

Original Investigation

Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder

A Randomized Clinical Trial

Adriana Feder, MD; Michael K. Parides, PhD; James W. Murrough, MD; Andrew M. Perez, MD; Julia E. Morgan, BA; Shireen Saxena, MScPH; Katherine Kirkwood, MS; Marije aan het Rot, PhD; Kyle A. B. Lapidus, MD, PhD; Le-Ben Wan, MD, PhD; Dan Iosifescu, MD; Dennis S. Charney, MD

IMPORTANCE Few pharmacotherapies have demonstrated sufficient efficacy in the treatment of posttraumatic stress disorder (PTSD), a chronic and disabling condition.

OBJECTIVE To test the efficacy and safety of a single intravenous subanesthetic dose of ketamine for the treatment of PTSD and associated depressive symptoms in patients with chronic PTSD.

DESIGN, SETTING, AND PARTICIPANTS Proof-of-concept, randomized, double-blind, crossover trial comparing ketamine with an active placebo control, midazolam, conducted at a single site (Icahn School of Medicine at Mount Sinai, New York, New York). Forty-one patients with chronic PTSD related to a range of trauma exposures were recruited via advertisements.

INTERVENTIONS Intravenous infusion of ketamine hydrochloride (0.5 mg/kg) and midazolam (0.045 mg/kg).

MAIN OUTCOMES AND MEASURES The primary outcome measure was change in PTSD symptom severity, measured using the Impact of Event Scale–Revised. Secondary outcome measures included the Montgomery-Asberg Depression Rating Scale, the Clinical Global Impression–Severity and –Improvement scales, and adverse effect measures, including the Clinician-Administered Dissociative States Scale, the Brief Psychiatric Rating Scale, and the Young Mania Rating Scale.

RESULTS Ketamine infusion was associated with significant and rapid reduction in PTSD symptom severity, compared with midazolam, when assessed 24 hours after infusion (mean difference in Impact of Event Scale–Revised score, 12.7 [95% CI, 2.5–22.8]; $P = .02$). Greater reduction of PTSD symptoms following treatment with ketamine was evident in both crossover and first-period analyses, and remained significant after adjusting for baseline and 24-hour depressive symptom severity. Ketamine was also associated with reduction in comorbid depressive symptoms and with improvement in overall clinical presentation. Ketamine was generally well tolerated without clinically significant persistent dissociative symptoms.

CONCLUSIONS AND RELEVANCE This study provides the first evidence for rapid reduction in symptom severity following ketamine infusion in patients with chronic PTSD. If replicated, these findings may lead to novel approaches to the pharmacologic treatment of patients with this disabling condition.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00749203

JAMA Psychiatry. 2014;71(6):681–688. doi:10.1001/jamapsychiatry.2014.62
Published online April 16, 2014.

+ Supplemental content at
jamapsychiatry.com

+ CME Quiz at
jamanetworkcme.com and
CME Questions page 720

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Adriana Feder, MD, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl, PO Box 1230, New York, NY 10029 (adriana.feder@mssm.edu).

Posttraumatic stress disorder (PTSD) is a chronic and disabling condition arising after exposure to a severe traumatic event, characterized by persistent reexperiencing, avoidance, and hyperarousal symptoms. In the general population, prevalence has been estimated at 7.8%, with higher rates in trauma-exposed populations, particularly among survivors of interpersonal violence.^{1,2} To date, few pharmacotherapies have demonstrated sufficient efficacy in PTSD; selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and other medications are associated with significant levels of nonresponse and persistent residual symptoms, even in responders.³⁻⁵

Accumulating evidence for the role of glutamate, the most widely distributed excitatory neurotransmitter, in mediating stress responsivity, the formation of traumatic memories, and the pathophysiology of PTSD, suggests a potential benefit for novel pharmacotherapeutic interventions for this disorder.^{6,7} Recently, intravenous (IV) ketamine, an antagonist of the glutamate *N*-methyl-D-aspartate (NMDA) receptor, has emerged as an effective, rapidly acting intervention for patients with treatment-resistant depression when administered at subanesthetic doses of 0.5 mg/kg.⁸⁻¹⁰ Ketamine is used for anesthesia at doses of 2 mg/kg or higher and for analgesia at subanesthetic doses. It is considered particularly safe because, unlike other anesthetics, it reliably preserves breathing reflexes.¹¹ Sympathomimetic effects include moderate increases in blood pressure, heart rate, cardiac output, and oxygen consumption.¹² Acute psychological adverse effects can include perceptual disturbance, dissociative symptoms, and short-term cognitive impairment.^{13,14}

Few previous studies have examined the effects of ketamine in trauma-exposed individuals, and results from these studies have been mixed. A retrospective study¹⁵ of peritraumatic esketamine medication for patients who had been in accidents reported increased dissociative and acute stress disorder symptoms among these patients, assessed retrospectively 1 year after injury, as well as higher PTSD symptom levels, compared with those who received racemic ketamine or opioids. In a second, prospective naturalistic study¹⁶ of patients who had been in accidents, the patients who received racemic ketamine scored significantly higher than those treated with opioid or nonopioid analgesics on dissociative and acute stress disorder symptoms, within 3 days after admission to the hospital. In contrast, a medical record review of a larger sample of burned servicemembers found a significantly lower prevalence of PTSD among patients who received ketamine during posttrauma surgical procedures than among those who did not (26.89 vs 46.42%; $P = .04$).¹⁷ Furthermore, in secondary analyses from ketamine clinical trials in mood disorders,¹⁸ patients with PTSD or a history of trauma did not exhibit clinically significant increases in psychotic, dissociative, or anxiety symptoms after a single ketamine infusion. In a recently published case report,¹⁹ IV ketamine administered with propofol was associated with rapid and marked symptom improvement in a veteran with treatment-resistant PTSD.

