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CLINICAL RESEARCH ARTICLE

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Self-compassion mediates treatment effects in MDMA-assisted therapy for posttraumatic stress disorder

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ABSTRACT

Background: Posttraumatic stress disorder (PTSD) is a severe condition often complicated by co-occurring disorders, such as major depression, alcohol use disorder, and substance use disorders. A well-powered phase 3 randomized, placebo-controlled trial has shown that MDMA-assisted therapy (MDMA-AT) may be an effective treatment for severe PTSD. However, the psychological mechanisms driving the therapeutic effects of MDMA-AT remain unclear. One potential mechanism is self-compassion, which is commonly conceptualized as a balance between compassionate self-responding (CS) – encompassing self-kindness, common humanity, and mindfulness – and uncompassionate self-responding (UCS) – encompassing self-judgment, isolation, and over-identification.

Objective: This secondary analysis aimed to explore whether MDMA-AT enhances aspects of self-compassion and if changes in self-compassion mediate the therapy's effectiveness in reducing PTSD severity, depressive, and alcohol and substance use symptoms.

Method: Eighty-two adults diagnosed with severe PTSD participated in a double-blind trial comparing three sessions of either MDMA-AT or placebo combined with therapy. Measures of PTSD severity, depressive symptoms, alcohol and substance use, and self-compassion were collected at baseline and 18 weeks later.

Results: MDMA-AT led to statistically significant improvements in both UCS and CS. Significant improvements were also observed across all six subscales of the Self-Compassion Scale, including self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identification, most with large effect sizes. Changes in UCS and CS significantly and fully mediated the effects of MDMA-AT compared to placebo plus therapy in reducing PTSD severity and depressive symptoms. Findings were not significant for alcohol and substance use outcomes.

Conclusions: These findings suggest that self-compassion may play a critical role in the therapeutic effects of MDMA-AT. Further research is needed to investigate the role of self-compassion in MDMA-AT to refine and develop more targeted, effective interventions for individuals with PTSD and co-occurring depression.

La autocompasión media los efectos del tratamiento en la terapia asistida con MDMA para el trastorno de estrés postraumático

Antecedentes: El trastorno de estrés postraumático (TEPT) es una condición grave que a menudo se complica por trastornos concurrentes, como la depresión mayor, el trastorno por consumo de alcohol y los trastornos por consumo de sustancias. Un ensayo aleatorizado y controlado con placebo de fase 3 bien potenciado ha demostrado que la terapia asistida con MDMA (MDMA-AT) puede ser un tratamiento eficaz para el TEPT grave. Sin embargo, los mecanismos psicológicos que impulsan los efectos terapéuticos de la MDMA-AT siguen sin estar claros. Un mecanismo potencial es la autocompasión, que se conceptualiza comúnmente como un equilibrio entre la autorrespuesta compasiva (CS, por sus siglas en inglés) – que abarca la autocompasión, la humanidad compartida y la atención plena – y la autorrespuesta no compasiva (UCS, por sus siglas en inglés) – que abarca el auto-juicio, el aislamiento y la sobreidentificación-.

Objetivo: Este análisis secundario pretendía explorar si la MDMA-AT mejora aspectos de la autocompasión y si los cambios en la autocompasión median en la eficacia de la terapia para reducir la gravedad del TEPT, los síntomas depresivos y de consumo de alcohol y sustancias.

Método: Ochenta y dos adultos diagnosticados con TEPT grave participaron en un ensayo doble ciego en el que se compararon tres sesiones de MDMA-AT o placebo combinadas con terapia. Se recogieron medidas de la gravedad del TEPT, síntomas depresivos, consumo de alcohol y sustancias, y autocompasión al inicio y 18 semanas después.

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HIGHLIGHTS

- MDMA-assisted therapy significantly improves self-compassion in individuals with severe posttraumatic stress disorder, showing large effect sizes across various aspects, including self-kindness and mindfulness.
- Changes in self-compassion play a key role in reducing posttraumatic stress and depressive symptoms, mediating the therapeutic effects of MDMA-assisted therapy.
- These findings highlight self-compassion as a potential target for developing more effective treatments for individuals with posttraumatic stress disorder and co-occurring depression.

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Resultados: MDMA-AT condujo a mejoras estadísticamente significativas tanto en UCS como en CS. También se observaron mejoras significativas en las seis subescalas de la Escala de Autocompasión, incluyendo la autocompasión, el auto-juicio, la humanidad compartida, el aislamiento, la atención plena y la sobreidentificación, la mayoría con grandes tamaños de efecto. Los cambios en UCS y CS mediaron de forma significativa y completa los efectos de MDMA-AT en comparación con placebo más terapia en la reducción de la gravedad del TEPT y los síntomas depresivos. Los hallazgos no fueron significativos para los resultados de consumo de alcohol y sustancias.
Conclusiones: Estos hallazgos sugieren que la autocompasión puede desempeñar un papel crítico en los efectos terapéuticos de la MDMA-AT. Es necesario seguir investigando el papel de la autocompasión en la MDMA-AT para perfeccionar y desarrollar intervenciones más específicas y eficaces para las personas con TEPT y depresión concurrente.

