?

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ABSTRACT

Introduction:

Ketamine is an alternative to opioids for prehospital analgesia following serious combat injury. Limited research has examined prehospital ketamine use, associated injuries including traumatic brain injury (TBI) and PTSD outcomes following serious combat injury.

Materials and Methods:

We randomly selected 398 U.S. service members from the Expeditionary Medical Encounter Database who sustained serious combat injuries in Iraq and Afghanistan, 2010-2013. Of these 398 patients, 213 individuals had charted prehospital medications. Clinicians reviewed casualty records to identify injuries and all medications administered. Outcomes were PTSD diagnoses during the first year and during the first 2 years postinjury extracted from military health databases. We compared PTSD outcomes for patients treated with either (a) prehospital ketamine (with or without opioids) or (b) prehospital opioids (without ketamine).

Results:

Fewer patients received prehospital ketamine (26%, 56 of 213) than only prehospital opioids (69%, 146 of 213) (5%, 11 of 213 received neither ketamine nor opioids). The ketamine group averaged significantly more moderate-to-serious injuries, particularly lower limb amputations and open wounds, compared with the opioid group (Ps < .05). Multivariable regressions showed a significant interaction between prehospital ketamine (versus opioids) and TBI on first-year PTSD ($P = .027$). In subsequent comparisons, the prehospital ketamine group had significantly lower odds of first-year PTSD (OR = 0.08, 95% CI [0.01, 0.71], $P = .023$) versus prehospital opioids only among patients who did not sustain TBI. We also report results from separate analyses of PTSD outcomes among patients treated with different prehospital opioids only (without ketamine), either morphine or fentanyl.

Conclusions:

The present results showed that patients treated with prehospital ketamine had significantly lower odds of PTSD during the first year postinjury only among patients who did not sustain TBI. These findings can inform combat casualty care guidelines for use of prehospital ketamine and opioid analgesics following serious combat injury.

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The emergence of ketamine as a novel treatment for posttraumatic stress disorder

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Abstract

A serious lack of effective pharmacotherapeutic interventions for posttraumatic stress disorder (PTSD) raises the urgent need for the development of novel treatments. Ketamine-a noncompetitive glutamate N-methyl-d-aspartate (NMDA) receptor antagonist in use for decades as an anesthetic and analgesic agent-has more recently been demonstrated to have rapid-onset antidepressant effects in patients with treatment-resistant depression (TRD). In the present review of ketamine as an emerging novel pharmacotherapeutic intervention for chronic PTSD, we discuss findings from the first proof-of-concept, randomized clinical trial (RCT) of single-dose intravenous ketamine in patients with chronic PTSD, as well as open-label studies and current practice. We introduce ongoing RCTs investigating the efficacy of repeated ketamine infusions in rapidly reducing symptoms and maintaining improvement in samples of individuals with PTSD stemming from civilian and military traumas. Additionally, we discuss mixed findings from published reports on ketamine administration in the acute aftermath of trauma. Studies in animal models of chronic stress have investigated molecular mechanisms underlying ketamine's effects, generating a shift in the conceptualization of PTSD as a disorder of impaired neural connectivity. We review animal studies examining the potential of ketamine to modify the expression of fear by altering memory reconsolidation or enhancing fear extinction, as well as

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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.

Citation

Liriano F, Hatten C, Schwartz TL. Ketamine as treatment for post-traumatic stress disorder: a review. Drugs in Context 2019; 8: 212305. DOI: 10.7573/dic.212305

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, 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

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Original Article

A retrospective study of ketamine administration and the development of acute or post-traumatic stress disorder in 274 war-wounded soldiers*

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Summary

The objective of this study was to explore whether ketamine prevents or exacerbates acute or post-traumatic stress disorders in military trauma patients. We conducted a retrospective study of a database from the French Military Health Service, including all soldiers surviving a war injury in Afghanistan (2010–2012). The diagnosis of post-traumatic stress disorder was made by a psychiatrist and patients were analysed according to the presence or absence of this condition. Analysis included the following covariables: age; sex; acute stress disorder; blast injury; associated fatality; brain injury; traumatic amputation; Glasgow coma scale; injury severity score; administered drugs; number of surgical procedures; physical, neurosensory or aesthetic sequelae; and the development chronic pain. Covariables related to post-traumatic and acute stress disorders with a $p \leq 0.10$ were included in a multivariable logistic regression model. The data from 450 soldiers were identified; 399 survived, of which 274 were analysed. Among these, 98 (36%) suffered from post-traumatic stress disorder and 89 (32%) had received ketamine. Fifty-four patients (55%) in the post-traumatic stress disorder group received ketamine vs. 35 (20%) in the no PTSD group ($p < 0.001$). The 89 injured soldiers who received ketamine had a median (IQR [range]) injury severity score of 5 (3–13 [1–26]) vs. 3 (2–4 [1–6] in the 185 patients who did not ($p < 0.001$). At multivariable analysis, only acute stress disorder and total number of surgical procedures were independently associated with the development of post-traumatic stress disorder. In this retrospective study, ketamine administration was not a risk factor for the development of post-traumatic stress disorder in the military trauma setting.

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Introduction

Ketamine has unquestionable advantages for pre-hospital anaesthesia [1, 2]. It is not clear, however, whether ketamine administration could increase or decrease psychological stress associated with traumatic events and thereby affect the subsequent development

Back to table of contents | Previous Article | Next Article

Articles

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A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder

Adriana Feder, M.D., Sara Costi, M.D., Sarah B. Rutter, M.A., Abigail B. Collins, B.S., Usha Govindarajulu, Ph.D., Manish K. Jha, M.D., Sarah R. Horn, M.A., Marin Kautz, M.A., Morgan Corniquel, M.A., Katherine A. Collins, Ph.D., M.S.W., Laura Bevilacqua, M.D., Ph.D., Andrew M. Glasgow, … See all authors

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Abstract

Objective:

Posttraumatic stress disorder (PTSD) is a chronic and disabling disorder, for which available pharmacotherapies have limited efficacy. The authors' previous proof-of-concept randomized controlled trial of single-dose intravenous ketamine infusion in individuals with PTSD showed significant and rapid PTSD symptom reduction 24 hours postinfusion. The present study is the first randomized controlled trial to test the efficacy and safety of repeated intravenous ketamine infusions for the treatment of chronic PTSD.

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