Combining Ketamine Infusions and Written Exposure Therapy for Chronic PTSD:

An Open-Label Trial

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Abstract

Objective: This open-label clinical trial examined the preliminary efficacy of combining a course of 6 ketamine infusions with a brief, evidence-based exposure-based psychotherapy—written exposure therapy (WET)—in patients with chronic posttraumatic stress disorder (PTSD).

Methods: The trial was conducted between June 2021 and October 2023. Patients with chronic PTSD and high-moderate to severe symptom levels received 6 intravenous ketamine infusions (0.5 mg/kg), 3 times a week for 2 consecutive weeks, plus 5 WET sessions over 2 weeks, beginning after the first 4 infusions and administered on different days than infusion days. The primary outcome was change in the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) scores from baseline (before the first infusion) to 12 weeks from start of WET ("Week 12").

Results: Fourteen eligible patients began treatment, and 13 completed all infusions and WET. The combined treatment was associated with large-magnitude improvement in PTSD symptom severity from baseline (mean CAPS-5 = 41.6 [SD = 6.2]) to Week 12 (CAPS-5 = 20.8 [14.8], Cohen *d* [95% CI] = 1.9 [1.0–2.8], $P < .001$). Nine (69%) patients were treatment responders (≥30% improvement on the CAPS-5). Response was rapid and also durable in 8 (61.5%) patients, assessed up to 6 months from baseline.

Conclusions: Preliminary findings from this open-label clinical trial suggest that the combined treatment may yield large-magnitude and durable reductions in PTSD symptoms for patients with more severe chronic PTSD. Large-scale randomized controlled trials are needed to determine the efficacy and potential synergistic effect of this promising combined treatment in this patient population.

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Randomized controlled trials (RCTs) of single and repeated intravenous ketamine infusions have shown rapid and robust improvements in posttraumatic stress disorder (PTSD) symptoms in predominantly civilian samples of patients with chronic PTSD,[1–3] a potentially promising intervention in the context of limited efficacy of currently available pharmacotherapies for this disorder.[4,5] After completion of infusions, however, response to ketamine is usually lost over a few weeks.[2] Among all currently available PTSD treatments, trauma-focused, exposure-based psychotherapies have the highest evidence base, with overall higher efficacy than pharmacotherapies. While they are considered the gold-standard intervention, they are still associated with high rates of nonresponse or limited response.[6,7] Chronic PTSD is characterized by abnormalities in fear extinction learning,[8–10] which can negatively affect response to exposure-based psychotherapies, thought to rely on adequate fear extinction learning.[11]

Chronic PTSD is increasingly recognized as a disorder of "synaptic disconnection."[8] Ketamine, also found to enhance fear extinction,[12–14] rapidly enhances neuroplasticity in the short term, a potent effect thought to persist for weeks after repeated administration.[12,13,15–17] This suggests that administering ketamine several times a week prior to initiating exposure-based psychotherapy may help enhance this type of psychotherapy. In turn, exposure-based

Clinical Points

- Among currently available treatments for chronic posttraumatic stress disorder, exposure-based psychotherapies have the highest evidence base but are limited by insufficient efficacy.
- Potential synergistic effects between ketamine and exposure-based psychotherapies might enhance treatment outcomes.
- The present open-label clinical trial aimed to examine the feasibility and preliminary efficacy of combining a course of 6 ketamine infusions with a brief exposure-based psychotherapy.

psychotherapy might help maintain response to repeated ketamine infusions for PTSD, as most ketamine responders experience symptom relapse following cessation of infusions.[2] To date, 2 published pilot trials have combined ketamine with manualized exposure-based psychotherapy for PTSD.[18,19] These trials administered only 1 ketamine infusion before starting modified prolonged exposure (PE)[18,19] or a total of 3 weekly infusions (before the first 3 of 10 weekly PE sessions),[19] respectively.

In recent years, written exposure therapy (WET) has emerged as a brief, efficacious, and scalable exposure-based psychotherapy for PTSD, shown to be noninferior to PE and cognitive processing therapy and potentially more tolerable, with lower drop-out rates.[20–25] The current open-label clinical trial aimed to examine the feasibility and preliminary efficacy of combining a course of 6 ketamine infusions—administered over 2 consecutive weeks—with WET in patients with high-moderate to severe chronic PTSD. We selected this frequency and total number of infusions based on the demonstrated efficacy of this protocol for individuals with chronic PTSD in our previous RCT of repeated ketamine administration.[2] Further, we chose to start WET after several ketamine infusions in order to "prime the brain" first, aiming to maximize ketamine's potential effect on neuroplasticity prior to initiating psychotherapy.