To our knowledge, no randomized clinical trial examining the effects of ketamine in patients with chronic PTSD has been previously conducted. We conducted a proof-of-

concept, randomized, double-blind crossover study to test the effect of a single IV subanesthetic dose of ketamine in patients with chronic PTSD compared with IV administration of the benzodiazepine midazolam, the active placebo control condition. We hypothesized that ketamine would be associated with significantly greater reduction in core PTSD symptom levels 24 hours after a single IV infusion. We further hypothesized that ketamine would have a rapid antidepressant effect in patients with PTSD.

Methods

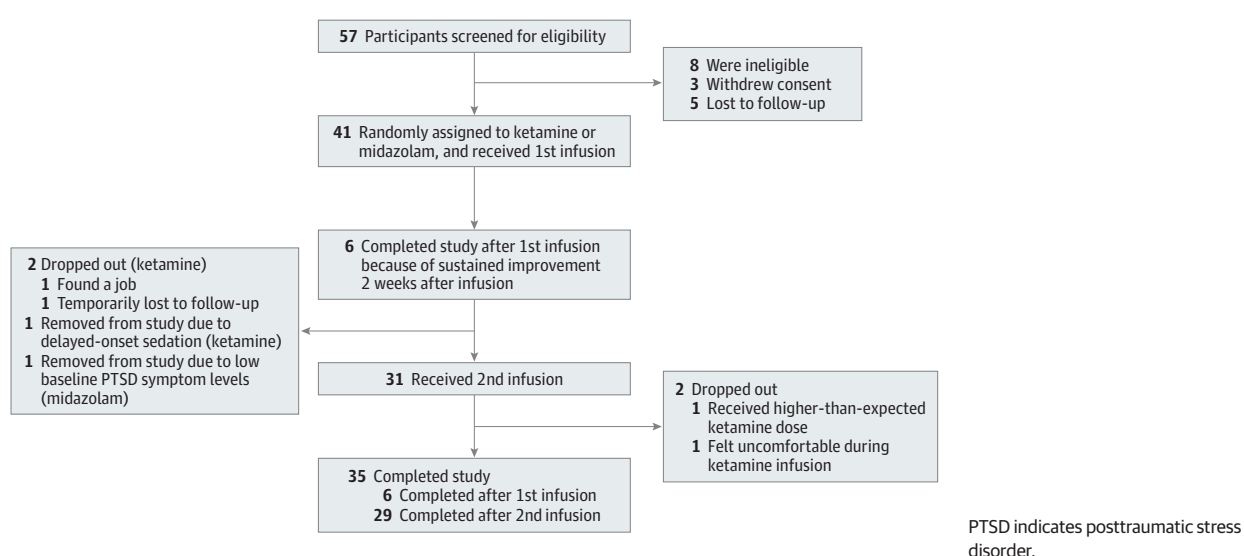
Patients with chronic PTSD were enrolled at the Icahn School of Medicine at Mount Sinai, New York, New York, between May 2009 and December 2012. Eligible participants were between 18 and 55 years of age, had a primary diagnosis of PTSD assessed with the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders–Patient Version²⁰ and a score of at least 50 on the Clinician-Administered PTSD Scale (CAPS).²¹ Exclusion criteria included a lifetime history of psychotic or bipolar disorder, current bulimia or anorexia nervosa, alcohol abuse or dependence in the previous 3 months, serious unstable medical illness or sleep apnea, active suicidal or homicidal ideation on presentation, or current use of any psychotropic medications. All patients underwent a physical examination and laboratory screening, including routine hematologic, biochemical, and urine toxicology testing, as well as undergoing electrocardiography to rule out unstable medical illness and active substance use. To receive the second IV infusion, a CAPS score of at least 50 was required prior to the second infusion. The institutional review board at Mount Sinai approved the study, and written informed consent was obtained from all study participants. Participants were compensated for their time.

Procedures

Study participants were free of concomitant psychotropic medications for 2 weeks prior to randomization and for the duration of the study. For each procedure day, patients were assigned to receive a single IV infusion of ketamine hydrochloride (0.5 mg/kg) or midazolam (0.045 mg/kg), administered over 40 minutes. The order of infusions (ketamine then midazolam or midazolam then ketamine) was randomly assigned, and administrations were 2 weeks apart. Midazolam was chosen as the active placebo control because its pharmacokinetic parameters and nonspecific behavioral effects are similar to those of ketamine. Only the research pharmacy was aware of drug identity, and all study personnel, including investigators, anesthesiologists, raters, patients, and data analysts, were blinded to randomization order.

