Combining Ketamine and Psychotherapy for the Treatment of Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis

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Posttraumatic stress disorder (PTSD) is a chronic and debilitating mental health condition associated with high treatment resistance, where 35%–50% of patients do not respond to established pharmacologic and psychotherapeutic interventions.[1–5] Ketamine is an emerging treatment for a number of psychopathologies such as major depressive disorder and PTSD, with a higher patient response than other pharmacologic agents.[6–11] Although the clinical data for ketamine in PTSD are preliminary, it is hypothesized to function by rapidly facilitating long-term potentiation, thereby allowing a patient to disengage from an established pattern of thought more readily.[10,12–20] However, ketamine has notable side effects, only lasts 1 week for PTSD, and must be administered intravenously in a hospital, rendering it impractical for long-term weekly administration.[6,10,21] Pharmacologically enhanced psychotherapy is one potential means of prolonging ketamine's effects, with the class of psychedelic medications (in which ketamine is included) yielding encouraging results.[22–24] Due to the potentially promising nature of this combined treatment model, this brief report will review all literature on the combination of ketamine and psychotherapy for the treatment of PTSD to determine whether it produces a sustained reduction in symptoms of PTSD.

Methods

This study consisted of a systematic review and meta-analysis of all published works on this topic,[25–28] according to the PRISMA guidelines,[29] before June 2021 across 5 databases, including MEDLINE, PsycINFO, Embase, CINAHL, and PTSDpubs. Database search terms were built around 3 themes: PTSD, psychotherapy, and ketamine. After duplicates were removed, search results were screened independently by 2 authors (A.E.P.M. and C.J.S.) at the abstract and full-text levels. The most important criteria were that (1) all studies included patients diagnosed with PTSD, (2) all studies included an intervention involving ketamine alongside any form of psychotherapy, and (3) all patients were assessed before and after treatment using either the Clinician-Administered PTSD Scale (CAPS)[30] or the PTSD Checklist (PCL).[31] Full-text review was subjected to a quality assessment using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) checklist.[32,33] Data were analyzed with the estimated weighted mean effect size for each measure (standardized mean difference [SMD]), comparing pre- and posttreatment symptom severity scores.

Results

After screening, 4 studies were deemed eligible,[25–28] 2 of which were of moderate quality and 2 of which were of low quality according to the GRADE assessment. A total of 34 patients were included across all studies, with diverse traumatic experiences. The studies included several ketamine administration protocols, including one used previously for treating depression[34] and one used for chronic pain.[35,36] In 2 of the studies, patients received 12 sessions over 10 weeks of Trauma Interventions using Mindfulness Based Extinction and Reconsolidation therapy alongside a single dose of ketamine, administered at the time of psychotherapy.[26,27,37] In the third study, patients received 10 weekly sessions of Prolonged Exposure therapy alongside 3 weekly doses of ketamine administered 24 hours prior to the first 3 sessions.[28,38] In the final study, patients received 5 daily sessions of exposure therapy over the course of a single ketamine infusion.[25] For both measures, all studies demonstrated a significant reduction in symptoms. The pooled SMD for the CAPS was −7.26 ($P = .005$; 95% CI, −12.28 to −2.25), while the pooled SMD for the PCL was −5.17 ($P < .001$; 95% CI, −7.99 to −2.35) (Figure 1).

Discussion

This study is the first in several years to review the literature on the combined efficacy of ketamine and

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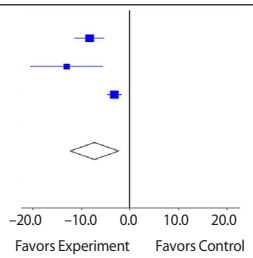
Figure 1. Forest Plots and Summary Statistics for Treatment Outcome

A. CAPS

Study	Pretreatment Mean	Pretreatment SD	Pretreatment N	Posttreatment Mean	Posttreatment SD	Posttreatment N	Weight %	SMD IV, Random [95% CI]
Pradhan 2018[27]	91.5	4.84	10	21.5	10.3	10	36.94	−8.33 [−11.34 to −5.32]
Pradhan 2017[26]	92.6	5.13	5	17.8	5.21	5	21.93	−13.07 [−20.53 to −5.61]
Shiroma 2020[28]	42.8	9.03	10	13.11	8.61	9	41.13	−3.21 [−4.67 to −1.75]
Overall			25			24	100.00	−7.26 [−12.28 to −2.25]

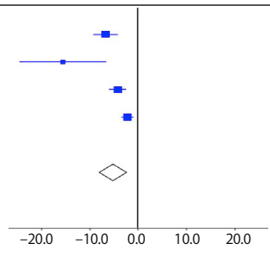
Heterogeneity: $\tau^2 = 15.363$; $\chi^2_1 = 14.28$; $P = .001$; $I^2 = 86\%$.
Test for overall effect: $z = 2.84$, $P = .005$.