1. Introduction

Posttraumatic stress disorder (PTSD) is a distressing psychological condition that can emerge following exposure to single or multiple traumatic events. PTSD often significantly compromises affected individuals' daily functioning, resulting in reduced productivity, high-cost healthcare utilization, as well as increased suicidality and mortality (Shea et al., 2010). Effect sizes for current Food and Drug Administration (FDA)-approved pharmacotherapies are small to moderate with high drop-out rates, and many patients do not respond adequately to treatment (Feduccia et al., 2019). More effective treatment approaches with lower dropout rates are urgently needed to address this widespread, serious, and potentially life-threatening condition. Additionally, ongoing maintenance dosing is often required to prevent relapse, posing another significant challenge. Although standard trauma-focused psychotherapies such as Prolonged Exposure or Cognitive Processing Therapy are effective for many individuals, a substantial proportion of patients either do not improve or drop out (Ehlers et al., 2010).

Increasing evidence demonstrates that MDMA-assisted therapy (MDMA-AT) should be evaluated further for individuals with PTSD. Phase 3 data have demonstrated clinically and statistically significant improvement in severe, chronic PTSD with an acceptable safety profile. Effect sizes were large, with higher tolerability than existing trauma-focused therapies and significantly lower drop-out rates (Mitchell et al., 2023; Mitchell, Bogenschutz, et al., 2023).

To advance our theoretical comprehension of how MDMA-AT operates in the context of PTSD, further investigation is needed into the psychological mechanisms that underpin MDMA-AT. Self-compassion has garnered scholarly attention, with a growing interest in its relevance to PTSD. Self-compassion has been defined and operationalized by Neff (Neff, 2003) as compassion directed towards oneself in challenging times. Self-compassion is often deficient in individuals with PTSD who struggle with feelings of low self-worth and self-blaming cognitions and appraisals (Játiva & Cerezo, 2014; Zeller et al., 2015). Low self-compassion is associated with anxiety, depression, self-criticism, and with poor treatment responses (Winders et al., 2020). A systematic review revealed an inverse relationship between self-compassion and PTSD (Gilbert & Irons, 2005), indicating that lower self-compassion may play a role in PTSD maintenance. Interventions that focus on self-compassion have been shown to reduce PTSD symptoms (Au et al., 2017; Kearney et al., 2021) and may do so by targeting underlying maladaptive cognitions and negative self-appraisals, decreasing avoidance, and upregulating self-soothing emotion regulation processes (Forkus et al., 2019; Kaurin et al., 2018; Tarber et al., 2016).

The construct of self-compassion, however, has some complexities, especially in how it is measured and interpreted in various contexts. The Self-Compassion Scale (SCS) (Neff, 2003), widely used in research, has prompted discussion about its dimensional structure and whether it fully captures the nuances of self-compassion. Most early research relied on a single-factor score of the SCS, but many contemporary scholars suggest that the SCS instead represents semi-independent, unipolar continuums with compassionate self-responding (CS) encompassing self-kindness, common humanity, and mindfulness – reflecting adaptive, caring responses to personal suffering – while uncompassionate self-responding (UCS) encompasses the more negative dimensions of the SCS (self-judgment, isolation, and over-identification), reflecting a tendency to be overly critical or negative towards oneself in the face of challenges (López et al., 2015; Muris et al., 2016; Wolfson et al., 2020). In this view, both increasing CS and decreasing UCS may be important, as they target PTSD symptoms in distinct ways. There is empirical support indicating that MDMA-AT contributes to an augmentation in self-compassion, suggesting its potential significance as a therapeutic mechanism. Studies involving both clinical and healthy volunteer samples have demonstrated an elevation in self-compassion following MDMA administration. In an

investigation of MDMA-AT for anxiety and psychological distress associated with life-threatening illnesses, participants exhibited statistically significant increases in self-compassion from baseline to various follow-up points, extending up to 12 months post-treatment (Barone et al., 2019). Additionally, qualitative reports from a phase 2 study on MDMA-AT for PTSD highlighted the participants' perceived improvements in self-compassion and self-awareness (Barone et al., 2019).

Moreover, a recent secondary analysis of a phase 3 trial investigating MDMA-AT for PTSD reported a significant increase in self-compassion (using a single-factor total score) between baseline and 18 weeks after baseline, relative to the Placebo + Therapy (PT) group (van der Kolk et al., 2024). In this post-hoc exploratory analysis, we build on these prior findings by examining how MDMA-AT specifically affects distinct self-compassion dimensions within the same phase 3 trial, using bifactor scoring to capture both compassionate and uncompassionate responding. Additionally, we explore the statistical relationships between changes in self-compassion and PTSD severity throughout the study. Finally, given research highlighting that PTSD frequently co-occurs with depressive disorders and alcohol and substance use (Goldstein et al., 2016) and that these comorbidities can magnify self-criticism, shame, and social withdrawal (Ullman et al., 2006), we also explored the statistical relationships between changes in self-compassion and depression, alcohol use, and substance use.

