Efficacy, Safety, and Durability of Repeated Ketamine Infusions for Comorbid Posttraumatic Stress Disorder and Treatment-Resistant Depression

C. Sophia Albott, MD, MA[a,b,*]; Kelvin O. Lim, MD[a,c]; Miriam K. Forbes, PhD[a]; Christopher Erbes, PhD[b]; Susanna J. Tye, PhD[d]; John G. Grabowski, PhD[a]; Paul Thuras, PhD[b]; Tegan M. Batres-y-Carr, BA[a]; Joseph Wels, MD[e]; and Paulo R. Shiroma, MD[a,b]

ABSTRACT

Objective: The present study examined the efficacy, safety, and durability of repeated ketamine infusions for the treatment of comorbid posttraumatic stress disorder (PTSD) and treatment-resistant depression (TRD) in a sample of veterans.

Methods: Individuals with comorbid *DSM-5*–defined PTSD and *DSM-IV*–defined major depressive disorder (N = 15) received 6 intravenous ketamine infusions (0.5 mg/kg) on a Monday-Wednesday-Friday schedule over a 12-day period from May 2015 to June 2016. Data from outcome measures were collected before and 24 hours after each infusion and weekly for 8 weeks following the final infusion.

Results: Continuous measures of symptom change were significant for both disorders and were associated with large effect sizes (mean decrease in PTSD Checklist for *DSM-5* score = 33.3 points [95% CI, 23.0–43.5 points], $P < .0005$, sample size–adjusted Cohen *d* [*d'*] = 2.17; mean decrease in Montgomery-Asberg Depression Rating Scale score = 26.6 points [95% CI, 23.0–30.2 points], $P < .0005$, $d' = 4.64$). The remission rate for PTSD was 80.0%, and the response rate for TRD was 93.3%. Participants in remission from PTSD after the infusion series (n = 12) had a median time to relapse of 41 days. Similarly, participants whose depression symptoms responded to the infusion series (n = 14) had a median time to relapse of 20 days. Repeated ketamine infusions were associated with transient increases in dissociative symptoms. No participant reported worsening of PTSD symptoms over the study duration.

Conclusions: This study, the first open-label study of repeated ketamine infusions in a comorbid population, found rapid and sustained improvement in PTSD and depression symptoms. This report suggests that repeated ketamine treatments are safe and may represent an efficacious treatment for individuals with comorbid PTSD and TRD.

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[a]Department of Psychiatry, University of Minnesota Medical School, Minneapolis, Minnesota

[b]Mental Health Service Line, Minneapolis VA Health Care System, Minneapolis, Minnesota

[c]Geriatric Research Education and Clinical Center, Minneapolis VA Health Care System, Minneapolis, Minnesota

[d]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota

[e]Department of Anesthesiology, Minneapolis VA Health Care System, Minneapolis, Minnesota

**Corresponding author:* C. Sophia Albott, MD, MA, Department of Psychiatry, University of Minnesota Medical School, F282/2A West, 2450 Riverside Ave, Minneapolis, MN 55454-1495 (albot002@umn.edu).

Trauma has a variety of psychiatric sequelae, often including multiple comorbid psychiatric diagnoses. Major depressive disorder (MDD) co-occurs in a majority of individuals with posttraumatic stress disorder (PTSD), and the co-occurrence of these disorders is associated with a more severe clinical presentation compared to either disorder alone.[1–5] Individuals with comorbid PTSD and MDD have worse functional impairment[6,7] and increased risk for suicide[8–10] compared to individuals with only one of these disorders. Further, the presence of either disorder diminishes treatment efficacy for the other and increases risk for treatment resistance.[10–12] Overall, the co-occurrence of PTSD and MDD appears to be an indicator of a more severe response to trauma exposure.[13] The high rates of comorbidity between PTSD and MDD have thus led to the suggestion that their co-occurrence may be better conceptualized as a general traumatic stress construct.[4,14,15]

Antidepressant agents, such as serotonin reuptake inhibitors, are recommended as first-line pharmacologic agents for the treatment of PTSD and MDD.[16,17] However, these agents have limited efficacy in establishing remission for either disorder in a substantial proportion of individuals. Data from the largest and longest clinical trial for the treatment of MDD, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[18] demonstrated that only 36.8% of individuals remitted from MDD after treatment with a first-line antidepressant medication. Similarly, antidepressant pharmacotherapy for PTSD is associated with high rates of residual PTSD symptoms, even among individuals who respond to these agents.[19–21] This literature attests to the inadequacy of standard antidepressant pharmacotherapy as a treatment for many individuals with a diagnosis of PTSD or MDD, let alone for individuals with the more complex and severe comorbid presentation.

As a consequence of the shortcomings of traditional antidepressants, there has been growing interest in the rapid antidepressant effects of ketamine—an *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist.[22–24] Six randomized clinical trials[22–29] of single-dose ketamine have been conducted in

Clinical Points

- Although comorbid posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) commonly co-occur and represent a sizeable public health burden, few evidence-based treatments address this common constellation.
- For individuals with comorbid PTSD and MDD as well as 2 or more antidepressant failures, this study provides the first open-label evidence that serial ketamine infusions may represent an efficacious treatment alternative.

individuals who failed to respond to multiple antidepressant treatments, a subgroup described as having treatment-resistant depression (TRD). These trials demonstrated consistent patterns in treatment trajectories, including a rapid antidepressant response that peaks 24 hours after ketamine administration and subsequently declines over the following 7 to 14 days.[22–29] Single-dose studies[30] of ketamine have demonstrated that acute stress symptoms do not worsen in subjects with PTSD and a history of trauma. A recent double-blind placebo-controlled trial[31] of a single dose of ketamine in individuals with chronic PTSD demonstrated rapid reduction in PTSD symptoms. Consonant with single-dose studies of ketamine for depression, improvement in PTSD symptoms was transient, with only 24.1% of individuals who received ketamine maintaining improvement 14 days post-infusion.[31]