METHODS

Participants and Procedure

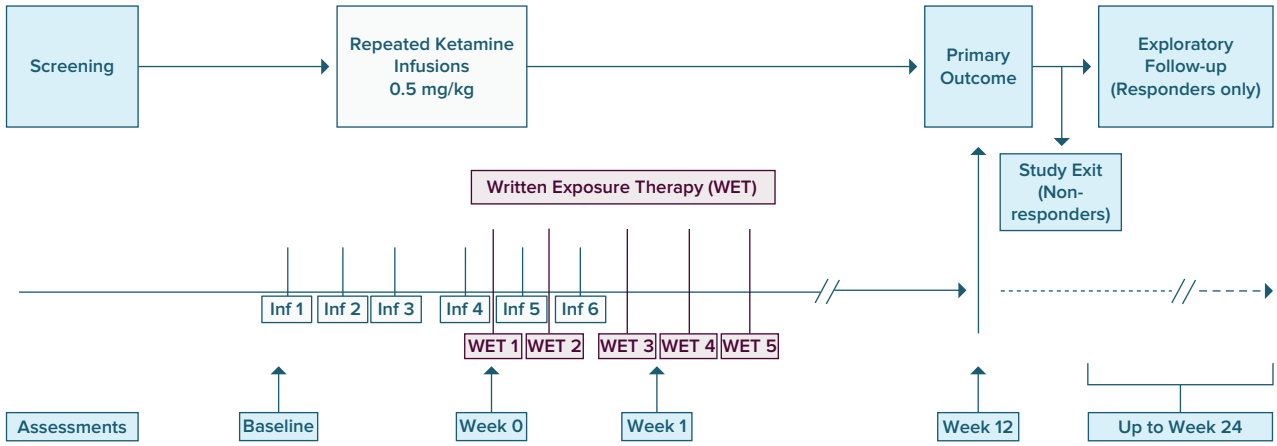
An open-label clinical trial was conducted between June 2021 and October 2023 at the Icahn School of Medicine at Mount Sinai (ISMMS). Eligible participants, recruited through advertising or clinician referrals, were aged 18–70 years, with a current primary diagnosis of chronic PTSD, defined as meeting *DSM-5* PTSD criteria on the Structured Clinical Interview for *DSM-5*,[26] of at least 3 months' duration, and a total score ≥30 on the past-month Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5).[27] Participants completed a medical history and physical examination conducted by a nurse practitioner, as well as laboratory testing and an electrocardiogram, followed by a review of all results by a study psychiatrist. Exclusion criteria included serious unstable medical illness, moderate/severe brain injury, alcohol/substance use disorder within the prior 3 months, active suicidal ideation, and bipolar or psychotic disorder. Concomitant medications at stable doses for at least 3 months were permitted, except for opioids and long-acting or daytime short-acting benzodiazepines. Concomitant evidence-based psychotherapy for PTSD (eg, PE, eye movement desensitization and reprocessing) was exclusionary. The study protocol was approved by the ISMMS institutional review board and registered on ClinicalTrials.gov (NCT04889664). All participants signed informed consent. They were compensated for each infusion day and each assessment, but not for WET sessions.

Six ketamine infusions (0.5 mg/kg over 40 minutes) were administered 3 times a week for 2 consecutive weeks.[2] The first WET session took place the day after the fourth infusion; the first 2 WET sessions were interleaved with the last 2 ketamine infusions—each on a different day—and the last 3 WET sessions were delivered the following week, schedule permitting, with a combined treatment duration of approximately 3 weeks (Figure 1).[2,17]

WET is a brief, evidence-based, exposure-based psychotherapy for PTSD comprising 5 total sessions with no between-session assignments. Fundamental WET components include a treatment rationale, psychoeducation, and directing individuals to write repeatedly about the details of a specific traumatic stressor linked to their symptoms, with particular attention to felt emotions and the meaning of the traumatic event, for 30 minutes per session.[20] The minimal therapist-patient contact, nominal time needed to train therapists, and brevity of treatment address challenges with implementing other exposure-based psychotherapies.[28] Several RCTs have demonstrated the efficacy and noninferiority of WET for PTSD compared to gold-standard and longer-duration exposure-based psychotherapies, with significantly lower treatment dropout rates.[23–25] In this study, WET was administered to participants via a HIPAA-compliant video telehealth platform, by licensed therapists trained and closely supervised by D.M.S., co-developer of WET.

The primary outcome was change in PTSD symptom severity, assessed with the CAPS-5, from baseline (before the first infusion) to 12 weeks following the start of WET ("Week 12"). Since prior trials of standalone WET showed continued gradual improvement up to 12 weeks from baseline, we selected this primary outcome time point to enable preliminary effect size comparisons between the combined intervention in this trial and WET alone from prior trials. The CAPS-5 was administered by trained, supervised study staff, weekly up to Week 12; CAPS-5 raters were not blinded to study time point. Treatment response was defined as ≥30%

Figure 1.
Study Flowchart[a]



[a]Graphical representation of the combined treatment and assessment time points. Participants with chronic PTSD received a course of 6 ketamine infusions and written exposure therapy (WET, 5 sessions). The first ketamine infusion started following the baseline assessment, and the first WET session began after completing the first 4 ketamine infusions (following the Week 0 assessment). The full combined treatment lasted approximately 3 weeks. The primary outcome was change in PTSD symptom severity, assessed with the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5), from baseline to 12 weeks from start of WET (Week 12). Only treatment responders at Week 12, defined as at least 30% improvement on the CAPS-5 total score from baseline, were additionally assessed, monthly, for up to 24 weeks from start of WET (Week 24).

improvement[2,29–31] in the total CAPS-5 score from baseline to Week 12. Exploratory outcomes included PTSD symptom severity at 3 weeks from start of WET (ie, 1 week after completion of the combined treatment) in order to evaluate rapid response, as well as the 4 *DSM-5* PTSD symptom clusters (CAPS-5 subscale scores), depressive symptoms, clinical global impression, and self-reported functional impairment.[32–34] Treatment responders at Week 12 were subsequently administered the CAPS-5 monthly up to 24 weeks from start of WET ("Week 24"), 6 months from baseline, to explore durability of the combined intervention.

Linear mixed-effects models were conducted to examine changes in primary and exploratory measures from baseline to Week 12. These models included time (baseline, Week 12) as a fixed effect, participant as a random effect, and scores on primary and exploratory measures as dependent variables. Cohen *d* with 95% CIs were computed to estimate the magnitude of changes in measures over time.

RESULTS

Fourteen eligible patients began study treatment (Supplementary Figure 1, CONSORT Diagram). Thirteen patients (100% female, mean [SD] age = 38.3 [7.5] years) who completed the full course of ketamine infusions and WET sessions were included in data analyses (Table 1). One patient was withdrawn by the study team after 3 infusions because of inappropriate behavior with study staff unrelated to the infusions.

Among the 13 patients included in data analyses, 8 (62%) presented with sexual assault/molestation during childhood and/or adulthood as their primary trauma, and the remaining 5 (39%) with other primary traumas, with mean PTSD duration of 18 years (Table 1). Six (46%) patients were on stable doses of psychotropic medications, and 7 (53.8%) were receiving concomitant non–evidence-based psychotherapy (Supplementary Table 1).

Combined treatment with ketamine infusions and WET was associated with large-magnitude improvement in PTSD symptom severity (total CAPS-5 score) from baseline to Week 12, the primary outcome (Table 2, Figure 2). At Week 12, 9 (69%) patients were treatment responders, and 7 (54%) no longer met *DSM-5* PTSD diagnostic criteria (Figure 3).