2. Methods

2.1. Participants

The present analysis assessed exploratory data from a two-arm, randomized, double-blind, placebo-controlled phase 3 study of the efficacy and safety of MDMA-assisted therapy for PTSD (NCT03537014) (Mitchell, Bogenschutz, et al., 2023). In this primary study, after providing informed consent, participants who were diagnosed with PTSD according to the DSM-5, completed the PTSD Checklist (PCL-5) (Blevins et al., 2015). To be eligible, participants needed to have experienced PTSD symptoms for at least six months and have a total severity score on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2018) of 35 or higher. Psychiatric disorders and ASUD in the past 12 months were assessed using the Mini-International Neuropsychiatric Interview for the DSM-5. Exclusion criteria comprised current primary psychotic disorder, bipolar I disorder, dissociative identity disorder, eating disorders with active purging, major depressive disorder with psychotic features, personality disorders, pregnancy, or lactation, as well as any significant medical condition that might be affected by an acute increase in heart rate or blood pressure. Participants were allowed to have a mild current alcohol or cannabis use disorder or a moderate alcohol or cannabis use disorder in early remission during the three months before enrolment, per DSM-5 criteria. However, participants were excluded if they had any other active alcohol and substance use disorder (ASUD) at any severity within the 12 months prior to enrolment (Mitchell, Bogenschutz, et al., 2023).

2.2. Procedure

The study was conducted across 15 study sites in the United States, Canada, and Israel with the ethics approval of local institutional review boards. The complete study methods have been described previously (Mitchell, Bogenschutz, et al., 2023). Following safety and eligibility screening and taper from psychiatric medications, participants underwent three 90-minute preparatory therapy sessions. Participants who met eligibility criteria (CAPS-5 score ≥ 35 as assessed by blinded independent raters), were then randomized to MDMA-AT or PT. In each of the three 8-hour experimental sessions, participants received a dose of MDMA or inactive placebo, with an initial dose followed by a supplemental half dose 1.5–2 h later (80 + 40 mg in the first session and escalated to 120 + 60 mg for the second and third sessions). The three 8-hour experimental session were spaced 4 weeks apart. The supplemental doses and the dose escalation could be withheld if tolerability issues emerged with the initial dose or if the participant declined. Following each experimental session, participants engaged in three 90-minute therapy sessions spaced one week apart. This interval allowed participants to process and incorporate insights from their experimental sessions into their lives. Blinding was maintained until after the database was locked to participants, site staff, and the sponsor. The outcome assessment took place eight weeks after the third experimental session (i.e. 18 weeks after baseline),

2.3. Outcome measures

The 26-item Self-Compassion Scale (SCS) (Neff, 2003) was used to assess self-compassion. Participants rate the frequency of their feelings regarding each item using a 5-point Likert scale, ranging from 1 ('Almost never') to 5 ('Almost always'). The subscales measure three positive dimensions of self-compassion, including self-kindness, common humanity, and mindfulness, and three negative dimensions of self-judgment, isolation, and overidentification. The former three are averaged to derive a score for compassionate self-responding (CS), and the latter three

are averaged to derive a score for uncompassionate self-responding (UCS). There is a debate among several scholars regarding the validity of Neff's original conceptualization that self-compassion forms a bipolar continuum, ranging from CS to UCS, which can be combined into a global single-factor total score (all items load on one factor) for SCS. Most contemporary scholars have argued that SCS instead comprises semi-independent, unipolar continuums of CS and UCS (López et al., 2015; Muris et al., 2016). Indeed, there is stronger support for the 2-factor (UCS and CS subscales) and the 6-factor (i.e. self-kindness, self-judgment, common humanity, isolation, mindfulness, over-identification subscales) scoring methods of the SCS over the use of a single, unidimensional score (Muris et al., 2016; 2022; and Lopez et al., 2015). Accordingly, in this paper we present the 2-factor and 6-factor scores.

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2018) is a 30-item structured diagnostic interview assessing PTSD diagnostic status and symptom severity, designed to be administered by clinicians and clinical researchers who have a working knowledge of PTSD. Administration requires identifying an index trauma or a series of related events (e.g. multiple combat tours) to serve as the foundation for symptom assessment. Questions target the 20 PTSD symptoms as defined by the DSM-5, the frequency and intensity of symptoms, and overall response validity, with specifications for the dissociative subtype. PTSD severity is determined by the clinician administering the interview. CAPS-5 data were assessed by a centralized pool of clinicians serving as independent assessors who were blinded to study design and thoroughly vetted for conflict of interest.

The Beck Depression Inventory-II (BDI-II) (Beck et al 1996) is a 21-item self-report questionnaire evaluating the severity of depression in normal and psychiatric populations. Questions address affective, cognitive, somatic, and vegetative symptoms, reflecting the DSM-5 criteria for major depression. Items are rated on a 4-point scale from 0 = symptom absent to 3 = severe symptoms. Scoring is achieved by adding the ratings for all 21 items (the minimum score is 0, and maximum score is 63).

The Alcohol Use Identification Test (AUDIT) is a 10-item self-report questionnaire designed to screen for hazardous alcohol consumption that may suggest Alcohol Use Disorder (AUD) or at-risk alcohol use (Saunders et al., 1993). The AUDIT evaluates alcohol consumption patterns, drinking behaviour, and alcohol-related issues over the past 12 months. In parallel, the Drug Use Identification Test (DUDIT) is an 11-item self-report measure to identify substance use patterns and drug-related problems (Berman et al,. 2005). The DUDIT assesses aspects such as frequent and heavy drug use, craving, relationship to drug use, and harmful use. At screening, respondents were asked to report on their drug and alcohol use over the past 12 months. At the end of the study, the instructions were modified, requesting participants to base their responses on the period since the completion of treatment.