Following admission to Mount Sinai's Clinical Research Unit and an overnight fast, an indwelling catheter was placed in the antecubital vein of the nondominant arm. Monitoring of pulse and blood pressure, pulse oximetry, and electrocardiographic monitoring were instituted (see Murrugh et al¹⁰ for details). Ratings were administered by a trained rater during infusions and 40, 120, and 240 minutes after infusion. A

Figure 1. Consolidated Standards of Reporting Trials Patient Flowchart



different trained rater, blinded to the ratings conducted during and after infusion on infusion days, administered ratings at preinfusion baseline and 24 hours (day 1) after infusion (before patients were discharged from the hospital), 48 hours (day 2) after infusion, 72 hours (day 3) after infusion, and 7 days (day 7) after infusion. Ratings were also administered 10 and 13 days after infusion, although data analyses focused on the first week after infusion owing to the expected duration of ketamine action. Patients were instructed to abstain from taking psychotropic medications and from using alcohol or substances of abuse for the duration of the trial. As already described, patients who scored 50 or higher on the CAPS 2 weeks after the first infusion received an infusion of the second study drug. Patients whose symptoms remained significantly improved 2 weeks after infusion (indicated by a CAPS score of <50 at 2 weeks) were considered to have completed the study after 1 infusion.

Outcomes

The primary outcome was PTSD symptom severity 24 hours after infusion, assessed with the Impact of Event Scale-Revised (IES-R).²² Twenty-four hours after infusion was selected as the primary end point because acute sedating and other side effects were expected to have resolved, while potential symptom improvement was expected to persist at 24 hours. Secondary outcome measures included the Montgomery-Asberg Depression Rating Scale (MADRS),²³ the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR),²⁴ and Clinical Global Impression-Severity (CGI-S) and -Improvement (GCI-I) scales²⁵ administered by a study clinician 24 hours, 48 hours, 72 hours, and 7 days after infusion. The IES-R was also administered 48 hours, 72 hours, and 7 days after infusion. The CAPS was administered at baseline and 7 days after infusion.

General side effects and possible dissociative, psychotomimetic, and manic symptoms were measured with the Pa-

tient-Rated Inventory of Side Effects,²⁶ the Clinician-Administered Dissociative States Scale,²⁷ the Brief Psychiatric Rating Scale, the 4-item positive symptoms subscale,²⁸ and item 1 (elevated mood) of the Young Mania Rating Scale.²⁹ The Patient-Rated Inventory of Side Effects is a 9-item self-report scale that inquires about side effects in 8 organ systems and other general side effects.

Statistical Analysis

The ability of ketamine to reduce PTSD symptoms was assessed in a proof-of-concept, randomized, double-blind, crossover trial. A total of 41 patients were enrolled, with order of treatment determined by randomization. The primary analysis adhered to a modified intention-to-treat principle, including all 29 patients with outcome assessments from both periods. A mixed-model approach was used to test effects of treatment, period, and carryover. An additional intention-to-treat analysis of covariance, adjusting for baseline IES-R score, was conducted with all 41 patients using only first-period data. All statistical tests were 2-sided .05-level tests. Secondary analyses of additional end points followed the same analytic approach as for the primary end point. No adjustment for multiple tests was made; all *P* values are reported at their nominal level. The primary interest was on changes in symptom outcomes observed during the first week, given the hypothesized duration of the effects of ketamine. A planned sample size of 40 patients randomly assigned to treatment order was estimated to provide 80% power to detect a hypothesized treatment difference in change in IES-R scores of 0.9 SD units 24 hours after infusion.

Secondary analyses also examined the effect of depression on PTSD symptoms and the interaction between treatment and depression. A mixed-model approach was used to examine the effects of treatment, baseline MADRS score, and 24-hour MADRS score using only first-period data. Safety and tolerability were analyzed using descriptive statistics.

Table 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	Ketamine ^a (n = 22)	Midazolam ^b (n = 19)
Age, mean (SD), y	36.4 (10.8)	35.7 (10.0)
Female, sex, No. (%)	13 (59.1)	6 (31.6)
Race, No. (%)		
Black	11 (50.0)	12 (63.2)
White	5 (22.7)	2 (10.5)
Other	6 (27.3)	5 (26.3)
Hispanic ethnicity, No. (%)	5 (22.7)	0 (0.0)
Education, ^c No. (%)		
<High school	1 (4.8)	0 (0.0)
High school graduate	3 (14.3)	3 (15.8)
Some college	12 (57.1)	14 (73.7)
≥4 Years of college	5 (23.8)	2 (10.5)
Unemployed, No. (%)	11 (50.0)	14 (73.7)
Married or cohabiting, No. (%)	5 (22.7)	3 (15.8)
Primary trauma, No. (%)		
Sexual assault or molestation	9 (40.9)	0 (0.0)
Physical assault or abuse	4 (18.2)	7 (36.8)
Accident or fire	1 (4.5)	3 (15.8)
Combat exposure	2 (9.1)	0 (0.0)
Witnessed violent assault or death	4 (18.2)	5 (26.3)
Witnessed 9/11 terrorist attacks	2 (9.1)	0 (0.0)
Duration of PTSD, mean (SD), y	14.2 (12.3)	11.9 (14.0)
History of treatment with psychotropic medication, No. (%)	11 (50.0)	8 (42.1)
CAPS score (past month), mean (SD)	82.5 (14.1)	77.1 (11.8)
QIDS-SR score, mean (SD)	12.4 (5.2)	11.3 (5.6) ^d

Abbreviations: CAPS, Clinician-Administered PTSD Scale; PTSD, posttraumatic stress disorder; QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Report.