B. PCL

Study	Pretreatment Mean	Pretreatment SD	Pretreatment N	Posttreatment Mean	Posttreatment SD	Posttreatment N	Weight %	SMD IV, Random [95% CI]
Pradhan 2018[27]	75.7	5.81	10	25.8	8.15	10	27.72	−6.75 [−9.25 to −4.26]
Pradhan 2017[26]	80.0	2.34	5	25.6	3.78	5	7.83	−15.63 [−24.52 to −6.74]
Shiroma 2020[28]	56.3	9.86	10	15.5	8.53	10	31.33	−4.24 [−5.95 to −2.53]
Keizer 2020[25]	55.33	11.52	9	27.11	12.36	9	33.12	−2.52 [−3.49 to −1.01]
Overall			34			34	100.00	−5.17 [−7.99 to −2.35]

Heterogeneity: $\tau^2 = 5.837$; $\chi^2_1 = 18.25$; $P = .001$; $I^2 = 83.56\%$.
Test for overall effect: $z = 3.6$, $P < .001$.



Abbreviations: CAPS = Clinician-Administered PTSD Scale, IV = inverse variance, PCL = PTSD Checklist, SMD = standardized mean difference.

psychotherapy for PTSD. The results of this meta-analysis indicate that this treatment may be highly effective, as seen by the significant improvements in symptoms on multiple measures. This demonstrates the potential feasibility of this treatment model and corroborates previous work.[10,37,39,40] Regarding limitations, due to the novelty of this research area, the sample size was very small. This prompted the inclusion of non-randomized studies to increase the sample, which lowered the quality of the evidence. In conclusion, these preliminary findings indicate the potential of ketamine-assisted psychotherapy for PTSD.

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Supplementary Material

Title of Brief Report: Combining Ketamine and Psychotherapy for the Treatment of Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis

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List of Supplementary Material

1. Table 1 Outcome Measures From Studies Included in the Analysis

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Supplementary Table 1. Outcome Measures From Studies Included in the Analysis

Outcome Measures

Study	CAPS.pre.treat.m	CAPS.pre.treat.sd	CAPS.pre.treat.n	CAPS.pre.plac.m	CAPS.pre.plac.sd
Pradhan 2018	91.5	4.84	10	86.2	9.05
Pradhan 2017	92.6	5.13	5	84.2	8.73
Shiroma 2020	42.8	9.03	10	.	.
Keizer 2020	.	.	.	.	.

Outcome Measures Continued

Study	CAPS.pre.plac.n	CAPS.post.treat.m	CAPS.post.treat.sd	CAPS.post.treat.n	CAPS.post.plac.m
Pradhan 2018	10	21.5	10.3	10	23.7
Pradhan 2017	4	17.8	5.21	5	23.4
Shiroma 2020	.	13.11	8.61	9	.
Keizer 2020	.	.	.	.	.

Outcome Measures Continued

Study	CAPS.post.plac.sd	CAPS.post.plac.n	PCL.pre.treat.m	PCL.pre.treat.sd	PCL.pre.treat.n
Pradhan 2018	9.63	10	75.7	5.81	10
Pradhan 2017	8.99	4	80	2.34	5
Shiroma 2020	.	.	56.3	9.86	10
Keizer 2020	.	.	55.33	11.52	9

Outcome Measures Continued

Study	PCL.pre.plac.m	PCL.pre.plac.sd	PCL.pre.plac.n	PCL.post.treat.m	PCL.post.treat.sd
Pradhan 2018	70.4	7.44	10	25.8	8.15
Pradhan 2017	70.4	8.62	4	25.6	3.78
Shiroma 2020	.	.	.	15.5	8.53
Keizer 2020	.	.	.	27.11	12.36

Outcome Measures Continued

Study	PCL.post.treat.n	PCL.post.plac.m	PCL.post.plac.sd	PCL.post.plac.n
Pradhan 2018	10	26.3	6.82	10
Pradhan 2017	5	26.6	7.63	4
Shiroma 2020	10	.	.	.
Keizer 2020	9	.	.	.

Trauma Type

Study	sexual	physical	emotional	motorvehical	combat
Pradhan 2018	8	6	1	1	1
Pradhan 2017	.	.	.	.	.
Shiroma 2020	4	1	.	.	5
Keizer 2020	2	2	.	.	10

Demographics

Study	Age.m	Age.sd	Age.n	duration.m	duration.sd
Pradhan 2018	39.1	11.45	10	15	8.99
Pradhan 2017	37.2	12.44	5	16.2	12.01
Shiroma 2020	45.1	14.93	10	21.7	15.55
Keizer 2020	33.67	7.33	9	4.44	3.17

Demographics Continued

Study	duration.n	proportion.male	proportion.fem	n.female
Pradhan 2018	10	0.2	0.8	8
Pradhan 2017	5	0	1	5
Shiroma 2020	10	0.7	0.3	3
Keizer 2020	9	0.73	0.27	3

Legend

Abbreviated Term	Definition
CAPS	Clinician-Administered PTSD Scale for DSM-5
PCL	PTSD Checklist
m	mean
n	sample size
sd	standard deviation
pre	pre-treatment
post	post-treatment
treat	treatment condition
plac	placebo condition
Age	Patient's age
duration	known duration of PTSD
proportion.male	proportion of patients identifying as male
proportion.fem	proportion of patients identifying as female