The combined treatment was also associated with large-magnitude improvements in the 4 *DSM-5* PTSD symptom clusters, with greatest improvement in avoidance symptoms (Table 2, Figure 2), and large-magnitude improvements in depressive symptoms, clinical global impression scores, and social and family/home functioning; 10 (77%) participants were assessed to be clinically "much improved" or higher (Table 2).

Rapid Response

One week after completion of the combined treatment (3 weeks from start of WET, "Week 3"), 10 (77%) patients were treatment responders, and 8 (62%) did not meet *DSM-5* PTSD diagnostic criteria (Figure 3). Only 1 of the treatment responders at Week 3 was no longer a responder by Week 12.

Maintenance of Response

Eight (61.5%) patients showed a durable response, including 7 who completed the Week-24 follow-up (6 months postbaseline) and an additional patient who was

Table 1.

Demographic and Clinical Characteristics of Study Participants

Characteristic		
Continuous variables	**Mean**	**SD**
Age, y	38.3	7.5
BMI	27.3	7
Duration of PTSD, y	18.1	14.0
CAPS-5 score (past month)	40.5	3.9
MADRS score (past week)	31.4	6.5
Categorical variables	**N**	**%**
Female, sex	13	100
Race		
Black	0	0
Asian	1	7.7
White	9	69.2
American Indian or Alaskan Native	1	7.7
More than 1 race	1	7.7
Unknown or do not wish to disclose	1	7.7
Hispanic ethnicity	4	30.8
Education		
≤ High school	0	0
High school graduate	0	0
Some college or trade school	2	15.4
Graduated 4 years of college	4	30.8
Some graduate/professional degree	1	7.7
Completed graduate/professional degree	6	46.2
Unemployed	2	15.4
Married or cohabiting	2	15.4
Primary trauma		
Sexual assault or molestation during childhood and/or adolescence	4	30.8
Sexual assault during adulthood	4	30.8
Physical assault or abuse during childhood and adolescence	2	15.4
Survivor of serious accident	1	7.7
Witness of violent assault	1	7.7
Survivor of 9/11 terrorist attacks	1	7.7
Current comorbid diagnoses		
Major depressive disorder	10	76.9
Persistent depressive disorder	6	46.2
Generalized anxiety disorder	10	76.9
Social anxiety disorder	5	38.5
Specific phobia	1	7.7
Binge eating disorder	1	7.7
Concomitant treatment with psychotherapy	7	53.8
Concomitant treatment with psychotropic medication at stable doses	6	46.2
Marijuana use during treatment phase[a]	1	7.7
Marijuana use during follow-up phase[b]	2	15.4

[a]One participant smoked marijuana and/or used edibles on weekends.
[b]During the follow-up phase, the same participant continued to smoke marijuana and/or used edibles on weekends; another participant used an edible for a migraine headache once on week 5.
Abbreviations: BMI = body mass index, CAPS-5 = Clinician-Administered PTSD Scale for DSM-5, MADRS = Montgomery-Asberg Depression Rating Scale, PTSD = posttraumatic stress disorder.

last available for follow-up at Week 20, all of whom did not meet *DSM-5* PTSD diagnostic criteria at this last follow-up (Figure 3, Supplementary Figure 2).

Safety and Side Effects

As in prior trials, any dissociative symptoms emerging during ketamine infusions were transient, resolving after infusion end; no significant psychotic or manic symptoms were observed (Supplementary Table 2). General side effects are reported in Supplementary Table 3.

DISCUSSION

This open-label clinical trial provides the first known preliminary evidence of large-magnitude PTSD symptom improvement, assessed 3 months from pretreatment

Table 2.

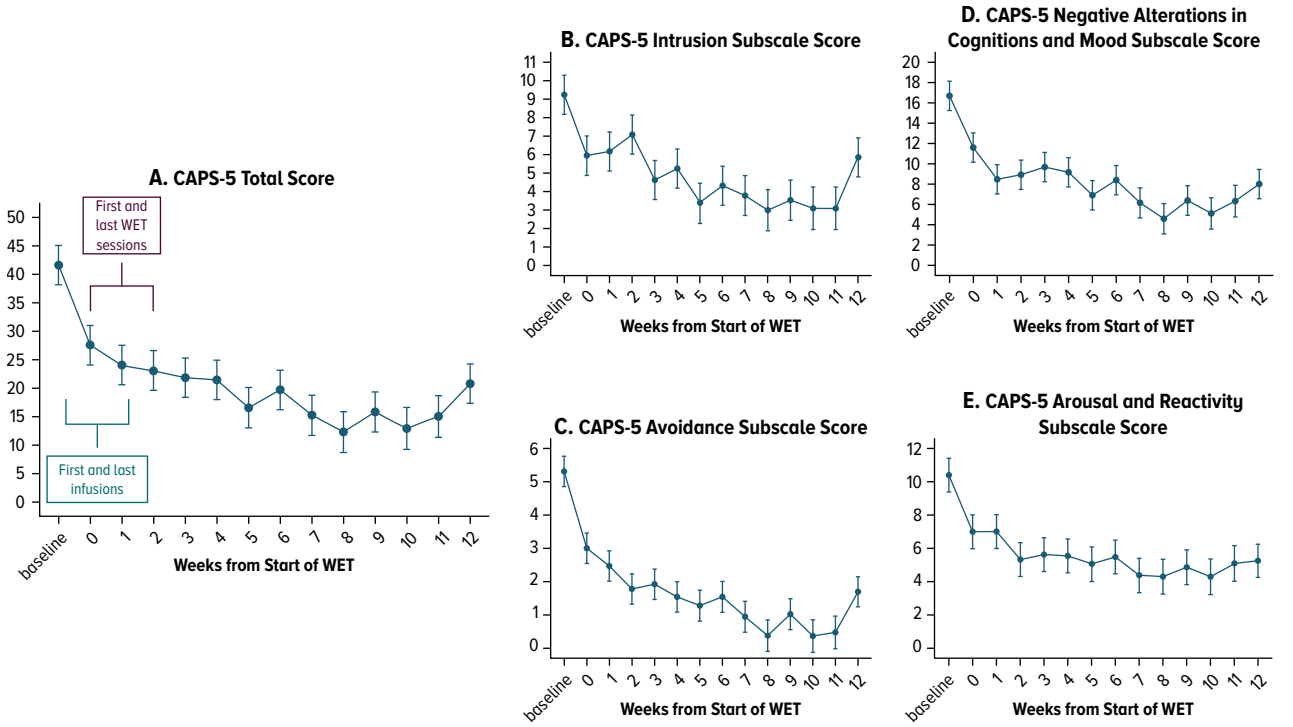
Pre- and Posttreatment Scores on Primary and Secondary (Exploratory) Measures