^a Patients randomly assigned to receive ketamine first.

^b Patients randomly assigned to receive midazolam first.

^c Missing data for 1 patient who was randomly assigned to receive ketamine first (n = 21).

^d Missing data for 4 patients who were randomly assigned to receive midazolam first (n = 15).

Results

Study Participants

Of 57 potential participants who completed informed consent procedures, 41 met eligibility criteria and were randomly assigned to receive ketamine or midazolam during the first infusion. All 41 patients received study medication and completed 24-hour ratings; 29 of them completed both infusions and ratings following each infusion (Figure 1). Of the remaining 12 participants, 6 (all of whom had been randomly assigned to receive ketamine first) completed the study at 2 weeks, following only their first infusion and ratings, because their CAPS scores were less than 50 at 2 weeks, precluding the second infusion. Two additional participants also had

a CAPS score of less than 50 at 2 weeks, one who received ketamine first and the other who received midazolam first, but they both received their second infusion a week later (eTable 1 in Supplement).

Demographic and Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics of patients randomly assigned to receive ketamine or midazolam. All patients had chronic PTSD, in most cases persisting for several years with moderate to severe symptoms (Table 1). Fewer than 50% of the participants had received psychotropic medication in the past, generally 1 or 2 antidepressants with partial or no response (although occasionally with good response), and few had received additional medications such as a benzodiazepine, a sedative-hypnotic agent, prazosin hydrochloride, or an atypical antipsychotic agent. Prior to beginning study procedures, only 2 patients required a psychotropic medication taper, one from topiramate and the other from amphetamine/dextroamphetamine mixed salts.

Primary Outcome

In the crossover analysis, total IES-R scores 24 hours after infusion were significantly improved with ketamine compared with midazolam (mean difference, 12.7 [95% CI, 2.5-22.8]; $P = .02$). There was no evidence of any period or residual effects for the crossover. In addition, symptoms in 7 patients randomly assigned to ketamine first remained significantly reduced after infusion, compared with only 1 patient randomly assigned to midazolam first. Analysis of IES-R scores at 24 hours based on the first period only, including all 41 randomly assigned patients, agreed closely (mean difference, 8.6 [95% CI, 0.94-16.2]; $P = .03$). Neither a diagnosis of major depressive disorder at screening nor the MADRS score at preinfusion baseline had a significant effect on the change in IES-R score at 24 hours.

Secondary Outcomes

Additional 24-Hour Outcomes and CAPS Scores at 7 days

Ketamine had a similar effect on the 3 PTSD symptom clusters, measured by the IES-R subscales (Table 2 and Figure 2). In crossover analyses with 29 patients, the CGI-S and CGI-I scores at 24 hours were also significantly better following ketamine (Table 2). Analysis of CGI-S and CGI-I scores at 24 hours based on the first period only, including all 41 randomly assigned patients, supported the findings from crossover analyses (Table 2). Crossover analyses (29 patients) of MADRS and QIDS-SR scores at 24 hours did not yield any significant effect of ketamine treatment over the control condition. The mean CAPS score 7 days after infusion did not differ significantly by treatment (mean difference between ketamine and midazolam, 8.7 [95% CI, -4.8 to 22.2]; $P = .20$) (eTables 2-4 in Supplement). Results did not change after analyses were conducted without the 2 patients who received their second infusion 1 week later.

