EUROPEAN JOURNAL OF PSYCHOTRAUMATOLOGY
2024, VOL. 15, NO. 1, 2297536
https://doi.org/10.1080/20008066.2023.2297536

EUROPEAN JOURNAL OF PSYCHO-TRAUMATOLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY FOR TRAUMATIC STRESS STUDIES

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH ARTICLE

OPEN ACCESS Check for updates

Preliminary evidence for the importance of therapeutic alliance in MDMA-assisted psychotherapy for posttraumatic stress disorder

Richard J. Zeifman[a], Hannes Kettner[b], Stephen Ross[a], Brandon Weiss[b], Michael C. Mithoefer[c], Ann T. Mithoefer[c] and Anne C. Wagner[d]

[a]Department of Psychiatry, NYU Grossman School of Medicine, NYU Langone Centre for Psychedelic Medicine, New York, NY, USA; [b]Centre for Psychedelic Research, Department of Brain Sciences, Faculty of Medicine, Imperial College London, London, UK; [c]MAPS Public Benefit Corporation (MPBC), San Jose, CA, USA; [d]Department of Psychology, Toronto Metropolitan University, Toronto, Canada

ABSTRACT

Background: MDMA-assisted psychotherapy (MDMA-AP) is a combined psychotherapeutic and pharmacologic intervention that shows promise in the treatment of posttraumatic stress disorder (PTSD). Although therapeutic alliance has been established as a key predictor across psychotherapies and is emphasised within MDMA-AP treatment manuals, research has not yet examined the relationship between therapeutic alliance and MDMA-AP treatment outcomes.
Objective: Examine whether therapeutic alliance predicts changes in PTSD symptoms following MDMA-AP.
Method: Twenty-three individuals with chronic PTSD participated in a MDMA-AP clinical trial that included a randomised (MDMA vs. placebo) and open-label phase. The present analyses focused on participants who were administered MDMA over the course of the randomised and open-label phases ($n = 22$). Therapeutic alliance was assessed using the Working Alliance Inventory at sessions baseline (pre-session 3) and sessions 4 and 9. PTSD symptoms were assessed using the Clinician Administered PTSD Scale and the Impact of Events Scale-Revised.
Results: Controlling for baseline clinician-assessed PTSD severity, therapeutic alliance at sessions 4 and 9 (but not baseline) significantly predicted post-MDMA-AP clinician-assessed PTSD severity. Controlling for baseline self-reported PTSD severity, therapeutic alliance at baseline (although this did not survive correction for multiple comparisons) and sessions 4 and 9 predicted post-MDMA-AP self-reported PTSD severity.
Conclusions: The present results provide the first preliminary evidence for the relationship between the therapeutic alliance and treatment outcomes within MDMA-AP for PTSD. These findings highlight the important role of psychotherapy, and common psychotherapeutic factors, within MDMA-AP. Replication in studies with larger and more diverse clinical samples remain necessary.

Trial registration: ClinicalTrials.gov identifier: NCT00090064.

Evidencia preliminar de la importancia de la alianza terapéutica en la psicoterapia asistida con MDMA para el trastorno de estrés postraumático

Antecedentes: La psicoterapia asistida por MDMA (MDMA-AP por sus siglas en inglés) es una combinación de intervención psicoterapéutica y farmacológica que muestra ser prometedora en el tratamiento del trastorno de estrés postraumático (TEPT). Aunque la alianza terapéutica ha sido bien establecida como un predictor clave a través de las psicoterapias y se enfatiza en los manuales de tratamiento MDMA-AP, la investigación aún no ha examinado la relación entre la alianza terapéutica y los resultados del tratamiento MDMA-AP.
Objetivo: Examinar si la alianza terapéutica predice cambios en los síntomas de TEPT después de MDMA-AP.
Método: Veintitrés individuos con TEPT crónico participaron en un ensayo clínico de MDMA-AP que incluyó una fase aleatorizada (MDMA vs placebo) y abierta. El presente análisis se centra en los participantes a los que se les administró MDMA en el curso de las fases aleatorias y abiertas ($n = 22$). La alianza terapéutica se evaluó utilizando el Inventario de Alianza de Trabajo en las sesiones iniciales (antes de la sesión 3) y en las sesiones 4 y 9. Los síntomas de TEPT se evaluaron utilizando la Escala de TEPT administrada por el Clínico y la Escala Revisada del Impacto de los Eventos.
Resultados: Al controlar según la severidad del TEPT evaluada por el clínico al inicio, la alianza terapéutica en la sesión 4 y 9 (pero no la inicial) predijo significativamente la severidad del TEPT post tratamiento evaluada por el clínico post MDMA-AP. Al controlar al inicio según la

ARTICLE HISTORY
Received 19 June 2023
Revised 22 November 2023
Accepted 14 December 2023

KEYWORDS
Posttraumatic stress disorder; MDMA; MDMA-assisted psychotherapy; therapeutic alliance; mechanism of change

PALABRAS CLAVE
Trastorno de estrés postraumático; MDMA; Psicoterapia asistida por MDMA; alianza terapéutica; mecanismos de cambio

HIGHLIGHTS

- Among individuals with chronic posttraumatic stress disorder, therapeutic alliance predicted changes in posttraumatic stress disorder severity following MDMA-assisted psychotherapy.
- Therapeutic alliance may play a key role in facilitating therapeutic improvement within MDMA-assisted psychotherapy.
- Further research remains necessary to confirm these preliminary findings and the role of therapeutic alliance in MDMA-assisted psychotherapy.