	Pretreatment	Posttreatment			
	Mean (SD)	Mean (SD)	*F*	*P*	*d* (95% CI)
CAPS-5 total	41.6 (6.2)	20.8 (14.8)	22.00	<.001	1.9 (1.0–2.8)
Intrusions	9.2 (2.1)	5.8 (4.1)	6.98	.014	1.1 (0.3–1.9)
Avoidance	5.3 (1.3)	1.7 (2.1)	26.99	<.001	2.1 (1.2–3.1)
NACM	16.7 (2.9)	8.0 (6.6)	18.75	<.001	1.8 (0.9–2.7)
AAR	10.4 (2.6)	5.2 (3.6)	17.17	<.001	1.7 (0.8–2.6)
MADRS	31.4 (6.5)	19.1 (13.2)	8.96	.006	1.2 (0.4–2.1)
CGI-S	4.9 (0.6)	3.2 (1.2)	19.23	<.001	1.8 (0.9–2.7)
CGI-I	NA	2.0 (0.9) 77% ≥ 2	–	–	–
SDS work[a]	4.1 (3.2)	3.4 (3.1)	0.25	0.63	0.2 (−0.6 to 1.0)
SDS social	6.1 (2.5)	3.1 (3.6)	6.02	0.022	1.0 (0.2–1.8)
SDS family/home	5.7 (2.9)	2.4 (2.4)	10.17	0.004	1.3 (0.5–2.1)

[a]SDS work scores were assessed in 10 participants who reported current employment.
Abbreviations: AAR = alterations in arousal and reactivity, CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*,[27] CGI-S = Clinical Global Impressions-Severity, CGI-I = Clinical Global Impressions-Improvement,[33] *d* = Cohen *d*, MADRS = Montgomery-Asberg Depression Rating Scale,[32] NA = not applicable, NACM = negative alterations in cognition and mood, SDS = Sheehan Disability Scale.[34]

Figure 2.

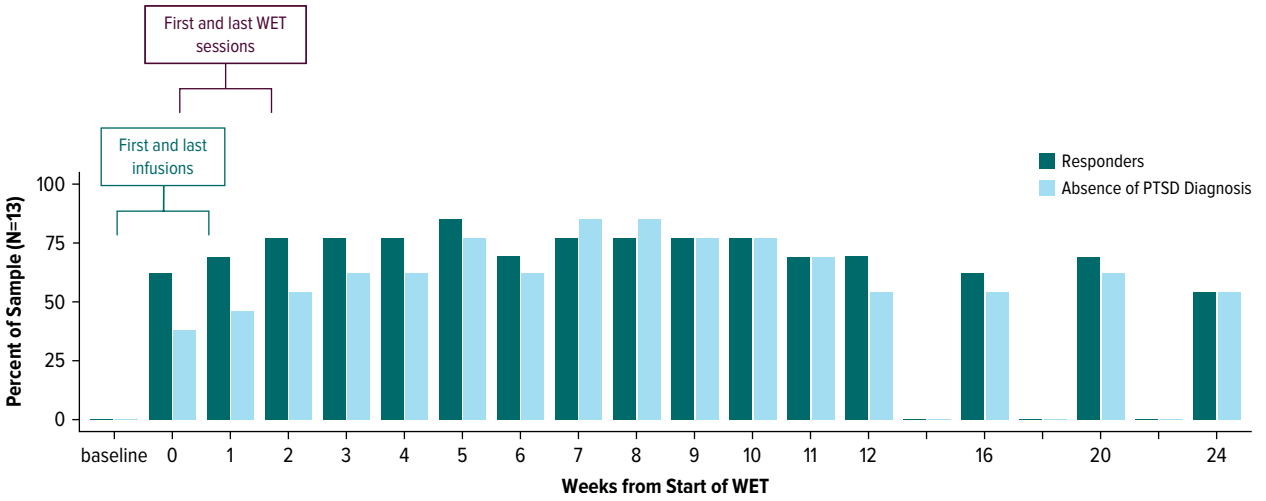
Improvement in PTSD Symptom Severity (Overall and Symptom Clusters), from Baseline to Week 12[a]



[a]The graphs show the change in the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) total and subscale scores, at each assessment time point from baseline (before the first infusion) to 12 weeks from start of written exposure therapy, WET (Week 12). Values reflect least-square means; error bars indicate standard error of the mean. The timing of the first and last infusions is marked in blue, and the timing of the first and last WET sessions in purple.

Figure 3.

Treatment Response and Loss of *DSM-5* PTSD Diagnosis, from Baseline to Week 12, and up to Week 24 in Treatment Responders[a]



[a]The graph shows the percentage of treatment responders (at least 30% improvement from baseline on the Clinician-Administered PTSD Scale for *DSM-5* [CAPS-5] total score) and percentage of patients who no longer met *DSM-5* diagnostic criteria for PTSD, including the primary and exploratory assessment time points. Patients were assessed weekly from baseline to Week 12, and treatment responders monthly thereafter up to 24 weeks from start of written exposure therapy, WET (Week 24). The timing of the first and last infusions is marked in blue, and the timing of the first and last WET sessions in purple.

baseline, in patients with high-moderate to severe chronic PTSD, following a combination of repeated ketamine infusions with WET, an evidence-based, brief exposure-based psychotherapy. With the exception of 1 patient who was exited early for a non–treatment-related reason, no patients dropped out before completing treatment. Over two-thirds (N = 9, 69%) of the combined treatment sample were treatment responders 3 months from baseline. All responders improved early in treatment, based on their assessment 1 week postcompletion of the combined treatment, and most of them maintained clinical response at the 6-month follow-up.