Comorbid Depressive Symptoms

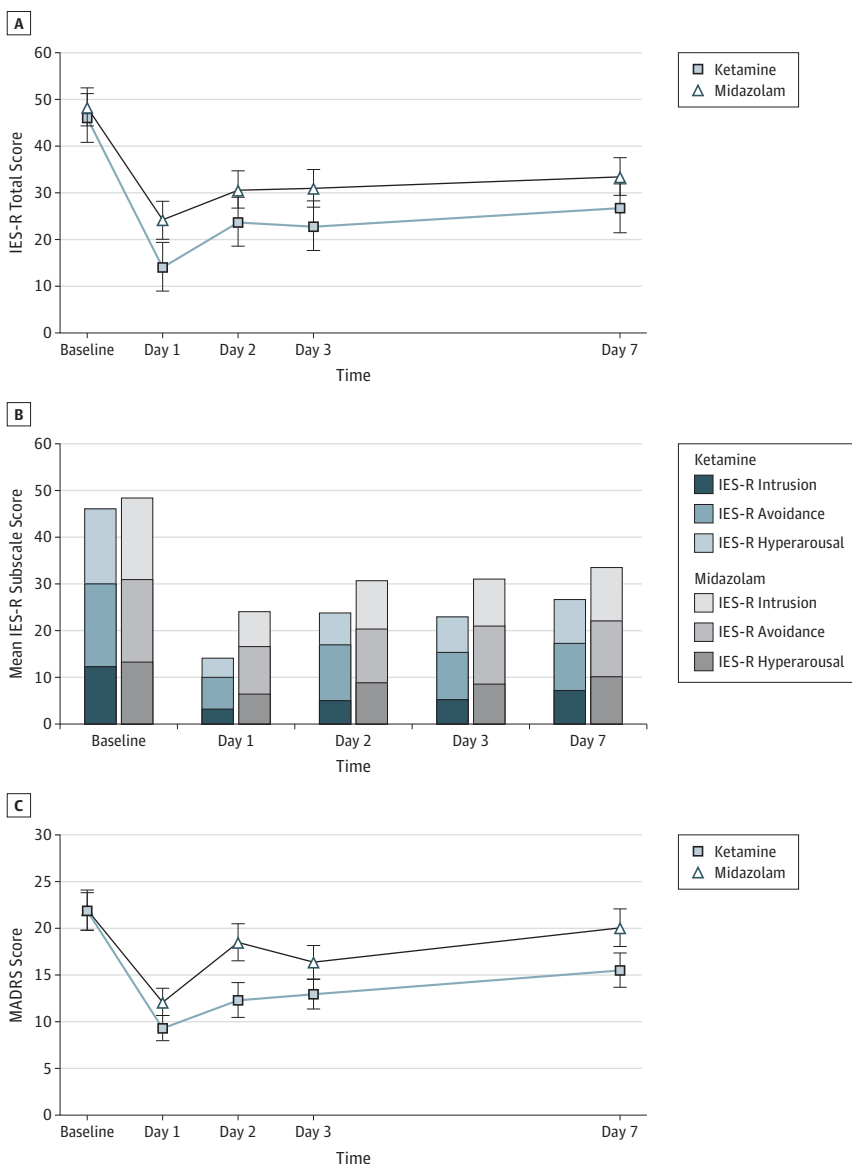
In additional first-period analyses with all 41 patients, treatment assignment ($\beta = 6.5$, $P = .0496$), MADRS score 24 hours

Table 2. Clinical Improvement at 24 Hours in IES-R Score and Secondary Outcomes: Crossover and First Infusion Results

Measure	Crossover (n = 29)		First Infusion (n = 41)	
	Mean Difference (95% CI)	P Value	Mean Difference (95% CI)	P Value
IES-R total score ^a	12.7 (2.5-22.8)	.02	8.6 (0.9-16.2)	.03
Intrusion	4.0 (-0.3 to 8.3)	.07	2.6 (-0.8 to 6.0)	.13
Avoidance	4.8 (0.2-9.3)	.04	3.3 (-0.7 to 6.8)	.06
Hyperarousal	3.9 (0.6-7.2)	.02	2.6 (0.2-4.9)	.03
CGI-S scale score	1.0 (0.1-1.9)	.03	0.9 (0.3-1.5)	.003
CGI-I scale score	1.2 (0.5-1.9)	.003	0.8 (0.2-1.3)	.005
QIDS-SR score	0.2 (-3.9 to 4.3)	.93	1.5 (-1.1 to 4.2)	.25
MADRS score	3.7 (-7.5 to 14.9)	.51	2.7 (-1.7 to 7.1)	.23

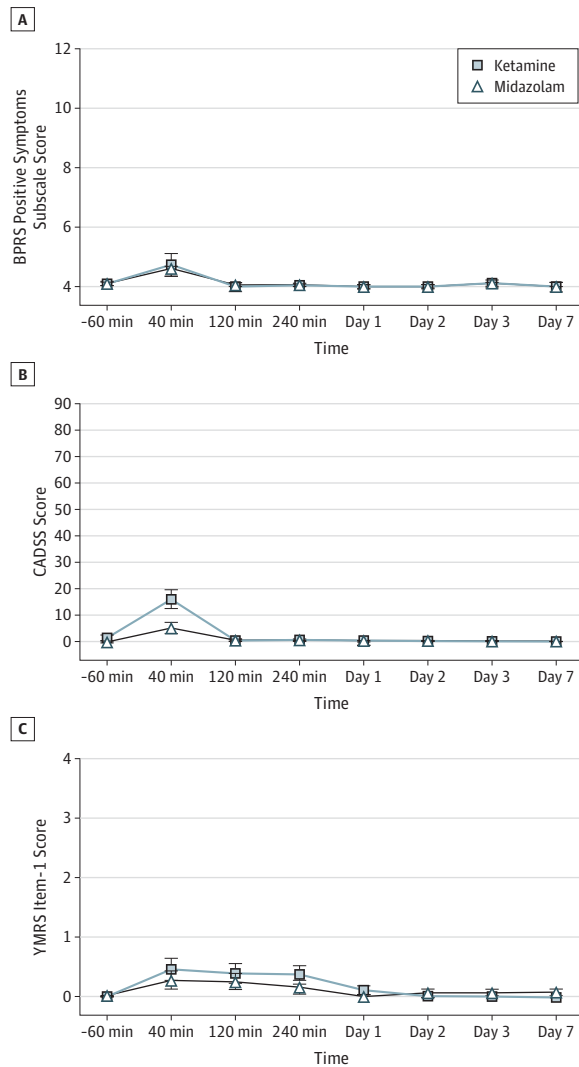
Abbreviations: CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; IES-R, Impact of Event Scale-Revised; MADRS, Montgomery-Asberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Report.
^a Primary outcome measure.