While treatment response is short-lived after single-dose ketamine infusions, open-label case series[32–35] have demonstrated repeated ketamine infusions are more effective, with a longer period of antidepressant response in individuals with TRD. However, no studies have examined repeated ketamine infusions for PTSD. It was therefore imperative to determine whether a repeated dosing regimen would extend the short-lived improvement in PTSD symptoms and to examine the efficacy of this dosing regimen for treating comorbid PTSD and TRD. On the basis of the reported efficacy for PTSD or TRD separately, we hypothesized that benefit would accrue in demonstrating the efficacy of ketamine for comorbid PTSD and TRD. Addressing this premise, we examined (1) the efficacy and safety of repeated ketamine infusions (6 infusions over a 2-week period) for individuals with comorbid PTSD and TRD; (2) the time to relapse, following repeated infusions, for both PTSD and depressive symptoms; and (3) whether the efficacy of repeated infusions for PTSD is limited to symptoms that overlap with depressive symptoms (eg, negative alterations in cognition and mood) or extends to symptoms unique to PTSD (eg, intrusion symptoms).

METHODS

Participants

The study was conducted at the Minneapolis VA Health Care System (MVAHCS) from May 2015 to June 2016; it was approved by the Institutional Review Board and registered at ClinicalTrials.gov (identifier: NCT02577250). Written informed consent was obtained from all participants before participation. Study participants included male and female veterans, aged 18–75 years, with diagnoses of moderate-to-severe[a] TRD and chronic PTSD. A trained study clinician determined PTSD and MDD diagnosis using the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5)[37,38] and the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Clinical Trials Version,[39] respectively. TRD was operationalized as a failure to achieve remission[b] from a minimum of 2 antidepressant medications in their current depressive episode according to the Antidepressant Treatment History Form.[40] Participants continued on stable doses of their current psychotropic medication(s) for the study duration. Exclusion criteria included any unstable medical[c] or nonpsychiatric central nervous system condition, moderate-to-severe traumatic brain injury, active substance use disorder (per *DSM-5* criteria) in the previous 6 months, lifetime history of *DSM-5*–defined psychosis or bipolar I or II disorder, or active suicidal ideation judged to present imminent risk. Women of childbearing potential were required to have a negative urine pregnancy test result and to remain on a medically accepted contraceptive for the study duration.

Procedures

Baseline assessments occurred up to 2 weeks before infusion commencement. All infusions occurred on the Flexible Acuity Ward at the MVAHCS and were administered by an advanced cardiovascular life support–trained study physician.[d] Each participant was confirmed to be *nil per os* (NPO) before infusion commencement. Digital pulse oximetry, blood pressure, heart rate, and respiratory rate were monitored throughout the infusion and recovery period. Participants completed 6 intravenous (IV) infusions (0.5 mg/kg ketamine hydrochloride given during 40 minutes) on a Monday-Wednesday-Friday schedule during a 12-day period. Side effects were recorded before each infusion, following infusion completion (40 minutes), and at 100 and 160 minutes post-infusion. All participants were monitored for a minimum of 2 hours post-infusion to ascertain the absence of clinically significant side effects.

Measures

The primary outcomes were change in PTSD symptom score, assessed with the PTSD Checklist for *DSM-5* (PCL-5),[41] and change in depression score, assessed with the Montgomery-Asberg Depression Rating Scale (MADRS).[42]

[a]Depression severity was assessed using the 17-item Hamilton Depression Rating Scale with all participants required to have a score greater than or equal to 14.[36]
[b]Remission was defined as elimination of depressive symptoms with restoration of premorbid level of functioning.
[c]All participants were confirmed to be medically fit to receive ketamine by physical examination, review of systems, vital signs, weight, and consultation with the study anesthesiologist.
[d]Because the doses of ketamine were considered moderate sedation, our institution did not require infusions to be administered by a clinician trained in conscious sedation, although the study anesthesiologist was available for consultation throughout the infusion and monitoring period.

Secondary outcomes included change in CAPS-5 score, proportion of individuals in remission[e] from PTSD (defined as PCL-5 total score < 33)[43] following completion of the infusion series, proportion of individuals meeting depression response criteria (≥ 50% improvement in baseline MADRS score) and depression remission criteria (MADRS score ≤ 9)[44] at the conclusion of the infusion series, change in scores on PCL-5 subscales (intrusion, avoidance, negative alterations in cognition and mood, and marked alterations in arousal and reactivity), and proportion of individuals relapsing for either PTSD or depression during the follow-up period. The PCL-5 and MADRS were administered 1 hour before and 24 hours after each infusion. Primary and secondary outcome measures were obtained weekly throughout an 8-week period following the sixth infusion.

Side effects and tolerability were assessed using the Clinician-Administered Dissociative States Scale (CADSS),[45] the 4-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+),[46] and the single elevated-mood item from the Young Mania Rating Scale (YMRS-1).[47]

Statistical Analysis

Descriptive statistics were calculated to summarize sociodemographic variables, primary and secondary outcomes, and side effect measures. Changes in outcome measures from baseline (pretest) to 24 hours after the sixth infusion (posttest) were examined using repeated-measures analyses of variance. Magnitude of change during treatment (pretest to posttest) and following treatment (posttest to follow-up after 4 weeks) were compared for PTSD and depression symptoms using the small sample size bias–adjusted Cohen *d* (*d*′) on a *z*-score distribution. Time to relapse was estimated using Kaplan-Meier survival analysis with a log rank test for participants who met criteria for PTSD remission and/or depression response at the conclusion of the infusion series.[f] Changes in side effects between time points were analyzed using paired *t* tests.