Preliminary findings suggest that combining WET with a course of 6 ketamine infusions might maintain PTSD symptom improvement for several months in many treatment responders, potentially avoiding or reducing the need for maintenance ketamine infusions, which commonly arises when administering ketamine as a standalone treatment.[2] In our previous RCT, after receiving 6 ketamine infusions over 2 consecutive weeks, median time to loss of response was approximately 6 weeks from baseline.[2] Of note, while patients with PTSD can receive ketamine infusions at ketamine clinical practices,[35] intravenous ketamine is presently off-label as it is not FDA-approved for the treatment of any psychiatric disorders. Only the enantiomer esketamine, administered intranasally, is FDA-approved as an adjunct intervention for patients with treatment-resistant depression or with depression accompanied by suicidal ideation, but not for PTSD.

Preliminary findings also suggest that compared to WET as a standalone treatment,[23–25] the combined treatment is associated with a more rapid response, as early as 1–2 weeks from baseline. Additionally, the mean effect size reduction in PTSD symptoms observed in the current study ($d = 1.9$) is numerically larger than the moderate-to-large-magnitude within-subject reductions in PTSD symptom severity observed at 10–12-week assessments following standalone WET,[23–25,36] but comparable to the large-magnitude reduction in these symptoms observed 2 weeks following ketamine administration.[2] While these findings suggest that ketamine might enhance the efficacy of WET, no definitive conclusion can be reached without conducting an RCT directly comparing the combined intervention with standalone WET (with placebo infusions).

Interest in potential synergistic effects between ketamine and exposure-based psychotherapies for PTSD stems from findings that ketamine opens a window of increased neuroplasticity,[15,37] particularly in brain regions subserving emotion processing and regulation, which also underlie threat processing and fear extinction learning, putative mechanisms behind exposure-based psychotherapies including WET.[11,38–40] Different ways of combining ketamine with evidence-based psychotherapies for PTSD are being examined.[41,42] In the current trial, we administered several infusions prior to starting psychotherapy and additionally administered the full course of psychotherapy within the estimated window of ketamine-related increased neuroplasticity, aiming to maximize the potential synergistic effect of these 2 interventions. Initial findings from neuroimaging studies of exposure-based psychotherapies for

chronic PTSD suggest that patients least likely to respond to exposure-based psychotherapies are those with poorer PFC inhibition of amygdala activation at pretreatment baseline.[43,44] Conversely, in our preliminary neuroimaging study of repeated ketamine for chronic PTSD, patients with lower top-down amygdala inhibition at pretreatment baseline were actually more likely to respond to ketamine.[17] While much further research is needed, combined findings across studies suggest the potential benefit of "priming the brain" with repeated ketamine infusions prior to initiating exposure-based psychotherapy in patients with chronic PTSD.

Results of the present open-label clinical trial support the feasibility and preliminary safety and efficacy of combining a course of repeated ketamine infusions with a brief exposure-based psychotherapy for individuals with high-moderate to severe chronic PTSD. The time commitment required for this combined intervention was substantial but time-limited, and no participant dropped out. The study is limited by its small sample size and the absence of a control group. Large-scale RCTs are needed to determine whether the combined therapies might have a synergistic effect, namely, whether repeated ketamine infusions might enhance the efficacy of WET and, in turn, whether adding WET can help maintain therapeutic effects of a course of ketamine infusions over time in patients with this disabling condition.

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Relevant Financial Relationships: **Drs Feder** and **Charney** are named co-inventors on issued patents in the US and outside the US filed by ISMMS related to the use of ketamine for the treatment of PTSD. ISMMS has entered into a licensing agreement with Frontier Pharmaceuticals, Inc., to develop intranasal ketamine as a treatment for PTSD. As a part of this agreement, ISMMS will receive consideration in the form of royalties, milestones payments, and equity. As named co-inventors, **Drs Feder** and **Charney** are entitled under ISMMS's intellectual property policy to a portion of any consideration received by ISMMS. **Dr Jha** has received contract research grants from Neurocrine Bioscience, Navitor/Supernus, and Janssen Research & Development; honorarium to serve as Section Editor of the Psychiatry & Behavioral Health Learning Network and as Guest Editor for Psychiatric Clinics of North America from Elsevier; consultant fees from Janssen Scientific Affairs and Boehringer Ingelheim; fees to serve on Data Safety and Monitoring Board for Worldwide Clinical Trials (Eliem and Inversargo), Vicore Pharma and IQVIA (Click); and honoraria for educational presentations from North American Center for Continuing Medical Education, Medscape/WebMD, Clinical Care Options, H.C. Wainwright & Co. and Global Medical Education. **Dr Costi** is currently funded by a Wellcome Trust Clinical Doctoral Research Fellowship and has provided consultation services for Guidepoint and TGC Crossover. **Dr Yehuda** has received funding from the Steven and Alexandra Cohen Foundation and from the Bob and Renee Parsons Foundation. **Dr Charney** is named co-inventor on patents filed by the ISMMS relating to the treatment for treatment-resistant depression, suicidal ideation, and other disorders. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc., and it has and will receive payments from Janssen under the license agreement related to these patents for the treatment of treatment-resistant depression and suicidal ideation. Consistent with the ISMMS Faculty Handbook (the medical school policy), Dr Charney is entitled to a portion of the payments received by the ISMMS. Since SPRAVATO has received regulatory approval for treatment-resistant depression, ISMMS and thus, through the ISMMS, Dr Charney, will be entitled to additional payments, beyond those already received, under the license agreement. Dr Charney is named co-inventor on several patents filed by ISMMS for a cognitive training intervention to treat depression and related psychiatric disorders. The ISMMS has entered into a licensing agreement with Click Therapeutics, Inc, and has and will receive payments related to the use of this cognitive training intervention for the treatment of psychiatric disorders. In accordance with the ISMMS Faculty Handbook, Dr Charney has received a portion of these payments and is entitled to a portion of any additional payments that the medical school might receive from this license with Click Therapeutics. Dr Charney is a named co-inventor on a patent application filed by ISMMS for systems and methods for providing a resilience building application to support mental health of subjects. This intellectual property has not been licensed. **Drs Charney** and **Murrough** are named co-inventors on a patent application filed by the ISMMS for the use of intranasally administered Neuropeptide Y (NPY) for the treatment of mood and anxiety disorders. This intellectual property has not been licensed. **Dr Sloan** receives royalty payments for the published treatment manual for written exposure therapy from American Psychological Press and royalty payments for an on-demand written exposure therapy workshop from PESI. **Dr Murrough** has provided consultation services and/or served on advisory boards for LivaNova, KetaMed, Inc, Merk, Cliniclabs, Inc., Biohaven Pharmaceuticals, Inc., Compass Pathfinder, Xenon Pharmaceuticals, and Clexio Biosciences. He is additionally named on a patent application filed by the ISMMS for the use of KCNQ channel openers to treat depression and related conditions. The other authors have no disclosures to report.