Figure 2. Changes in Posttraumatic Stress Disorder and Depressive Symptom Levels During the First Period



Change in the Impact of Event Scale-Revised (IES-R) total score, the IES-R mean subscale scores, and the Montgomery-Asberg Depression Rating Scale (MADRS) score over 1 week for the first period (n = 41). Error bars represent standard errors. For this study, the IES-R was modified to inquire about symptoms over the previous 24 hours (instead of the previous 7 days).

Figure 3. Emergence of Psychotic, Dissociative, and Manic Symptoms During the First Period



Change in the Brief Psychiatric Rating Scale (BPRS) Positive Symptoms subscale score (4 items corresponding to the positive symptoms of psychosis), the Clinician-Administered Dissociative States Scale (CADSS) score, and the Young Mania Rating Scale (YMRS) item-1 score (elevated mood) over 1 week for the first period (n = 41). Error bars represent standard errors. On the CADSS, 27 of 39 participants (69%) reported at least 1 dissociative symptom of at least moderate intensity while receiving ketamine, and 13 of 31 participants (42%) reported at least 1 dissociative symptom of at least moderate intensity while receiving midazolam, measured 40, 120, and 240 minutes after infusion.

after infusion ($\beta = 0.9, P = .0004$), and baseline IES-R score ($\beta = 0.2, P = .04$) were shown to have significant effects on the IES-R score 24 hours after infusion, with ketamine showing significantly better improvement than midazolam. Baseline MADRS score and the interaction between 24-hour MADRS score and treatment were not significant predictors of IES-R score 24 hours after infusion.

Durability of Drug Effect

Generalized linear mixed modeling analyses of the first period only, including all 41 randomized patients, evaluated

IES-R, MADRS, and QIDS-SR scores 24, 48, and 72 hours and 7 days after infusion as a function of treatment, time, and treatment-by-time interaction (Figure 2). Analyses demonstrated a significant effect of treatment on the IES-R score (differences of least squares means estimate, $-8.32 [P = .046]$) and the QIDS-SR score ($-2.73 [P = .050]$) and a significant effect of time on the IES-R, MADRS, and QIDS-SR scores. The effect of treatment on the MADRS score approached significance ($-3.99 [P = .052]$). There were no significant treatment-by-time interactions.

Adverse Events

Dissociative symptoms after treatment with ketamine were short-lived, peaking at 40 minutes, and had resolved by the next assessment 120 minutes from start of infusion (Figure 3). No emergence of significant psychotic or manic symptoms was observed (Figure 3). One participant dropped out after his second infusion (ketamine), stating that he felt uncomfortable during the infusion owing to likely dissociative effects. Infusion was discontinued after 15 minutes for another patient who received a higher dose of ketamine in error. Three patients required acute treatment with β -blockers during ketamine infusion because of blood pressure elevation (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >100 mm Hg). With the Patient-Rated Inventory of Side Effects, the most frequently reported general adverse effects of ketamine (vs midazolam) in the first 24 hours following infusion included blurred vision (36% vs 19%), dry mouth (21% vs 16%), restlessness (23% vs 10%), fatigue (21% vs 23%), nausea/vomiting (21% vs 3%), poor coordination (15% vs 3%), and headache (13% vs 13%) (eTable 5 in Supplement).

Discussion

A single dose of ketamine, compared with a psychoactive placebo control medication, was associated with rapid reduction in core PTSD symptoms in patients with chronic PTSD, and benefit frequently was maintained beyond 24 hours. Symptoms remained significantly reduced at 2 weeks in 7 patients who responded to ketamine compared with 1 patient who responded to midazolam, as indicated by a CAPS score of less than 50. These data provide the first randomized, controlled evidence that NMDA receptor modulation can lead to the rapid clinical reduction of core PTSD symptoms in patients with chronic PTSD. Greater reduction in PTSD symptom severity following ketamine infusion compared with midazolam infusion remained significant even after adjusting for baseline and 24-hour depressive symptom severity. Although the reductions in PTSD and depressive symptoms might be related, this finding suggests an effect of ketamine on PTSD symptom levels over and above the effects on depressive symptoms. Ketamine was also associated with the reduction in comorbid depressive symptoms, possibly broadening the therapeutic use of NMDA receptor modulation for the treatment of depressive symptoms in PTSD patients, who frequently have comorbid major depressive disorder. Patients also showed improvement in global clinical ratings following ketamine infusion. Although reduction in

depressive symptoms in patients with PTSD who received ketamine was less pronounced than that reported in studies of patients with treatment-resistant major depressive disorder, this sample was not selected for the presence of major depressive disorder or for depressive symptom severity.

We also demonstrated that a single dose of IV ketamine is a safe and generally well-tolerated intervention for patients with chronic PTSD; ketamine was associated with only transient dissociative symptoms, without significant emergence of psychotic or manic symptoms. These initial findings also allay concerns about possible worsening of PTSD symptoms following ketamine administration, at least in patients with chronic PTSD, including any sustained induction or worsening of dissociative symptoms. Our findings necessitate replication and further study.