2.4. Statistical methods

Participants who met criteria for endorsing any use of alcohol or substances (defined as an AUDIT or DUDIT score >0) at baseline were included in this analysis. This approach was chosen to mitigate floor effects and more optimally address the current aims of assessing whether MDMA-AT leads to clinically meaningful changes in hazardous alcohol and substance use. Descriptive analyses were performed on demographic (age, gender, ethnicity, race), baseline, and outcome variables. Pearson correlation coefficients were analysed for all variables at study baseline and study termination time points (see Supplementary eTable 1 for results).

One-way ANCOVA models, adjusting for respective baseline scores and CAPS-5 dissociative subtype (Yes = 1 and No = 0), compared treatment group differences in change scores, defined as the difference between study termination values and baseline values (i.e. [Follow-up] − [Baseline]), for UCS, CS, and the six SCS subscales. Consequently, a positive change score indicates improvement (e.g. higher CS or lower UCS) from baseline to follow-up. We used the Benjamini-Hochberg method (Benjamini & Hochberg, 1995) to control the false discovery rate (FDR) at a level of 0.05 across (a) UCS and CS (2 analyses) and (b) the six SCS subfactors (6 analyses). Between-group Cohen's *d* effect sizes were calculated for statistically significant treatment effects between treatment groups.

For mediation analyses, we employed PROCESS Macro (model 4), entering these same difference scores (Follow-up − Baseline) for both mediator (M) and outcome (Y) variables, while controlling for each variable's baseline value. Treatment condition (MDMA-AT vs. PT) was entered as the independent variable (X). The following variables were entered separately as the outcome variables: CAPS-5, BDI-II, AUDIT, and DUDIT. UCS and CS were entered separately as the mediators. Additionally, we conducted mediation analyses for each of the six SCS subscales entered as mediators; those results are presented in Supplementary eTable 2. PROCESS uses an ordinary least squares or logistic regression-based path analytical framework for estimating the direct and indirect effects. Following recommendations by Preacher and Hayes (Preacher & Hayes et al., 2008), bootstrapping methods can be used for estimating the standard errors of parameter estimates and the bias-corrected

confidence intervals (CI) of the indirect effects. Indirect effects were considered significant when the bias-corrected CI did not include zero (Preacher & Hayes et al., 2008). Statistical significance was set at an alpha level of 0.05. All analyses were conducted using SPSS Version 27.

3. Results

3.1. Sample characteristics

Participants were recruited from 2018 to 2020. A total of 90 participants were randomized and received either MDMA-AT or PT. Three participants in the MDMA and four in the placebo group withdrew from the study, leaving a total of 82 participants that completed both baseline and study termination assessments. Only participants who provided complete data at both time points were used in the present analyses (Mitchell, Bogenschutz, et al., 2023).

Table 1 provides a summary of demographic and baseline variables relevant to the present study. The total study sample consisted of participants that were mostly female (64.6%), White (80.3%), non-Hispanic or Latinx (92.7%), and had a mean age of 41.4 (SD = 12.22) years. Mean baseline CAPS-5 total severity score was 43.84 (SD = 6.00) indicating severe PTSD, and mean BDI-II score was 32.27 (SD = 13.01), indicating severe depression. Among the participants, 21 (25.61%) reported a history of AUD without current AUD at the time of enrolment. Additionally, 14 (17.1%) reported past substance use disorders. The mean UCS score was 3.86 (SD = 0.80), and mean CS score was 2.46 (SD = 0.80). Within the placebo group, two (2.50%) participants reported current mild cannabis use disorder. At baseline, 69 (84.1%) participants had an AUDIT score of 1 or higher, indicating some alcohol use, while 48 (58.5%) participants had a DUDIT score of 1 or higher, suggesting any use of substances over the past 12 months. Within the placebo group, two (2.5%) participants reported current mild cannabis use disorder. For correlation coefficients by condition at study baseline and termination time points, see Supplementary Material (eTable 1).

3.2. Primary endpoint changes

The MDMA-AT group showed significantly greater between-group changes in UCS, CS, and the six SCS subscales (from baseline to study follow-up) compared with the PT group, while controlling for CAPS dissociative subtype and respective SCS baseline score. Results were as follows using FDR-corrected p-values: UCS [$F(1, 78) = 30.91$, $p < .001$]; CS [$F(1, 78) = 26.83$, $p < .001$]; Self-Kindness [$F(1, 78) = 25.81$, $p < .001$]; Common Humanity [$F(1, 78) = 10.37$, $p = .002$]; Mindfulness [$F(1, 78) = 32.32$ $p < .001$]; Isolation [$F(1, 78) = 15.22$, $p < .001$]; Overidentified [$F(1, 78)$

Table 1. Demographics and baseline characteristics.