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Supplementary Material: Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Combining Ketamine Infusions and Written Exposure Therapy for Chronic PTSD: An Open-label Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Methods

This open-label clinical trial was conducted between June 2021 and October 2023 at the Icahn School of Medicine at Mount Sinai (ISMMS) Depression and Anxiety Center for Discovery and Treatment (DAC).

Exploratory Outcomes

Exploratory outcome measures were the four DSM-5 PTSD symptom clusters (CAPS-5 subscale scores) (1), the Montgomery-Äsberg Depression Rating Scale (MADRS) (2), the Clinical Global Impressions severity (CGI-S) and improvement (CGI-I) scales (3), and the Sheehan Disability Scale (4).

Side Effect and Safety Measures

Measures included the Clinician-Administered Dissociative States Scale (CADSS) (5), the 4-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) (6), the first item (elevated mood) of the Young Mania Rating Scale (YMRS) (7), and the Patient-Rated Inventory of Side Effects (PRISE) (8) on infusion days, and the PRISE and the Columbia – Suicide Severity Rating Scale (C-SSRS) administered weekly from baseline to Week 12, and additionally during the monthly follow-up assessments in treatment responders (9).

Additional Results (Exploratory)

Supplementary Table 1 lists concomitant psychotropic medications by study participant and whether the participant was concurrently engaged in non evidence-based psychotherapy.

As stated in the manuscript*, treatment response* was defined as ≥30% improvement in the total CAPS-5 score (*PTSD symptom severity*) from baseline to Week 12 (primary outcome time point). All 9 treatment responders remained responders (still showed ≥30% improvement on the CAPS-5) at their last follow-up, and only 1 responder met DSM-5 PTSD criteria again at their last follow-up (Week 24).

Depressive Symptoms in Treatment Responders at Weeks 12 and 24:

The following summarizes ***change in depressive symptoms*** over time, assessed with the MADRS, in these 9 treatment responders.

- 3 participants were >50% improved at both Week 12 and at their last follow-up
- 3 were >50% improved at Week 12 but depressive symptoms had returned by Week 24 (including the responder who met DSM-5 PTSD criteria again at Week 24)
- 1 showed no improvement at Week 12 but was >50% improved by Week 24
- 2 did not reach 50% improvement either at Week 12 or Week 24

Suicidal ideation in Treatment Responders at Weeks 12 and 24:

Among the 9 treatment responders, on the C-SSRS, 2 had passive thoughts of death at baseline; in both patients, these thoughts had resolved at Week 12 and were not present at Week 24. An additional treatment responder had suicidal ideation without intent to act at baseline. These thoughts had fully resolved at Week 12; at Week 24, this patient reported passive thoughts of dying but no suicidal ideation.

Self-reported Functional Impairment in Treatment Responders at Week 24:

Self-reported functional impairment on the SDS in 9 treatment responders at their last assessment (Week 24 for 8 responders, and Week 20 for one responder):

- 5 treatment responders reported no functional impairment and 1 reported minimal impairment (total SDS=1)
- 1 responder was 50% improved compared to baseline
- 1 responder was 41% improvement compared to baseline
- 1 responder (who met DSM-5 PTSD criteria again at Week 24) reported the same functional impairment at Week 24 than at baseline

Safety and Side Effects

Any dissociative symptoms emerging during ketamine infusions were transient, resolving after infusion end; no significant psychotic or manic symptoms were observed (see **Supplementary Table 2**). On the PRISE, the most frequent general side effects on infusion days, recorded after start of infusions, were fatigue (38%), dizziness (31%), blurred vision (23%), numbness in parts of the body (23%), and headache (15%) (see **Supplementary Table 3**). At other time points during the two weeks of infusions, covering the periods from discharge to home post-infusion until the next assessment, the most frequent general side effects recorded with the PRISE were fatigue (85%), headache (23%), nausea (15%), and decreased appetite (15%) (see **Supplementary Table 3**).

