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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DOI Number: 10.4088/JCP.24m15622

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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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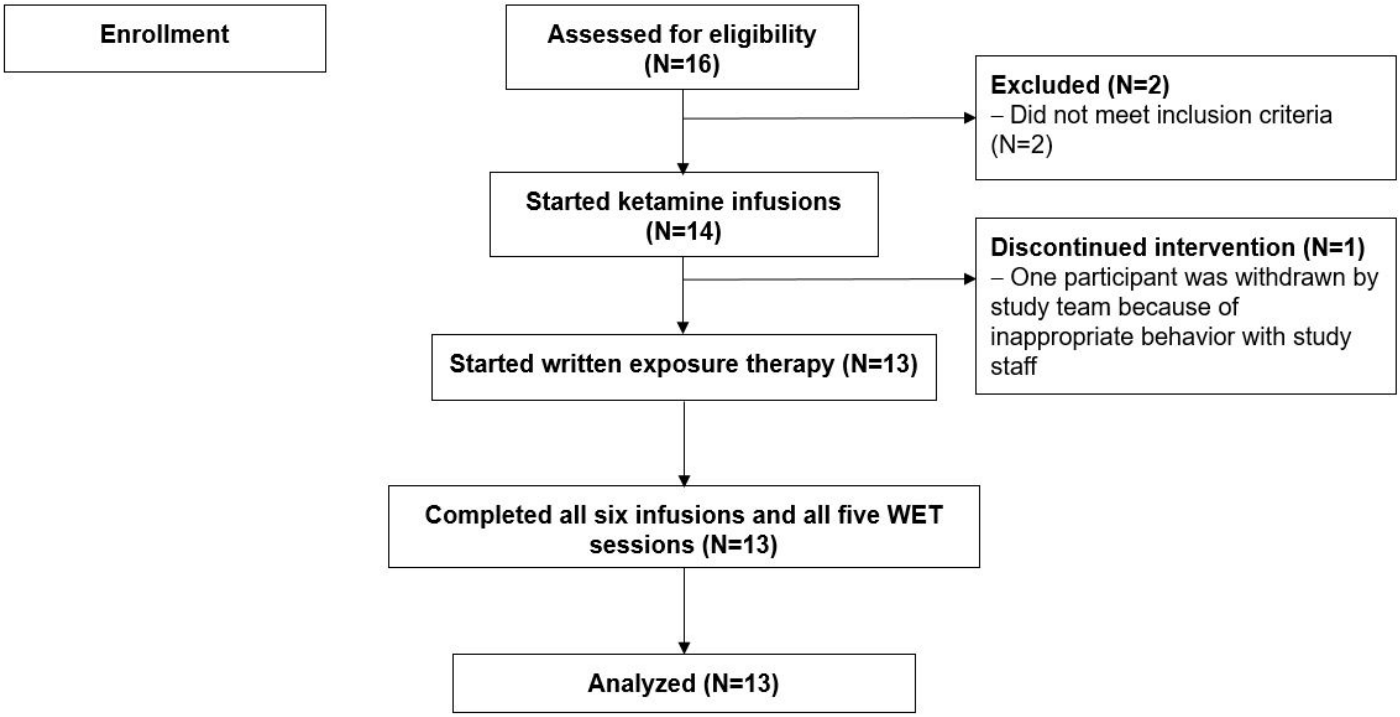
Figures and Tables

Supplementary Figure 1. CONSORT Diagram



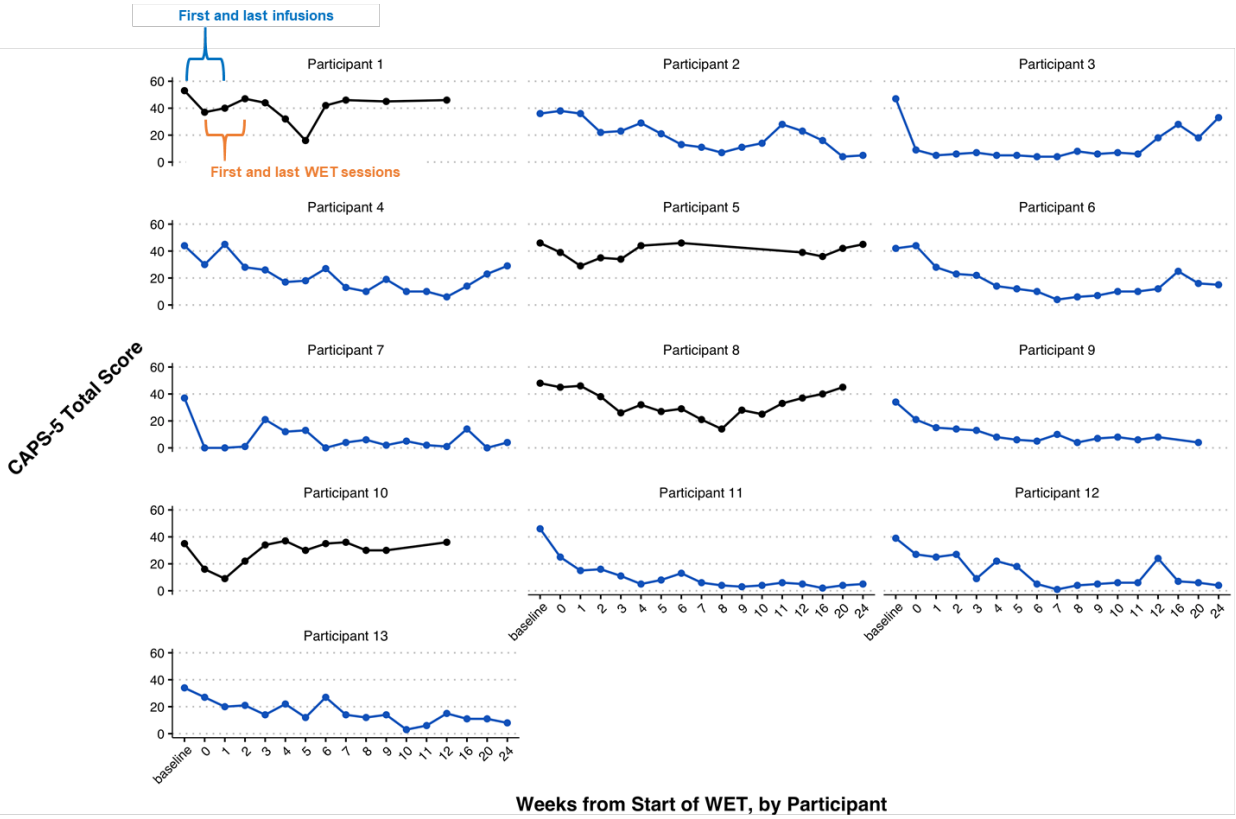
Note: WET, written exposure therapy

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%