RESULTS

Study Participants

Twenty-four individuals provided signed informed consent and underwent screening procedures. Eligibility criteria were met by 19 participants; 2 participants withdrew consent before treatment, and 1 individual withdrew from the study after the first infusion due to personal circumstances. Another individual completed all 6 infusions; however, this individual's outcome data were incomplete secondary to a change in the study protocol and thus were excluded from the analyses. Table 1 presents sociodemographic and baseline characteristics of participants who received all 6 infusions and had complete outcome data (N = 15).

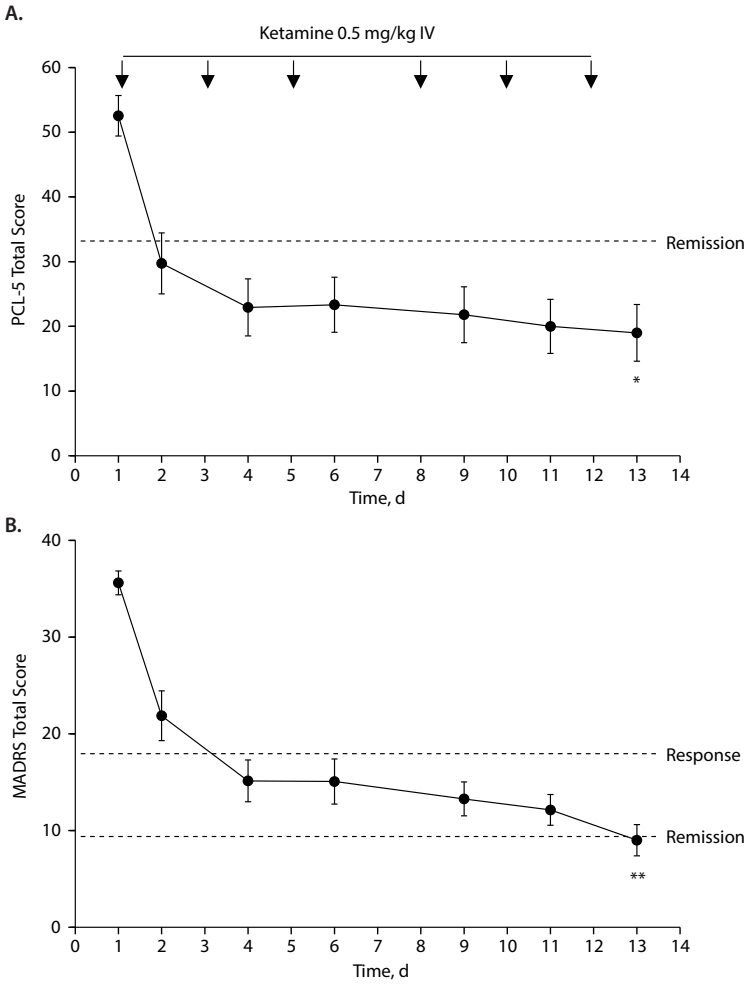
Table 1. Demographics and Clinical Characteristics of the Study Sample (N = 15)[a]

Variable	Value
Sociodemographics	
Age at enrollment, y	52.1 ± 14.4
Female, n (%)	5 (33.3)
Ethnic minority, n (%)	1 (6.7)
Education, y	14.8 ± 2.3
Married, n (%)	11 (73.3)
Depression characteristics	
Baseline depression (HDRS score)	26.8 ± 7.3
Baseline depression (MADRS score)	35.6 ± 4.8
Age at onset of MDD, y	24.5 ± 11.0
Duration of current MDE, y	24.3 ± 17.7
Single MDE in lifetime, n (%)	12 (75)
No. of failed antidepressant trials (current MDE)	3.1 ± 1.0
Lifetime history of ECT, n (%)	1 (6.7)
Lifetime history of suicide attempt, n (%)	3 (20.0)
PTSD characteristics	
Baseline PTSD (CAPS-5 score)	39.7 ± 9.3
Age at onset of PTSD, y	26.0 ± 12.3
Duration of PTSD symptoms, y	26.1 ± 18.4
Primary trauma, n (%)	
Combat exposure	8 (53.3)
Sexual assault	5 (33.3)
Accident or fire	1 (6.7)
Physical assault or abuse	1 (6.7)
Order of onset, n (%)	
Depressive symptoms first	9 (60.0)
PTSD symptoms first	3 (20.0)
Simultaneous onset	3 (20.0)
Additional comorbid psychiatric conditions (current or lifetime), n (%)	
Obsessive-compulsive disorder	1 (6.7)
Panic disorder	1 (6.7)
Attention-deficit/hyperactivity disorder	1 (6.7)
Borderline personality disorder	1 (6.7)
Past substance use disorder	4 (26.7)
No. of psychoactive medications per participant at enrollment	2.9 ± 1.9
No. of antidepressant medications per participant at enrollment[b]	1.3 ± 0.9
Concomitant psychotropic medications by class per participant at enrollment, n (%)	
SRI	2 (13.3)
SNRI	5 (33.3)
Tricyclic/heterocyclic antidepressant	2 (13.3)
Other antidepressant[c]	7 (46.7)
Mood stabilizer[d]	5 (33.3)
Antipsychotic	2 (13.3)
Benzodiazepine[e]	2 (13.3)
Z-drug sedative-hypnotic	5 (33.3)
Stimulant	3 (20)
Opiate	3 (20)
Prazosin	4 (26.7)

[a]Values shown as mean ± SD unless otherwise noted.
[b]Current number of antidepressant medications references the number of antidepressants that each participant was taking at study entry. This number does not reflect the number of medications participants were required to have minimally failed for study entry, per the Antidepressant Treatment History Form (ATHF).
[c]Includes bupropion, mirtazapine, trazodone, and nefazodone.
[d]Includes antiepileptic medications and lithium.
[e]Although 2 participants were prescribed benzodiazepine medications, neither took these medications in the hours preceding infusions as all participants were required to be NPO.
Abbreviations: CAPS-5 = Clinician Administered PTSD Scale for *DSM-5*, ECT = electroconvulsive therapy, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MDE = major depressive episode, NPO = nil per os, PTSD = posttraumatic stress disorder, SRI = serotonin reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, Z-drug = nonbenzodiazepine anti-insomnia drug.