	MDMA-AT	Placebo + therapy	Total sample
Age (years), mean (SD)	44.18 (13.1)	38.53 (10.6)	41.42 (12.22)
Sex, *n* (%)			
Male	18 (42.9%)	11 (27.5%)	29 (35.4%)
Female	24 (57.14%)	29 (72.5%)	53 (64.6%)
Ethnicity, *n* (%)			
Hispanic or Latinx	3 (7.1%)	2 (5.0%)	5 (6.1%)
Not Hispanic or Latinx	39 (92.9%)	37 (92.5%)	76 (92.7%)
Not reported	0	1 (2.50%)	1 (1.2%)
Race, *n* (%)			
American Indian/Alaska Native	3 (7.14%)	0	3 (3.7%)
Asian	0	5 (12.8%)	5 (6.2%)
Black or African American	0	2 (5.1%)	2 (2.5%)
White	37 (88.1%)	28 (71.8%)	66 (80.3%)
More than one	2 (4.8%)	4 (10.3%)	6 (7.4%)
Trauma History, *n* (%)			
Veteran status	10 (23.8%)	5 (12.0%)	15 (19.3%)
Served in combat area	6 (14.3%)	4 (10.0%)	10 (12.2%)
Multiple trauma (yes)	38 (90.5%)	36 (90.0%)	74 (90.2%)
Developmental trauma	37 (88.1%)	32 (80.0%)	69 (84.1%)
Alcohol Use Disorder, *n* (%)			
Past (yes)	13 (31.0%)	8 (20.0%)	21 (25.6%)
Current (yes)	0	0	0
Substance Use Disorder, *n* (%)			
Past (yes)	8 (19.1%)	6 (12.5%)	14 (17.1%)
Current (yes)	0	2 (5.0%)	2 (2.4%)
Baseline Measures			
CAPS-5 Severity, mean (SD)	43.98 (6.2)	43.7 (5.9)	43.84 (6.0)
UCS, mean (SD)	3.78 (0.8)	3.95 (0.78)	3.86 (0.8)
CS, mean (SD)	2.58 (0.97)	2.36 (0.67)	2.47 (0.8)
BDI-II, mean (SD)	30.60 (13.3)	34.03 (12.6)	32.27 (13.0)
AUDIT, mean (SD)	4.26 (4.3)	2.83 (3.3)	3.56 (3.9)
≥ 1 Any use, *n* (%)	37 (88.1%)	32 (80.0%)	69 (84.1%)
DUDIT, mean (SD)	2.69 (4.4)	3.48 (4.6)	3.07 (4.5)
≥ 1 Any use, *n* (%)	25 (59.5%)	23 (57.5%)	48 (58.5%)

Table 2. Changes across dimensions of the Self-Compassion Scale by treatment group.

	MDMA + Therapy		Placebo + Therapy				
Self-Compassion Scale	Baseline Mean (SD)	Termination Mean (SD)	Baseline Mean (SD)	Termination Mean (SD)	[a]Between-Group Change (SD)	[b]FDR *p*-value	[c]Cohen's *d*
Uncompassionate Self-Responding (UCS)	3.78 (0.80)	2.63 (0.93)	3.95 (0.78)	3.67 (1.05)	−0.88 (1.03)	<.0001	1.23
Compassionate Self-Responding (CS)	2.28 (0.97)	3.63 (0.80)	2.36 (0.67)	2.71 (0.76)	0.81 (1.04)	<.0001	1.10
Self-Kindness	2.36 (1.00)	3.58 (0.96)	2.14 (0.86)	2.51 (0.94)	0.94 (1.19)	<.0001	1.10
Self-Judgment	3.92 (0.99)	2.59 (0.94)	4.06 (0.83)	3.81 (1.15)	−1.10 (1.16)	<.0001	1.34
Common Humanity	2.59 (1.10)	3.45 (0.98)	2.26 (0.75)	2.66 (0.96)	0.65 (1.27)	.002	0.72
Isolation	3.75 (0.90)	2.71 (1.09)	4.03 (0.87)	3.68 (1.14)	−0.72 (1.20)	<.0001	0.86
Mindfulness	2.80 (1.03)	3.85 (0.71)	2.66 (0.71)	2.95 (0.75)	0.84 (0.96)	<.0001	1.25
Overidentified	3.67 (0.90)	2.60 (0.96)	3.76 (0.91)	3.53 (1.08)	−0.84 (1.09)	<.0001	1.17

[a]ANCOVA models were adjusted for respective baseline scores and CAPS-5 Dissociative subtype.
[b]*P*-values tested for between-group subjects' comparison of MDMA-assisted therapy ($N = 42$) change scores vs. Therapy with placebo ($N = 40$) change scores between baseline and study termination using estimated marginal means adjusted for respective baseline scores and CAPS-5 Dissociative subtype. *P* values were FDR-corrected using the Benjamini-Hochberg method (Berman et al., 2005).
[c]Cohen's *d* effect sizes correspond to between-group mean changes using estimated marginal means.

= 24.33, $p < .001$]; and Self-Judgment [$F(1, 78) = 36.43$, $p < .001$]. Cohen's *d* effect sizes comparing the mean changes between treatment groups were large for UCS, CS, and the remaining subscales, except for Common Humanity, which had a moderate effect size ($d = 0.72$). Descriptive means, between-group change scores (using estimated marginal means), test statistics, and effect sizes are presented in Table 2.