CONTACT Richard J. Zeifman richard.zeifman@nyulangone.org Department of Psychiatry, NYU Grossman School of Medicine, NYU Langone Centre for Psychedelic Medicine, 1 Park Avenue, New York, NY 10016, USA
Supplemental data for this article can be accessed online at https://doi.org/10.1080/20008066.2023.2297536

severidad del TEPT por auto-reporte, la alianza terapéutica al inicio (aunque esto no sobrevivió a la corrección para comparaciones múltiples) y en las sesiones 4 y 9 predijeron la severidad del TEPT auto-reportada post-MDMA-AP.
Conclusiones: Los resultados actuales proporcionan la primera evidencia preliminar de la relación entre la alianza terapéutica y los resultados del tratamiento en MDMA-AP para TEPT. Estos hallazgos resaltan el importante papel de la psicoterapia y los factores psicoterapéuticos comunes, dentro de la MDMA-AP. Sigue siendo necesario la replicación en estudios con muestras clínicas mas grandes y diversas.

Posttraumatic stress disorder (PTSD) is a chronic and debilitating disorder, characterised by symptoms of re-experiencing, avoidance, negative alterations in mood and cognition, and alterations in arousal and reactivity after experiencing a traumatic event (American Psychiatric Association, 2013). Despite the existence of several evidence-based psychotherapeutic (American Psychological Association, 2017) and pharmacological treatments for PTSD, there remains a need for exploring additional PTSD interventions that may help to optimise outcomes and reduce treatment dropout (Bryant, 2019; Krystal et al., 2017). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy (MDMA-AP) is a promising novel intervention for PTSD, with several randomised controlled (Mitchell et al., 2021; Mithoefer et al., 2011, 2018; Oehen et al., 2013; Ot'alora et al., 2018) and uncontrolled (Jardim et al., 2021; Monson et al., 2020; Wang et al., 2021) trials suggesting that MDMA-AP leads to significant reductions in PTSD and depression severity. For instance, a recently completed Phase 3 placebo-controlled trial found that, relative to placebo-assisted therapy, MDMA-AP decreased PTSD severity functional impairment, and depressive symptoms (Mitchell et al., 2021). Given its therapeutic potential, it is important to understand MDMA-AP's underlying mechanisms of change.

Importantly, MDMA-AP is a combined pharmacologic-psychotherapeutic intervention in which two therapists provide psychotherapy and/or psychological support prior to, during, and following MDMA administration. Accordingly, the psychotherapeutic component of MDMA-AP is assumed to play an important role in facilitating positive therapeutic outcomes (Mithoefer et al., 2016). However, research has not yet formally examined the role of psychotherapeutic factors in the context of MDMA-AP. A broad swathe of research indicates that therapeutic alliance (i.e. the collaborative relationship developed between a patient and therapist; Bordin, 1979) is an essential component of psychotherapeutic interventions broadly (Flückiger et al., 2018). Therapeutic alliance is most commonly measured using the Working Alliance Inventory (Horvath & Greenberg, 1989), which was developed based on a transtheoretical model of therapeutic alliance (Bordin, 1979). The WAI consists of the three components: (a) bonds (trust acceptance, and confidence between the client and therapist[s]); (b) goals (agreement on treatment priorities and intended outcomes); and (c) tasks (agreement on the means and processes through which treatment priorities and outcomes are facilitated). Research suggests that the strength of the therapeutic alliance is a key predictor of treatment outcomes generally (Flückiger et al., 2018), as well as within the context of PTSD treatment (Howard et al., 2022). For instance, it is estimated that therapeutic alliance accounts for 12% of the variance in PTSD treatment outcomes (Howard et al., 2022). Although the role of the therapeutic alliance is highlighted within the MDMA-AP treatment manual (http://maps.org/treatment-manual) and research publications (e.g. Feduccia et al., 2019), empirical research has not yet explored the effect of therapeutic alliance on MDMA-AP treatment outcomes. Therefore, using data from a previously published clinical trial of MDMA-AP for PTSD (Mithoefer et al., 2011), we examined therapeutic alliance as a predictor of both self-reported and clinician-assessed PTSD outcomes.