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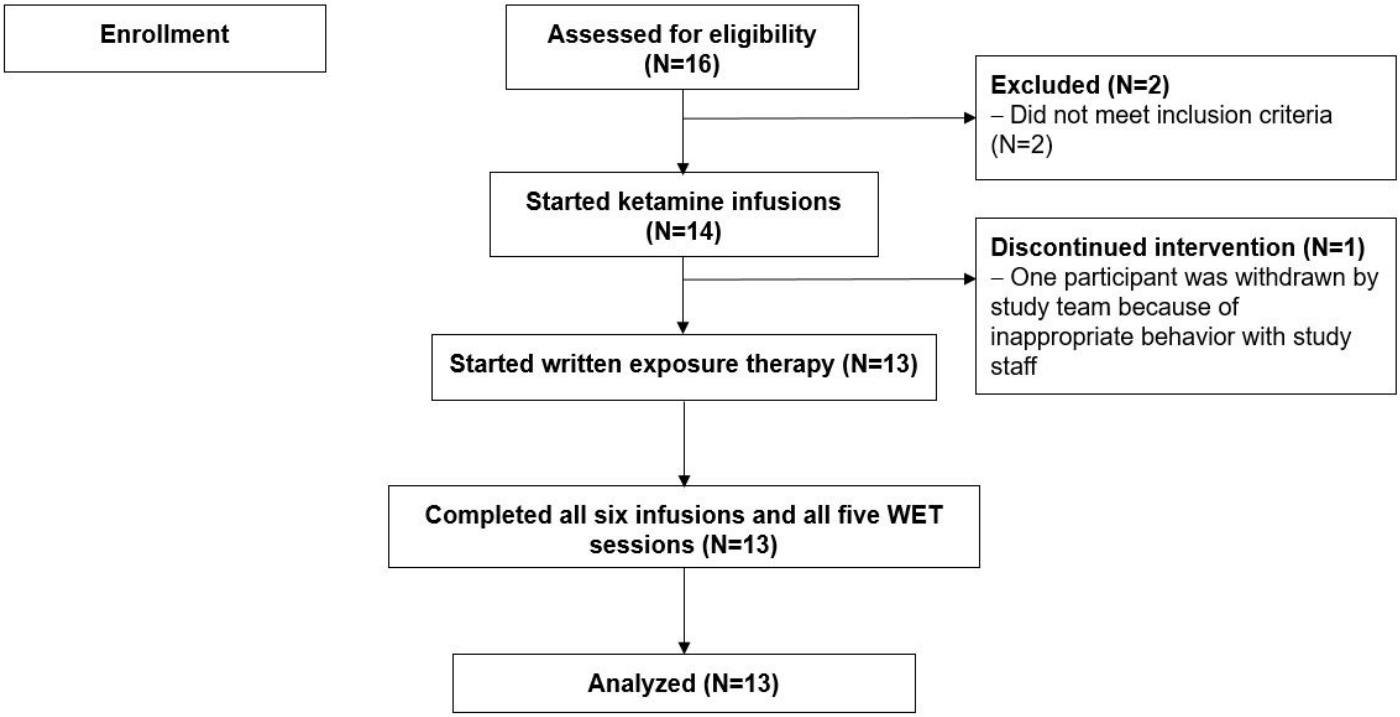
Figures and Tables

Supplementary Figure 1. CONSORT Diagram



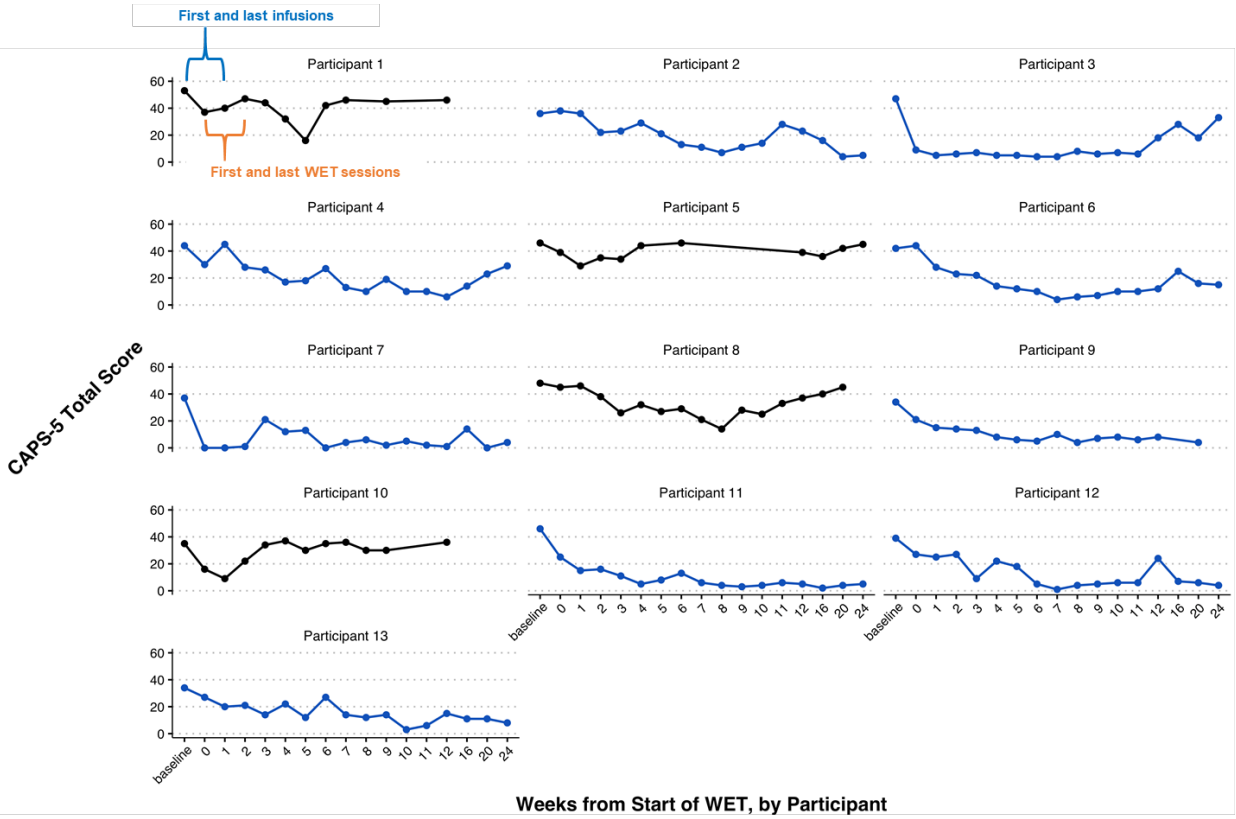
Note: WET, written exposure therapy

Supplementary Table 1: Concomitant Psychotropic Medications and Engagement in Concurrent Psychotherapy, by Participant