3.3. Indirect effect of change in uncompassionate and compassionate self-responding on clinical outcomes

Indirect effect beta values and CIs for ΔUCS and clinical outcomes were as follows: ΔCAPS-5 Total Severity ($B = 8.63$; SE = 1.96; 95% bias-corrected bootstrap CI = 5.14, 12.78) and ΔBDI-II ($B = 8.51$; SE = 1.84; CI = 5.07, 12.28). ΔUCS score did not show a significant indirect effect on ΔAUDIT ($B = 0.23$; SE = 0.41; CI = −0.56, 1.14) or ΔDUDIT ($B = 1.24$; SE = 0.90; CI = −.012, 3.30). Results for ΔCS and clinical outcomes were as follows: ΔCAPS-5 Total Severity ($B = 7.08$; SE = 1.95 CI = 3.71, 11.27) and ΔBDI-II ($B = 8.01$; SE = 1.98; CI = 4.48, 12.28). ΔCS score did not show a significant indirect effect on ΔAUDIT ($B = -0.40$; SE = 0.42; CI = −1.29, 0.42) or ΔDUDIT ($B = 0.40$ SE = 0.76; CI = −1.01, 2.06). Figure 1 displays the *p*-values for the A, B, C, and C′ paths for significant findings. All C′ paths were non-significant, indicating that the findings were consistent with full mediation. Mediation analysis results for each of the six SCS subscales are presented in Supplementary eTable 2.

4. Discussion

In this secondary analysis, we investigated whether MDMA-AT led to significant improvements in dimensions of self-compassion among individuals with a primary diagnosis of PTSD. We then examined whether improvements in self-compassion may function as a meaningful mechanism of action in MDMA-AT by mediating reductions in PTSD severity. Additionally, we assessed whether these changes mediated reductions in psychological conditions commonly co-occurring with PTSD, such as depression and hazardous alcohol and substance use. The current analyses found that MDMA-AT, compared to PT, significantly improved all dimensions of self-compassion, namely UCS, CS, and all six subscales of the SCS. These enhancements were observed from the baseline assessment to study termination with mostly large effect sizes. Changes in UCS and CS were each found to statistically mediate the effects of MDMA-AT on improvements in PTSD severity and depression. Due to the limited recruitment of participants with severe levels of ASUD and the narrow distribution of AUDIT scores, significant changes from baseline and sensitive risk measures could not be adequately explored.

Effect sizes for the UCS models were generally larger than those for CS. The greatest between-group effect sizes on the SCS emerged for self-judgment ($d = 1.34$) and UCS ($d = 1.27$). Furthermore, mediation models for all clinical outcomes consistently favoured UCS. This construct encompasses the more negative dimensions of the SCS – self-judgment, isolation, and over-identification – and reflects a tendency to be overly critical or negative towards oneself in the face of challenges, representing a key psychological vulnerability to emotion regulation difficulties (Jativa & Cerezo 2014). Such a self-critical perspective can foster feelings of inadequacy, doubt, and shame or guilt. The finding that improvements in UCS most strongly predicted mental health outcomes aligns with previous research showing its stronger links to outcomes like depression (Muris et al., 2016; Lopez et al., 2015). These results emphasize the value of assessing CS and UCS as distinct constructs, rather than relying exclusively on the total self-compassion score, to better predict outcomes and refine therapeutic interventions (Muris et al., 2016). Clinical approaches that target reducing self-judgment, over-