The strengths of our study include the enrollment of patients with moderate to severe PTSD symptom levels, the use of the active placebo control midazolam, which strengthened the blind (compared with saline solution) because midazolam can also induce transient psychoactive effects, and the shielding of the primary outcome rater from adverse effects occurring during the day of infusion. Of note, ketamine demonstrated a superior effect to that of midazolam, despite the fact that midazolam may have a potential acute benefit in a study of patients with chronic PTSD, because it is also a well-known anxiolytic. Although practice guidelines recommend against the use of benzodiazepines for the treatment of PTSD,^{4,30} only 2 randomized clinical trials examining benzodiazepine efficacy in PTSD treatment have been published.^{31,32} Benzodiazepines, through their actions on the γ -aminobutyric acid A receptor complex, have demonstrated anxiolytic, sedative, hypnotic, muscle relaxant, and amnesic effects in patients with anxiety disorders and other conditions.^{33,34}

The biological mechanisms underlying the effects of ketamine, a glutamate NMDA receptor antagonist, in patients with PTSD are unknown. The role of glutamate in memory formation, including trauma-related memories, and in the pathophysiology of PTSD has recently received increased attention.^{6,7,35} Although acute stress enhances glutamate trans-

mission in the prefrontal cortex, chronic stress disrupts it.^{36,37} Animal studies have demonstrated reductions in synaptic density and complexity in the prefrontal cortex and hippocampus secondary to chronic stress.³⁷ More recently, ketamine has been shown to rapidly increase the number and function of synaptic connections in the prefrontal cortex, rapidly reversing behavioral and neuronal changes resulting from chronic stress in rats, partially through activation of the mammalian target of rapamycin signaling pathway and stimulation of brain-derived neurotrophic factor signaling.³⁷⁻³⁹

The limitations of our study include the fact that several patients did not receive a second infusion, but in half of these patients, this second infusion was prevented per protocol because of sustained reduction in PTSD symptom levels 2 weeks after ketamine infusion. Ketamine was associated with transient but higher rates of dissociative symptoms than midazolam, likely affecting the blind. The present study also does not address the important question of the safety or efficacy of ketamine in combination with other psychotropic medications in PTSD. Ketamine is associated with very few drug-drug interactions, and no contraindications exist to its combination with antidepressants, benzodiazepines, or other psychotropic medications.

Conclusions

Our results provide the first evidence that a single dose of IV ketamine was associated with rapid reduction of core PTSD symptoms and reduction in comorbid depressive symptoms in patients with chronic PTSD and that it was generally well tolerated without clinically significant persistent dissociative symptoms. Future studies are needed for replication, and they should examine the efficacy and safety of ketamine administration beyond a single infusion for patients with chronic PTSD, explore the use of ketamine anesthesia to prevent the emergence of PTSD symptoms in surgical patients with a history of trauma, investigate the mechanisms of ketamine action, and identify pretreatment predictors of response to this intervention.

ARTICLE INFORMATION

Submitted for Publication: August 20, 2013; final revision received January 2, 2014; accepted January 7, 2014.

Published Online: April 16, 2014.
doi:10.1001/jamapsychiatry.2014.62.

Author Affiliations: Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Feder, Murrough, Morgan, Lapidus, Wan, Iosifescu, Charney); Department of Health Evidence and Policy, Icahn School of Medicine at Mount Sinai, New York, New York (Parides, Kirkwood); Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York (Murrough, Lapidus, Iosifescu, Charney); Department of Anesthesiology, Icahn School of Medicine at Mount Sinai, New York, New York (Perez); School of Public Health, Charité-Universitätsmedizin Berlin, Berlin,

Germany (Saxena); Department of Psychology, University of Groningen, Groningen, the Netherlands (aan het Rot); Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, New York (Charney).

Author Contributions: Drs Feder and Parides had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Feder, aan het Rot.

Acquisition, analysis, or interpretation of data: Feder, Parides, Murrough, Perez, Morgan, Saxena, Kirkwood, Lapidus, Wan, Iosifescu, Charney.

Drafting of the manuscript: Feder, Parides, Kirkwood.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Feder, Parides, Kirkwood.

Obtained funding: aan het Rot.

Administrative, technical, or material support: Murrough, Perez, Morgan, Saxena, aan het Rot, Lapidus, Wan.

Study supervision: Feder, Parides, Murrough, Perez, Iosifescu, Charney.

Conflict of Interest Disclosures: Dr Charney and the Icahn School of Medicine at Mount Sinai have been named on a use patent application of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and received approval from the US Food and Drug Administration for this indication, Dr Charney and Mount Sinai could benefit financially. In the present year, after study completion, Drs Charney and Feder and Mount Sinai were named on a use patent application of ketamine for the treatment of PTSD. If ketamine were shown to be effective in the treatment of PTSD and received approval from the US Food and Drug Administration for this indication, Drs Charney

and Feder and Mount Sinai could benefit financially. No other disclosures are reported.

Funding/Support: This study was funded by grant W81XWH-08-1-0602 from the Department of the Army-US Army Medical Research Acquisition Activity (Dr Charney, principal investigator).