[e]Although depression symptom response is a well-defined metric in depression research, there is no equivalent metric for PTSD. Thus, only remission from PTSD was assessed as an outcome.
[f]Ie, individuals who were able to relapse.

Figure 1. Change in Mean (A) PTSD Symptom and (B) Depressive Symptom Levels After Repeated Ketamine Infusions in a Sample of Individuals (N = 15) With Comorbid Chronic PTSD and TRD[a]



[a](A) Change in PTSD symptoms as measured by the PCL-5. (B) Change in depression severity as measured by the MADRS. Error bars represent standard errors. IV ketamine (0.5 mg/kg) was administered during a 12-day period on a Monday-Wednesday-Friday schedule, corresponding to days 1, 3, 5, 8, 10, and 12. MADRS and PCL-5 were administered at baseline and at 24 hours after each infusion when the peak antidepressant response was hypothesized to occur. Cohen *d'* values are sample size–adjusted values. The timing of the ketamine infusions shown at the top of part A applies to part B as well.

*Mean change in PCL-5 score was significantly decreased 24 hours after the sixth infusion (day 13) compared to baseline (day 1; $P < .0001$) and was associated with a large effect size (Cohen $d' = 2.17$).

**Mean change in MADRS score was significantly decreased 24 hours after the sixth infusion (day 13) compared to baseline (day 1; $P < .0001$) and was associated with a large effect size (Cohen $d' = 4.64$).

Abbreviations: IV = intravenous, MADRS = Montgomery-Asberg Depression Rating Scale, PCL-5 = PTSD Checklist for *DSM-5*, PTSD = posttraumatic stress disorder, TRD = treatment-resistant depression.

Efficacy

The mean within-subject change in PTSD symptoms significantly decreased over the course of treatment from baseline to 24 hours after the sixth ketamine infusion ($F_{2.62,36.70} = 30.169$, $P < .0005$, $d' = 2.17$) (Figure 1A; Table 2). Similarly, the mean within-subject change in depression symptoms significantly decreased over the course of treatment ($F_{2.79,39.03} = 56.713$, $P < .0005$, $d' = 4.64$) (Figure 1B; Table 2). The effect size for mean decrease in symptom severity during treatment was 2.14 times larger for depression compared to PTSD, and this difference was significant ($z = 2.92$, $P = .003$).

Secondary Outcomes

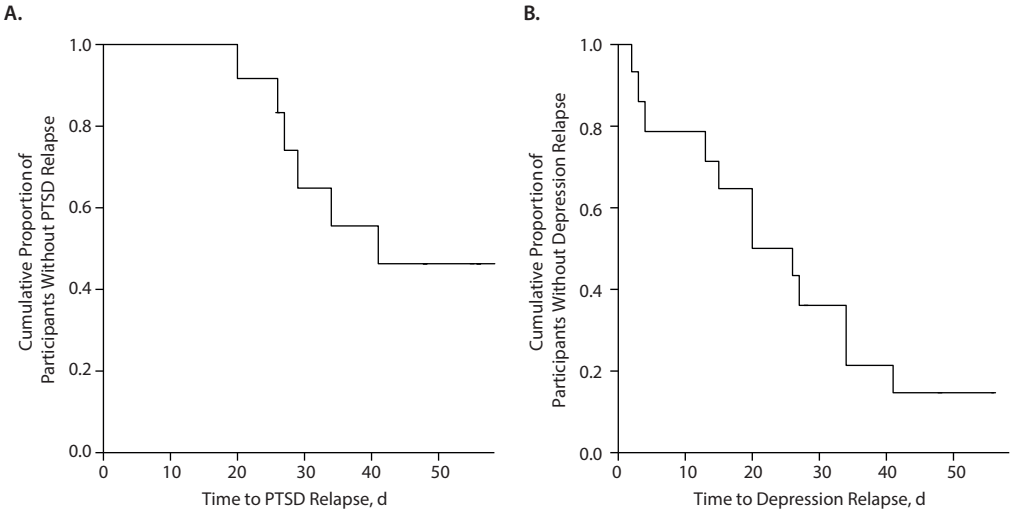
PTSD symptom severity assessed by clinician interview (CAPS-5) demonstrated a significant reduction in total score after completion of the 6-infusion series ($t_{14} = 6.44$, $P < .0005$, $d' = 1.85$) (Table 2). After the first infusion, 9 (60.0%) of 15 individuals remitted from PTSD, whereas 12 (80.0%) of 15 individuals were in PTSD remission after the sixth infusion (Figure 1). Depression response criteria were met by 3 (20.0%) of 15 participants after the first infusion whereas 14 (93.3%) of 15 individuals showed depression response after the sixth infusion. Depression remission was observed in 2 (13.3%) of 15 individuals after the first infusion and in 9 (60.0%) of 15 individuals after the sixth infusion. Repeated ketamine infusions demonstrated significant reductions in all 4 PTSD symptom clusters ($d' \geq 1.49$) (Table 2).