Study Phase	Treatment Phase, *Standing*	Treatment Phase, *PRN*	Post-Treatment Phase, *Standing*	Post-Treatment Phase, *PRN*	Concomitant Psychotherapy
Patient 1	Lamotrigine	Alprazolam at bedtime	Lamotrigine	Alprazolam at bedtime, sometimes also in the daytime	No
Patient 2	Mirtazapine, desvenlafaxine XR, amphetamine/ dextroamphetamine ER four times a week	Melatonin at bedtime	Mirtazapine, desvenlafaxine XR, amphetamine/dextroamphetamine ER four times a week	Melatonin at bedtime	Yes
Patient 3	Alprazolam at bedtime (took the night before her first infusion), doxylamine	Amphetamine/dextroamphetamine **Clonazepam 0.25 mg at bedtime one and two days after the last WET session.	Alprazolam at bedtime, doxylamine	Amphetamine/dextroamphetamine	Yes
Patient 4	-	-	-	-	Yes
Patient 5	Escitalopram, buspirone	-	Escitalopram, buspirone (patient self-discontinued during Week 6)	-	No
Patient 6	Bupropion, amphetamine/ dextroamphetamine, topiramate	Lorazepam at bedtime, Zolpidem	Bupropion, amphetamine/ dextroamphetamine, topiramate	Lorazepam at bedtime, zolpidem	Yes
Patient 7	-	-	-	Alprazolam once on week 4	No
Patient 8	-	-	-	-	No
Patient 9	-	-	-	-	No
Patient 10	-	-	-	Took lorazepam once on week 5, once on week 6	Yes
Patient 11	-	-	-	-	Yes
Patient 12	Quetiapine, prazosin, sertraline, bupropion	Alprazolam	Quetiapine, prazosin, sertraline, bupropion	Alprazolam once or twice during Weeks 4, 5, 6, and 9 and three times during Week 12	No
Patient 13	-	-	-	-	Yes

Note: Patient 1 took alprazolam once in the daytime (0.5 mg) during the Treatment Phase, in the afternoon of the day after the second WET session. Patient 3 took clonazepam (0.25 mg) twice during the Treatment Phase, at bedtime one and two days after the last WET session.

Supplementary Figure 2. Effect of the Combined Treatment on PTSD Symptom Severity, by Participant



Note: The graphs show the change in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score, at each assessment time point, for each individual participant (N=13).

Participants with chronic PTSD received a course of 6 ketamine infusions and written exposure therapy (WET, 5 sessions). Only treatment responders at Week 12, defined as at least 30% improvement on the CAPS-5 total score from baseline, were additionally assessed, monthly, for up to 24 weeks from start of WET (Week 24).

The timing of the first and last infusions is marked in blue, and the timing of the first and last WET sessions in orange, on Participant 1's graph.

Supplementary Table 2. Emergence of Dissociative, Psychotomimetic, and Manic Symptoms from Pre-infusion to Post-infusion Discharge on Ketamine Infusion Days, across all Six Ketamine Infusions

	CADSS Score Mean (SD)	BPRS Positive Symptoms Subscale Score Mean (SD)	YMRS Item-1 Score Mean (SD)
Baseline	0.68 (2.33)	4.01 (0.20)	0.04 (0.13)
+40 minutes	7.03 (6.04)	4.26 (0.71)	0.37 (0.58)
+120 minutes	0.58 (1.34)	4.00 (0.00)	0.17 (0.44)

Note: Mean scores (and standard deviation, SD) on the Clinician-Administered Dissociative States Scale (CADSS), the 4-item Positive Symptoms Subscale of the Brief Psychiatric Rating Scale (BPRS), and the first item (elevated mood) of the Young Mania Rating Scale (YMRS) at baseline, and 40 minutes and 120 minutes from infusion start, across all participants and all six infusions.

Supplementary Table 3: General Side Effects during the Two Weeks of Ketamine Infusions, on the Patient-Rated Inventory of Side Effects (PRISE)

Adverse Event	On infusion days, covering the periods from infusion start until discharge to home				Covering the periods after discharge to home until the next assessment			
	1st week of infusions		2nd week of infusions		1st week of infusions		2nd week of infusions	
	N	%	N	%	N	%	N	%
Gastrointestinal								
Diarrhea	0	0	0	0	0	0	0	0
Dry mouth	0	0	0	0	0	0	0	0
Constipation	0	0	0	0	0	0	0	0
Nausea/vomiting	0	0	0	0	2	15%	0	0
Heart								
Dizziness on standing	0	0	0	0	0	0	0	0
Palpitations (skipping a beat)	0	0	0	0	0	0	0	0
Chest pain	0	0	0	0	0	0	0	0
Skin								
Rash	0	0	0	0	0	0	0	0
Itching	0	0	0	0	0	0	0	0
Dry skin	0	0	0	0	0	0	0	0
Increased Perspiration	0	0	0	0	1	8%	1	8%
Nervous System								
Headache	2	15%	2	15%	3	23%	1	8
Tremors	0	0	0	0	0	0	0	0
Poor coordination	0	0	0	0	0	0	0	0
Dizziness	4	31%	4	31%	1	8	0	0
Eyes/Ears								
Ringing in ears	0	0	0	0	0	0	0	0
Blurred vision	3	23%	1	8%	0	0	0	0
Genital/Urinary								
Difficulty urinating	0	0	0	0	0	0	0	0
Frequent urination	0	0	1	8			1	8
Painful urination	0	0	0	0	0	0	0	0
Menstrual irregularity	0	0	0	0	1	8	0	0
Sleep								
Sleeping too much	0	0	0	0	0	0	0	0
Difficulty sleeping	0	0	0	0	1	8%	1	8%
Sexual Functioning								
Loss of sexual desire	0	0	0	0	0	0	0	0
Trouble achieving orgasm	0	0	0	0	0	0	0	0
Trouble with erections	0	0	0	0	0	0	0	0
Other								
Anxiety	1	8%	0	0	0	0	0	0
Poor concentration	0	0	0	0	0	0	0	0
General malaise	0	0	0	0	0	0	0	0
Restlessness	0	0	0	0	0	0	0	0
Fatigue	5	38%	3	23%	11	85%	2	15%
Decreased energy	1	8%	1	8%	0	0	0	0
Other, specify	8	62%	3	23%	2	15%	1	8%