Role of the Sponsor: The funding agency had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Solara Calderon, BA, provided assistance with participant recruitment and ratings. Jazmin Moral, LCSW, provided assistance with clinical assessments and ratings. The Clinical Research Unit staff at Mount Sinai provided assistance with study procedures. Jess Brallier, MD, an anesthesiologist, provided occasional assistance with study procedures. They all received financial compensation.

REFERENCES

- Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995;52(12):1048-1060.
- Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. *Arch Gen Psychiatry*. 1998; 55(7):626-632.
- Ravindran LN, Stein MB. Pharmacotherapy of PTSD: premises, principles, and priorities. *Brain Res*. 2009;1293:24-39.
- Jeffreys M, Capehart B, Friedman MJ. Pharmacotherapy for posttraumatic stress disorder: review with clinical applications. *J Rehabil Res Dev*. 2012;49(5):703-715.
- Committee on Treatment of Posttraumatic Stress Disorder; Board on Population Health and Public Health Practice; Institute of Medicine. *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence*. Washington, DC: National Academies Press; 2008.
- Nair J, Singh Ajit S. The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectr*. 2008;13(7):585-591.
- Riaza Bermudo-Soriano C, Perez-Rodriguez MM, Vaquero-Lorenzo C, Baca-Garcia E. New perspectives in glutamate and anxiety. *Pharmacol Biochem Behav*. 2012;100(4):752-774.
- Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63(8):856-864.
- Mathew SJ, Shah A, Lapidus K, et al. Ketamine for treatment-resistant unipolar depression: current evidence. *CNS Drugs*. 2012;26(3):189-204.
- Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. 2013; 170(10):1134-1142.
- Fabbri LP, Batacchi S, Linden M, et al. Anaesthesia for urological endoscopic procedures in adult outpatients. *Eur J Anaesthesiol*. 1995;12(3): 319-324.
- Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med*. 2008;26(9):985-1028.
- Duncan EJ, Madonick SH, Parwani A, et al. Clinical and sensorimotor gating effects of ketamine in normals. *Neuropsychopharmacology*. 2001;25(1): 72-83.
- Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994;51(3):199-214.
- Schönenberg M, Reichwald U, Domes G, Badke A, Hautzinger M. Effects of peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. *Psychopharmacology (Berl)*. 2005;182(3): 420-425.
- Schönenberg M, Reichwald U, Domes G, Badke A, Hautzinger M. Ketamine aggravates symptoms of acute stress disorder in a naturalistic sample of accident victims. *J Psychopharmacol*. 2008;22(5): 493-497.
- McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. *J Trauma*. 2008;64(2 suppl):S195-S198; Discussion S197-S198.
- Zeng MC, Niciu MJ, Luckenbaugh DA, et al. Acute stress symptoms do not worsen in posttraumatic stress disorder and abuse with a single subanesthetic dose of ketamine. *Biol Psychiatry*. 2013;73(12):e37-e38.
- D'Andrea D, Andrew Sewell R. Transient resolution of treatment-resistant posttraumatic stress disorder following ketamine infusion. *Biol Psychiatry*. 2013;74(9):e13-e14.
- First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders—Research Version (Patient Edition) (SCID-I/P)*. New York, NY: Biometrics Research Dept, Columbia University at NYSPI; 2002.
- Weathers FW, Keane TM, Davidson JR. Clinician-administered PTSD scale: a review of the first ten years of research. *Depress Anxiety*. 2001;13 (3):132-156.
- Weiss DS, Marmar CR. The Impact of Event Scale-Revised. In: Wilson J, Keane TM, eds. *Assessing Psychological Trauma and PTSD*. New York, NY: Guilford; 1996:399-411.
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.
- Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573-583.
- Guy W. *ECDEU Assessment Manual for Psychopharmacology—Revised, 1976*. Rockville, MD; US Dept of Health, Education, and Welfare; Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration; National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.
- Rush AJ, Fava M, Wisniewski SR, et al; STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004;25(1): 119-142.
- Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress*. 1998;11(1):125-136.
- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. *Psychopharmacol Bull*. 1988;24:97-99.
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429-435.
- VA/DoD Clinical Practice Guidelines: management of post-traumatic stress disorder and acute stress reaction (2010). US Department of Veterans Affairs web site. <http://www.healthquality.va.gov/ptsd/>. Accessed March 11, 2014.
- Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *J Clin Psychiatry*. 1990;51(6):236-238.
- Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. *Ann Pharmacother*. 2004;38(9):1395-1399.
- López-Muñoz F, Alamo C, García-García P. The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: half a century of anxiolytic drugs. *J Anxiety Disord*. 2011;25(4):554-562.
- Dubovsky SL. Approaches to developing new anxiolytics and antidepressants. *J Clin Psychiatry*. 1993;54(suppl):75-83.
- Steckler T, Risbrough V. Pharmacological treatment of PTSD—established and new approaches. *Neuropharmacology*. 2012;62(2):617-627.
- Yuen EY, Wei J, Liu W, Zhong P, Li X, Yan Z. Repeated stress causes cognitive impairment by suppressing glutamate receptor expression and function in prefrontal cortex. *Neuron*. 2012;73(5): 962-977.
- Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012;338(6103):68-72.
- Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010;329(5994):959-964.
- Li N, Liu RJ, Dwyer JM, et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry*. 2011;69 (8):754-761.