Relapse Rate

Individuals whose PTSD symptoms were in remission (n = 12) and/or whose depression symptoms responded (n = 14) to the ketamine infusion series were followed for up to 56 days to estimate time to relapse (Figure 2). All 12 individuals in remission from PTSD also had response for depression; 3 individuals demonstrated depression response without PTSD remission. At 14 days posttreatment, 80% of the total sample (n = 12) were in PTSD remission, 40% (n = 6) were in depression remission, and 66.7% (n = 10) had response for depression. Of the 12 individuals in PTSD remission, the median time to relapse was 41 days, with the 50th and 75th percentiles at 41 and 27 days, respectively (Figure 2A). The 25th percentile was not calculated because 6 individuals (50% of individuals in PTSD remission; 40% of the total sample) remained in remission from PTSD throughout the follow-up period. Of the 14 individuals with depression response, the median time to relapse was 20 days with the 25th and 75th percentiles at 34 and 13 days, respectively (Figure 2B). Two individuals (14.3% of individuals with depression response; 13.3% of the total sample) did not have a relapse of depression symptoms and remained responders through the follow-up period.

Paired-samples *t* tests showed that the mean PTSD symptom severity was significantly higher at 4 weeks' follow-up (n = 10), compared to symptoms 24 hours after the sixth infusion ($t_9 = 3.42$, $P = .008$), but this change was associated with a small effect size ($d' = 0.24$).

Figure 2. Kaplan-Meier Survival Curves for (A) PTSD and (B) Depression Symptoms Following Repeated Ketamine Infusions[a]



[a](A) Survival analyses for PTSD symptoms during the 8-week follow-up period. Relapse was defined as PCL-5 total score > 33. Median time to PTSD relapse was 41 days, but a standard error could not be calculated because 50% of the sample remained in remission for the duration of the follow-up period. (B) Survival analyses for depression symptoms during the 8-week follow-up period. Relapse was defined as < 50% improvement from baseline MADRS total score. Median ± SE time to depression relapse was 20 ± 6.86 days.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, PCL-5 = PTSD Checklist for *DSM-5*, PTSD = posttraumatic stress disorder.

Table 2. Clinical Improvement (mean change) in Posttraumatic Stress Disorder (PTSD) and Depressive Symptoms From Baseline to 24 Hours After the Sixth Ketamine Infusion and Associated Effect Sizes[a]

	Difference			
Measure	Mean	95% CI	*P*	Cohen *d'*
PCL-5 score				
Total	33.27	23.04–43.50	< .0005	2.17
Intrusion	8.27	4.26–12.23	.001	1.49
Avoidance	3.53	2.07–5.00	< .0005	1.67
Negative alterations in mood/cognition	11.47	8.19–14.74	< .0005	2.10
Changes in arousal/ reactivity	10.67	7.47–13.87	< .0005	2.10
MADRS total score	26.60	22.98–30.22	< .0005	4.64
CAPS-5 total score	18.93	12.62–25.24	< .0005	1.85

[a]The *P* values result from repeated-measures analyses of variance comparing baseline (pretest) to 24 hours after the sixth ketamine infusion (posttest). Statistical significance was defined at an α level of .05. Magnitude of change during treatment (pretest to posttest) was assessed using Cohen *d'* on a *z*-score distribution. Cohen *d'* values are sample size–adjusted values.

Abbreviations: CAPS-5 = Clinician Administered PTSD Scale for *DSM-5*, CI = confidence interval, MADRS = Montgomery-Asberg Depression Rating Scale, PCL-5 = PTSD Checklist for *DSM-5*, PTSD = posttraumatic stress disorder.

The mean depression symptom severity was also significantly higher at 4 weeks' follow-up (n = 11) compared to symptoms 24 hours after the sixth infusion ($t_{10} = 4.76$, $P = .001$) and was associated with a large effect size ($d' = 1.42$). The effect size for mean increase in symptom severity at 4 weeks' follow-up was 5.92 times larger for depression compared to PTSD, and this difference in effect sizes approached significance ($z = 1.92$, $P = .054$).