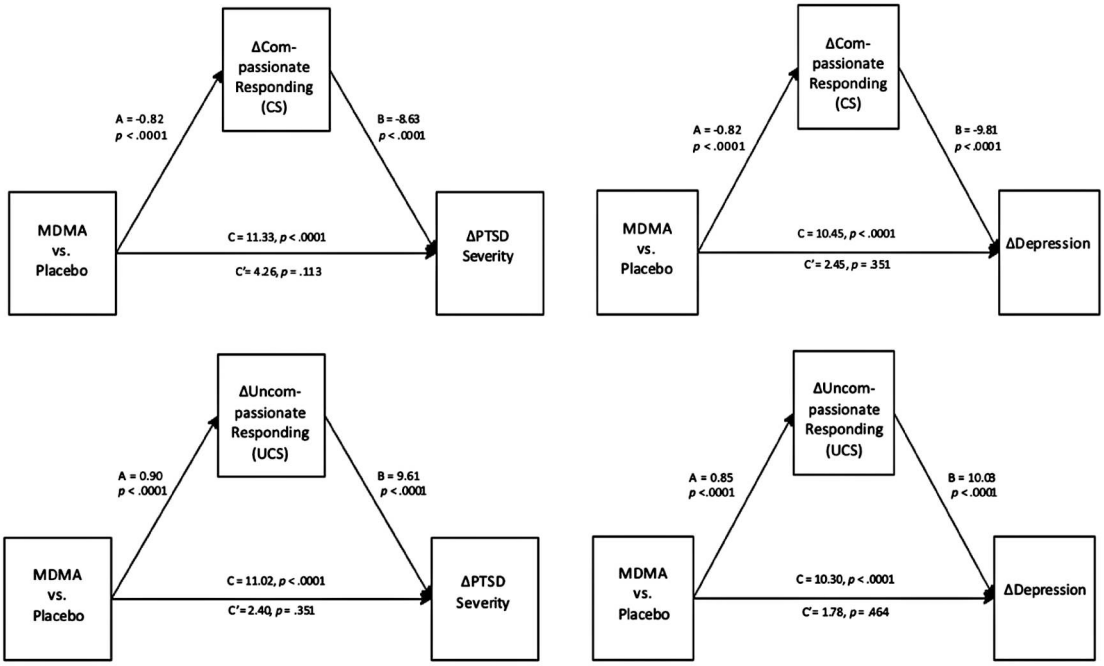

Figure 1. Path diagram depicting the associations between MDMA-assisted therapy (Treatment), changes in self-compassion (Mediator), and reductions in PTSD symptom severity (Outcome). All depicted paths (A, B, and C) are statistically significant ($p < .0001$). All C′ paths were non-significant, indicating that the findings were consistent with full mediation.

identification, and avoidance of distressing internal experiences – while helping individuals disengage from negative self-concepts (e.g. 'I'm broken') – may exert a greater treatment impact than those focusing only on augmenting compassionate self-responding (CS).

Our findings also support the idea that self-compassion may have efficacy in mediating improvements in depression symptoms that often co-occur with PTSD. Previous research has shown that individuals with co-occurring PTSD and MDD engage in emotional avoidance and employ expressive suppression and rumination strategies more frequently than those with PTSD alone (Post et al., 2021), suggesting that the relationship between PTSD and MDD is partly due to a shared repertoire of emotion regulation strategies to manage negative affect. Clinical populations with lower levels of uncompassionate self-responding may engage in fewer emotional avoidance strategies, thereby facilitating a natural exposure process and increasing self-compassion-focused, approach-oriented coping responses to stress or intense emotions (Post et al., 2021). Additionally, an uncontrolled study found that self-compassion and rumination served as significant mediators of psychedelic-related improvements in depression and anxiety, further underscoring the broader therapeutic potential of self-compassion (Fauvel et al., 2023). While our study did not support an association between self-compassion and alcohol misuse, previous research has identified such a correlation (Van Dam et al., 2011; Wisener & Khoury, 2021; Brooks et al., 2012). Overall, self-compassion holds promise as a transdiagnostic and transtheoretical mechanism of action in therapy, representing a compelling target for future interventions (Ferrari et al., 2019; Van Dam et al., 2011).

Furthermore, classic self-compassion interventions – such as Compassion-Focused Therapy (CFT) – have been shown to alleviate PTSD symptoms by decreasing shame and maladaptive self-blame (Au et al., 2017; Kearney et al., 2021). By combining MDMA with interventions that specifically focus on building self-compassion (e.g. mindfulness, self-kindness exercises), clinicians could capitalize on MDMA's unique pharmacological profile to reduce avoidance and shame, thereby accelerating the internalization of more compassionate self-concepts. Additionally, MDMA's social bonding effects – including increased feelings of closeness and empathy (Wardle & de Wit, 2014) may parallel the acceptance-of-self that is central to self-compassion. MDMA has known acute pro-social and anxiolytic properties, potentially reducing fear and defensiveness in-session. This reduced fear may facilitate the therapeutic work of processing trauma, allowing patients to develop greater self-kindness (i.e. CS) while diminishing harsh self-criticism (i.e. UCS). Psychotherapy may also play a critical role; for instance, therapists trained in acceptance – or compassion-based frameworks might help patients leverage MDMA's pro-social effects to practice kinder self-talk and reconceptualize traumatic memories. This approach may present a more cohesive and inclusive therapeutic strategy that targets impairments

that significantly contribute to the emergence of various psychopathological conditions.

Considering the potential transdiagnostic efficacy of self-compassion in mitigating negative outcomes associated with PTSD, self-compassion interventions might also be fruitful in addressing moral injury, which often provokes feelings of shame and remorse from having violated core moral beliefs and is becoming increasingly prevalent among the United States Veteran population (Koenig & Zaben 2021). The overlap between moral injury and depression may be similarly significant because depression often follows traumatic experiences (Nichter et al., 2019). As research in this area advances, MDMA-AT may emerge as a valuable and inclusive therapeutic strategy for Veterans and other individuals grappling with the intricate challenges of moral injury and who may not readily meet criteria for a PTSD diagnosis.

The neurobiological mechanisms of MDMA administration and self-compassion appear to share similarities, particularly in their effects on brain regions and neurotransmitter systems involved in emotion regulation and memory reprocessing. Both MDMA and self-compassion have been found to influence threat-regulatory mechanisms linked to the amygdala, a crucial brain region involved in fear processing and threat recognition, which is frequently dysregulated in individuals with PTSD. For example, research indicates that MDMA administration decreases cerebral blood flow to the amygdala and the coupling between the medial prefrontal cortex (mPFC) and hippocampus – regions linked to executive control and learning/memory, respectively – in healthy populations (Carhart-Harris et al., 2015). Additionally, MDMA has been found to enhance resting state functional connectivity between the amygdala and hippocampus in individuals with PTSD (Singleton et al., 2023). Findings from the latter study also revealed that reductions in functional connectivity (FC) from pre – to post-therapy during a script listening task – specifically between the left amygdala and the right PCC, left PCC, and left insula, as well as between the left isthmus cingulate and left hippocampal tail – were strongly and significantly correlated with improvements in PTSD symptoms (Singleton et al., 2023). Similarly, positive associations have been found between self-compassion and negative ventromedial prefrontal cortex-amygdala connectivity in response to negative stimuli, which is associated with healthy emotion regulation processes (Parrish et al., 2018). These mechanisms could play a crucial role in enhancing an individual's ability to process traumatic memories through the reduction of amygdala hyperactivity and the inhibition of excessive top-down regulation of executive functions in limbic emotional processing. Additionally, both MDMA and self-compassion connect to the oxytocin system, which fosters trust, empathy, and regulates anxiety through social closeness (Kosfeld et al., 2005). MDMA has been found to trigger oxytocin release (Hysek et al., 2012, 2014), while higher trait self-compassion has been found to correlate with greater oxytocin receptor gene expression (Wang et al., 2019) and salivary oxytocin during stress and recovery (Bowlin et al., 2012). This release may reduce amygdala hyperactivity, thereby lowering self-criticism and fear surrounding traumatic memories. By encouraging openness and vulnerability, MDMA-AT may lead to lasting improvements in emotion regulation and reduced self-criticism.

4.1. Limitations

Several limitations of this work should be considered. It should be noted that due to the post-hoc and exploratory nature of this study, it is possible that there are other mediators of MDMA-AT that were not examined here. These untested mediators could offer further insights into the experimental effects of MDMA-AT. Additionally, the entry-level criteria required participants to have severe symptoms, which may have biased the results; it's possible that including individuals with mild or moderate symptoms could have yielded different outcomes, potentially altering the overall analysis and the observed effects of the intervention. Future MDMA-AT research would benefit from the inclusion of additional validated psychological variables such as psychological flexibility, emotion regulation, and attachment, and examinations of how these constructs relate to self-compassion. There is therefore a need for further research to clarify a more nuanced understanding of the relationships between PTSD, psychological inflexibility, self-compassion, and related variables.

Moreover, because self-compassion and PTSD severity were measured at the same follow-up time point, our study cannot definitively establish whether increases in self-compassion precede, co-occur with, or follow reductions in PTSD symptoms. Future trials should collect multiple, staggered assessments of self-compassion and PTSD outcomes, which would clarify temporal precedence and strengthen causal interpretations. The clinical interpretation of these findings is constrained by several factors, including the limited inclusion of ASUD participants – restricted to those with mild or moderate symptoms in early remission – and the study's exploratory nature. Additionally, the sample was relatively homogeneous, consisting predominantly of non-Hispanic White individuals. Epidemiological data show that in the United States, the lifetime prevalence of PTSD is highest among Black individuals, compared to Hispanic and White populations; moreover, sexually and gender diverse populations experience higher rates and greater severity of PTSD than the general population (George et al.,

2019). Despite these disparities, people from minoritized racial/ethnic groups and sexual and gender minority communities encounter significant barriers to care, leading to underrepresentation in both general clinical trials and MDMA-AT studies (Michaels et al., 2018). To address these gaps, future trials should prioritize the inclusion of BIPOC individuals who may substantially benefit from treatment (Michaels et al., 2018). Additionally, functional unblinding could have posed a limitation in the parent trial, and it was not formally assessed. However, when participants were informed of their actual treatment assignments, over 10% had guessed their treatment arm incorrectly, which suggests that there was some uncertainty regarding treatment assignment among the participants (Mitchell, Bogenschutz, et al., 2023). A final limitation is that over one-third of participants reported prior MDMA use (Mitchell, Bogenschutz, et al., 2023), which may have amplified expectancy bias.

4.2. Conclusion

In conclusion, the findings of this study suggest that self-compassion may play a vital role in explaining how MDMA-AT improves functioning in individuals with PTSD. Our findings suggest that MDMA-AT significantly improves dimensions of self-compassion compared with PT and that improvements in self-compassion (both UCS and CS) statistically mediate the effects of MDMA-AT on PTSD severity and depressive symptoms. The results contribute to a growing body of research implicating self-compassion as an important psychological mechanism in the therapeutic benefits of MDMA-AT for individuals with PTSD. Further investigations into the interplay between self-compassion and MDMA-AT may lead to more targeted and effective interventions for those struggling with PTSD and other psychosocial challenges. Integrating formal components of self-compassion-based interventions into MDMA-AT could meaningfully enhance clinical and psychological outcomes in the treatment of PTSD and co-occurring conditions.

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Data availability statement

The data used for the exploratory analysis in this publication were made available to the authors via a data use agreement with the organizer of the source phase 3 trial (clinical trials.gov identifier, NCT03537014), Lykos Therapeutics. The data that support the findings of this publication are available upon reasonable request. All data requests should be directed to the corresponding author, who will confirm with Lykos Therapeutics if the request is subject to any confidentiality or licencing constraints.

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