Side Effects

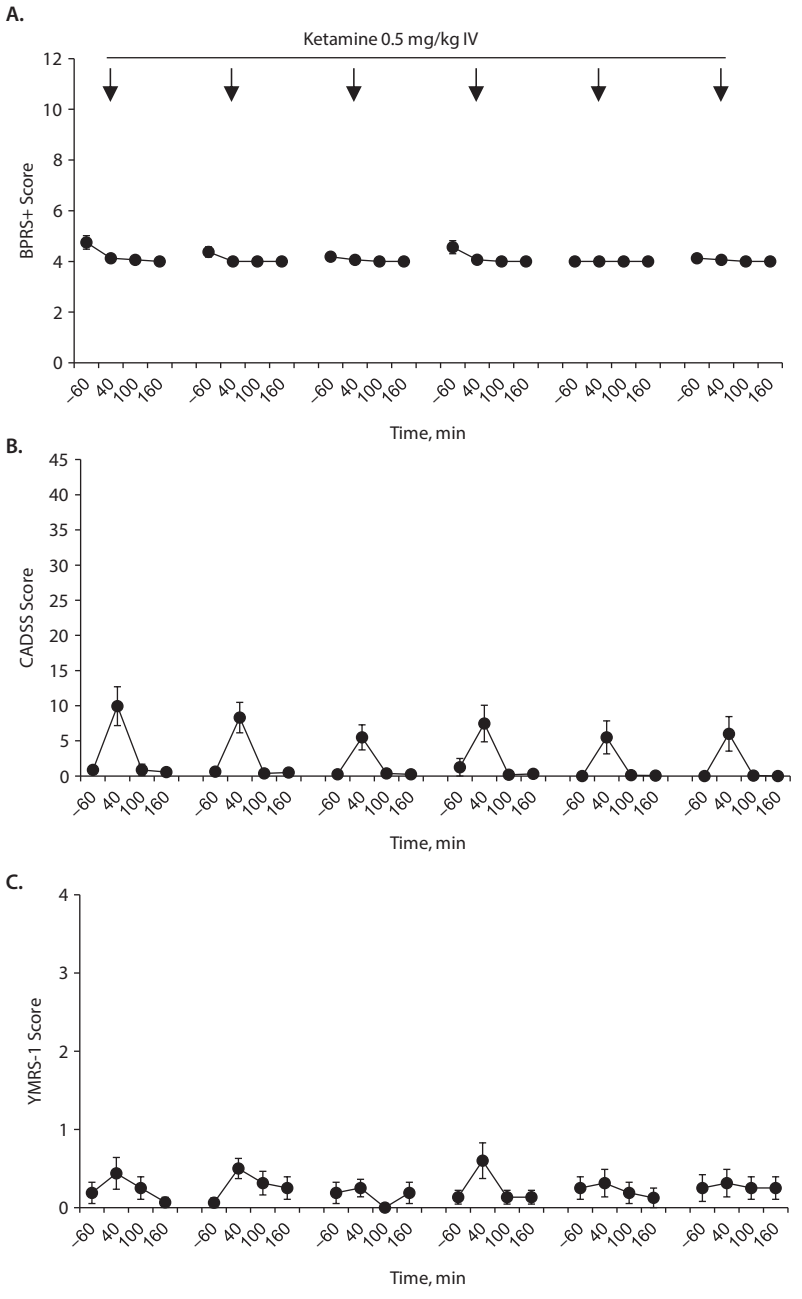
A small increase in dissociative symptoms was observed immediately after each ketamine infusion, but these symptoms returned to baseline levels by the end of the recovery period (Figure 3). Pre-infusion increases in psychotomimetic symptoms (in the form of paranoia) were observed in 7 individuals. However, ketamine was associated with a decrease in psychotomimetic symptoms post-infusion, which persisted through the recovery period (Figure 3). No significant increase in elevated mood symptoms was observed (Figure 3). There was no trend suggesting an increase in dissociative or psychotomimetic side effects over the 6-infusion course (Figure 3). No veterans experienced a worsening of PTSD symptoms from baseline at any point during the trial. Three participants (20%) required treatment with β-blockers[g] because of blood pressure elevation (systolic blood pressure > 180 mm Hg and/or diastolic blood pressure > 100 mm Hg).

DISCUSSION

Our data provide the first evidence that repeated infusions of subanesthetic ketamine effectively and rapidly reduce symptoms associated with comorbid chronic PTSD and TRD in a veteran population. Although this was a diagnostically complex and severely ill population, we found substantial and enduring response in PTSD and depression symptoms using the repeated infusion regimen, which was safe and well-tolerated. These findings have important therapeutic implications for previously treatment-resistant individuals.

[g]One-time dose administered during the infusion.

Figure 3. Mean Change in (A) Psychotic, (B) Dissociative, and (C) Manic Symptoms During 6 Repeated Ketamine Infusions[a]



[a]Change in (A) BPRS+ subscale score (4 items consistent with the positive symptoms of psychosis), (B) CADSS total score, and (C) YMRS-1 score during the course of the 6-infusion series. Error bars represent standard errors. The timing of the ketamine infusions shown at the top of part A applies to parts B and C as well.

Abbreviations: BPRS+ = Brief Psychiatric Rating Scale Positive Symptoms, CADSS = Clinician-Administered Dissociative States Scale, YMRS-1 = Young Mania Rating Scale single item score (elevated mood).

Compared with previous studies of antidepressant agents for PTSD, the 6-infusion regimen achieved larger effect sizes.[h] In a recent meta-analysis[48] of treatments for PTSD, the largest effect size for antidepressant pharmacotherapy was for paroxetine ($g = 0.74$), with the majority falling in the small to medium range ($g = 0.14$–0.74). In this study, repeated ketamine infusions also demonstrated significant improvement across PTSD symptom clusters, which highlights the effectiveness of the repeated dosing regimen for PTSD symptoms over and above depressive symptom response. The greatest treatment effect sizes were observed for the negative alterations in cognition and mood cluster and for the marked alterations in arousal and reactivity cluster, which may be related to depression symptom overlap. However, large effect sizes were also observed for improvements in the avoidance and intrusion clusters, which suggests an effect of ketamine on PTSD-specific symptoms. Moreover, the effectiveness of the ketamine intervention across PTSD symptom subclusters and depression symptoms suggests the disorders may share a common underlying substrate, supporting the idea of a generalized traumatic stress syndrome.[4,14,15]

Repeated infusions resulted in a longer period of symptom reduction for PTSD and depression compared to single infusions for either disorder. In the only other study of ketamine for PTSD,[31] 24.1% of individuals receiving a single ketamine infusion demonstrated significant PTSD symptom reduction 2 weeks post-infusion. In the current study, 80% of our sample with PTSD remission maintained response for 2 weeks, more than 3 times the rate reported for a single infusion.[31] Moreover, the median time to PTSD relapse was 41 days, with 50% of the sample remaining in remission throughout the follow-up period. The results were similarly positive for depression symptom reduction compared to results with single infusions. A meta-analysis[49] of randomized controlled trials of single infusions of ketamine for depressive symptoms reported a pooled response rate of 10.9% and a pooled remission rate of 2.6% at 14 days posttreatment. In contrast, following repeated ketamine infusions, 66.7% of individuals remained in response, and 40% of individuals continued in remission from depressive symptoms 14 days post–infusion series. It is important to note that the aforementioned studies were placebo-controlled and, as such, the response and remission rates are not directly comparable to the present open-label study. Nevertheless, our higher response rates provide preliminary evidence that multiple

[h]Although Hedges *g* and sample size–adjusted Cohen *d* (*d'*) use different calculations for determining effect sizes, they are comparable standardized metrics using the same convention for interpreting magnitude of effect.

ketamine infusions may achieve a more durable period of response for both PTSD and depression symptoms.

This study was not powered to detect moderating or mediating effects for improvement or relapse in depression symptoms on PTSD symptoms, or vice versa. Nevertheless, comparison of effect sizes for depression and PTSD symptoms enables standardized contrasting of the degree of symptom change. There was a statistically significant difference in effect sizes between depression symptoms and PTSD symptoms after the 6-infusion series, in which the treatment effect for depressive symptoms was significantly greater than that for PTSD symptoms. Depressive symptoms also had a 5.9 times larger effect size for mean symptom relapse in the 4 weeks following treatment compared to PTSD symptoms. Thus, while it appears that the acute treatment response was stronger for depression, the PTSD treatment response may be more sustained. This observation was also reflected in the median times to relapse, which were greater for PTSD than for depression.

Differences in the magnitude of effect after the infusion series and at 4 weeks of follow-up suggest that differences, and commonalities, may exist in biological processes or neural circuits affected by the ketamine intervention. The effect of ketamine on these processes may impact disease symptoms in different ways. Preclinical studies[50,51] have demonstrated that glutamatergic signaling plays a role in depression, stress responsivity, traumatic memory formation, and the pathophysiology of PTSD. Chronic stress has been shown to mediate reciprocal neuroplastic changes in the amygdala compared to the prefrontal cortex and hippocampus[52]—structures known to be affected in PTSD and depression.[53–57] Thus, the improvement across PTSD symptom clusters, as well as differences in PTSD and depression relapse rates, supports the notion that ketamine has differential effects on neuroplastic processes depending on the neuroanatomical locations. Alternatively, the study design, which required individuals to evaluate their PTSD symptoms daily to weekly, may have represented a form of exposure therapy that facilitated extinction learning. Given ketamine's demonstrated role in rapidly stimulating synaptic plasticity,[58,59] ketamine may have enhanced extinction learning via these mechanisms, thereby extending the period of remission for PTSD symptom clusters. Other glutamatergic modulators, such as D-cycloserine, have demonstrated similar effects.[60]

This study also demonstrated that the regimen of repeated ketamine infusions was safe and well-tolerated. Ketamine was associated with transient increases in dissociative symptoms that peaked immediately following infusion cessation but resolved within 2 hours. We also saw no significant emergence of manic or psychotic symptoms associated with repeated infusions. This finding replicates those of Feder et al.[31] Our results extend those findings by demonstrating that multiple exposures to a dissociative anesthetic does not result in the sustained worsening of dissociative symptoms in individuals with chronic PTSD.

The strengths of this study include the enrollment of individuals with moderate-to-severe symptom levels and the inclusion of military veterans with chronic PTSD. In previous studies,[61,62] veterans from the Vietnam era with combat-related PTSD have been noted to be particularly treatment refractory with regards to both medication and psychotherapy. In the current study, 50% of the participants were Vietnam-era veterans, all of whom responded to the intervention. Repeated ketamine infusions may be well-suited to this highly refractory population.

Our study had several limitations. Notably, the open-label design without a placebo control limits the interpretation of efficacy. Our preliminary findings warrant further examination in a larger placebo-controlled clinical trial. A larger study could also address moderating and mediating effects of improvement and relapse in PTSD and depression symptoms.

In conclusion, this study is the first prospective study of repeated infusions of subanesthetic ketamine for comorbid PTSD and TRD. The treatment was associated with rapid response of PTSD symptoms and symptoms of previously treatment-resistant depression. Further, the maintenance of response for both PTSD and depressive symptoms was more durable than the periods of response reported in extant single-infusion studies. Repeated infusions were well-tolerated by all individuals without any worsening of dissociative symptoms outside of the acute infusion period. In short, repeated ketamine infusions may represent an efficacious, durable, and safe treatment for a clinically complex and high-risk population that has historically been difficult to treat.

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REFERENCES

1. Rytwinski NK, Scur MD, Feeny NC, et al. The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. *J Trauma Stress*. 2013;26(3):299–309.
2. Hankin CS, Spiro A 3rd, Miller DR, et al. Mental disorders and mental health treatment among US Department of Veterans Affairs outpatients: the Veterans Health Study. *Am J Psychiatry*. 1999;156(12):1924–1930.
3. Shore JH, Vollmer WM, Tatum EL. Community patterns of posttraumatic stress disorders. *J Nerv Ment Dis*. 1989;177(11):681–685.
4. O'Donnell ML, Creamer M, Pattison P. Posttraumatic stress disorder and depression following trauma: understanding comorbidity.

Am J Psychiatry. 2004;161(8):1390–1396.
5. Shalev AY, Freedman S, Peri T, et al. Prospective study of posttraumatic stress disorder and depression following trauma. *Am J Psychiatry*. 1998;155(5):630–637.
6. Breslau N, Davis GC, Andreski P, et al. Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Arch Gen Psychiatry*. 1991;48(3):216–222.
7. Post LM, Zoellner LA, Youngstrom E, et al. Understanding the relationship between co-occurring PTSD and MDD: symptom severity and affect. *J Anxiety Disord*. 2011;25(8):1123–1130.
8. Oquendo MA, Friend JM, Halberstam B, et al. Association of comorbid posttraumatic stress disorder and major depression with greater risk for suicidal behavior. *Am J Psychiatry*. 2003;160(3):580–582.
9. Bolton JM, Pagura J, Enns MW, et al. A population-based longitudinal study of risk factors for suicide attempts in major depressive disorder. *J Psychiatr Res*. 2010;44(13):817–826.
10. Pukay-Martin ND, Pontoski KE, Maxwell MA, et al. The influence of depressive symptoms on suicidal ideation among US Vietnam-era and Afghanistan/Iraq-era veterans with posttraumatic stress disorder. *J Trauma Stress*. 2012;25(5):578–582.
11. Friedman ES, Davis LL, Zisook S, et al. Baseline depression severity as a predictor of single and combination antidepressant treatment outcome: results from the CO-MED trial. *Eur Neuropsychopharmacol*. 2012;22(3):183–199.
12. Kaplan MJ, Klinetob NA. Childhood emotional trauma and chronic posttraumatic stress disorder in adult outpatients with treatment-resistant depression. *J Nerv Ment Dis*. 2000;188(9):596–601.
13. Bedard-Gilligan M, Duax Jakob JM, Doane LS, et al. An investigation of depression, trauma history, and symptom severity in individuals enrolled in a treatment trial for chronic ptsd. *J Clin Psychol*. 2015;71(7):725–740.
14. Sher L. A model of suicidal behavior in war veterans with posttraumatic mood disorder. *Med Hypotheses*. 2009;73(2):215–219.
15. Dekel S, Solomon Z, Horesh D, et al. Posttraumatic stress disorder and depressive symptoms: joined or independent sequelae of trauma? *J Psychiatr Res*. 2014;54:64–69.
16. VA/DoD Clinical Practice Guideline Working Group. *Management of Post-Traumatic Stress*. Washington, DC: VA Office of Quality and Performance; 2010.
17. American Psychiatric Association. *American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric Disorders: Compendium 2006*. Washington, DC: American Psychiatric Association; 2006.
18. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–1917.
19. Ravindran LN, Stein MB. Pharmacotherapy of PTSD: premises, principles, and priorities. *Brain Res*. 2009;1293:24–39.
20. Jeffreys M, Capehart B, Friedman MJ. Pharmacotherapy for posttraumatic stress disorder: review with clinical applications. *J Rehabil Res Dev*. 2012;49(5):703–715.
21. Institute of Medicine. *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence*. Washington, DC: National Academies Press; 2008.
22. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47(4):351–354.
23. 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.
24. 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.
25. Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010;67(8):793–802.
26. Zarate CA Jr, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry*. 2012;71(11):939–946.
27. Sos P, Klirova M, Novak T, et al. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuroendocrinol Lett*. 2013;34(4):287–293.
28. Lai R, Katalinic N, Glue P, et al. Pilot dose—response trial of iv ketamine in treatment-resistant depression. *World J Biol Psychiatry*. 2014;15(7):579–584.
29. Lapidus KAB, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry*. 2014;76(12):970–976.
30. 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.
31. Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2014;71(6):681–688.
32. aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry*. 2010;67(2):139–145.
33. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry*. 2013;74(4):250–256.
34. Rasmussen KG, Lineberry TW, Galardy CW, et al. Serial infusions of low-dose ketamine for major depression. *J Psychopharmacol*. 2013;27(5):444–450.
35. Shiroma PR, Johns B, Kuskowski M, et al. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord*. 2014;155:123–129.
36. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
37. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress*. 1995;8(1):75–90.
38. Weathers FW, Blake DD, Schnurr PP, et al. The Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5). US Department of Veterans Affairs website. https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp. 2013.
39. First MB, Williams JB, Spitzer RL, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-CT)*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2007.
40. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):10–17.
41. Weathers FW, Litz BT, Keane TM, et al. The PTSD Checklist for *DSM-5* (PCL-5). US Department of Veterans Affairs website. https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp. 2013.
42. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
43. Bovin MJ, Marx BP, Weathers FW, et al. Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychol Assess*. 2016;28(11):1379–1391.
44. Hawley CJ, Gale TM, Sivakumaran T, Hertfordshire Neuroscience Research group. Defining remission by cut off score on the MADRS: selecting the optimal value. *J Affect Disord*. 2002;72(2):177–184.
45. 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.
46. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10(3):799–812.
47. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
48. Watts BV, Schnurr PP, Mayo L, et al. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry*. 2013;74(6):e541–e550.
49. Newport DJ, Carpenter LL, McDonald WM, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry*. 2015;172(10):950–966.
50. Nair J, Singh Ajit S. The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectr*. 2008;13(7):585–591.
51. Riaza Bermudo-Soriano C, Perez-Rodriguez MM, Vaquero-Lorenzo C, et al. New perspectives in glutamate and anxiety. *Pharmacol Biochem Behav*. 2012;100(4):752–774.
52. Vyas A, Mitra R, Shankaranarayana Rao BS, et al. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci*. 2002;22(15):6810–6818.
53. Drabant EM, McRae K, Manuck SB, et al. Individual differences in typical reappraisal use predict amygdala and prefrontal responses. *Biol Psychiatry*. 2009;65(5):367–373.
54. Carrion VG, Weems CF, Richert K, et al. Decreased prefrontal cortical volume associated with increased bedtime cortisol in traumatized youth. *Biol Psychiatry*. 2010;68(5):491–493.
55. Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. *Neuroimaging Clin N Am*. 2007;17(4):523–538.
56. Britton JC, Phan KL, Taylor SF, et al. Corticolimbic blood flow in posttraumatic stress disorder during script-driven imagery. *Biol Psychiatry*. 2005;57(8):832–840.
57. Jovanovic T, Ely T, Fani N, et al. Reduced neural activation during an inhibition task is associated with impaired fear inhibition in a traumatized civilian sample. *Cortex*. 2013;49(7):1884–1891.
58. Li N, Lee B, Liu R-J, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010;329(5994):959–964.
59. Li N, Liu R-J, 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.
60. de Kleine RA, Hendriks G-J, Kusters WJC, et al. A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. *Biol Psychiatry*. 2012;71(11):962–968.
61. Friedman MJ. Drug treatment for PTSD. Answers and questions. *Ann N Y Acad Sci*. 1997;821:359–371.
62. Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *JAMA*. 2007;297(8):820–830.

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