1. Methods

1.1. Participants

The clinical trial aimed to enrol a total of 21 individuals with PTSD with replacement of drop-outs (clinicaltrials.gov; NCT00090064). To be eligible for the clinical trial, participants were required to meet the following criteria: (a) aged ≥18; (b) chronic PTSD (based on the DSM-IV) resulting from a crime-related or military related traumatic experience; (c) moderate to severe PTSD severity (based on a Clinician Administered PTSD Scale [CAPS; Blake et al., 1990] score of ≥ 50); (d) at least one unsuccessful PTSD treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI) and one course of psychotherapy or unwillingness to engage in conventional PTSD treatment; (e) absence of current psychiatric comorbidities including borderline personality disorder or DSM-IV Axis I disorders (with the exception of anxiety disorders, affective disorders other than bipolar I disorder, substance abuse or dependence disorder in remission for ≥60 days,

and eating disorder without active purging); (f) absence of major medical conditions; (g) absence of pregnancy; (h) use of effective birth control if female and able to have children; (i) weigh less than 50 kg; (j) proficiency in the English language. The study specifically aimed to recruit 20 individuals with treatment-resistant (failed pharmacotherapy *and* psychotherapy) PTSD (of ≥ 5 years in duration) and one veteran with military-related PTSD (≥1 and ≤5 years in duration) with failed PTSD treatment *or* unwillingness to engage in conventional PTSD treatment.

Participants were recruited through internet advertisements and by sending letters to psychotherapists. Participants completed an initial telephone screen to determine eligibility and then an in-person visit to review and sign informed consent, followed by an interview with an independent rater and physician to further determine eligibility. Participants were obligated to taper off of and abstain from using psychotropic medications throughout the study. However, use of study physician approved sedative hypnotics or anxiolytics was permitted between experimental sessions. Ethical approval for the study was received from the Copernicus Group Independent Review Board (IRB), Research Triangle Park, NC, USA. MDMA was produced by David E Nichols, PhD for the study sponsor (Multidisciplinary Association for Psychedelic Studies [MAPS]).

1.2. Procedures

The parent study was a clinical trial (clinicaltrials.gov; NCT00090064) that included a double-blind randomised controlled phase (Phase 1) followed by an open-label phase (Phase 2). Participants were initially randomised to two experimental sessions in which they were administered either (a) MDMA (125 mg) or (b) inactive placebo (lactose) (Phase 1). Following a protocol amendment, the final 9 participants were allowed to receive a supplement half-dose of MDMA (62.5 mg) or placebo in all of their experimental sessions (administered 2 h into the experimental session). Four participants in the MDMA group and 4 participants in the placebo group received supplemental doses in this manner. Individuals in both conditions also received non-drug psychotherapy. In Phase 1, participants received two preparatory psychotherapy sessions (sessions 1 and 2), two experimental sessions (sessions 3 and 8), and eight additional non-drug psychotherapy sessions (sessions 4–7 and 9–12), including one the day after each experimental session (sessions 4 and 9). Additional sessions were permitted, if needed, on a case-by-case basis. In Phase 2, participants in the placebo condition were eligible to receive two open-label MDMA sessions (sessions 13 and 17) each of which was followed by three psychotherapy sessions (sessions 14–16 and 18–20). Following a protocol amendment, four participants initially in the placebo condition and five participants initially in the MDMA condition received an additional (i.e. a third) MDMA session.

Sixty percent of participants were randomised to receive MDMA and 40% of participants were randomised to placebo (with replacement of dropouts). Thirteen individuals (including one individual with military-related PTSD that was not required to be treatment-resistant) were initially randomised to the MDMA condition and 8 individuals were randomised to placebo. Two individuals assigned to the MDMA condition dropped out of treatment prior to their second experimental session (due to travelling difficulties for one individual and resumption of medication for depression relapse for the other individual) and two additional individuals were subsequently randomised to the MDMA condition. The two participants who dropped out of treatment and one individual with military-related PTSD (that was not required to be treatment-resistant) were excluded from the primary outcomes paper (Mithoefer et al., 2011) but are included here due to: (a) meeting criteria for PTSD; (b) receiving psychotherapy and at least one MDMA-assisted psychotherapy session; and (c) to ensure that findings are not biased by treatment dropout (e.g. due to poor therapeutic alliance). One individual in the placebo arm opted not to receive open-label MDMA and is therefore excluded from the present analysis. Due to limited sample size, all participants ($n = 22$) administered MDMA (whether in Phase 1 or 2) are included in the present analyses. For study flow, see Figure 1. For study procedures, see Figure 2.

The study was conducted in accordance with the MDMA-AP treatment manual (http://maps.org/treatment-manual), utilising a psychotherapeutic platform administered by a dyad therapy team, and inclusive of preparatory sessions, administration of MDMA/placebo, and post-dosing integration sessions. Preparatory sessions focused on orienting participants to the therapeutic approach, the structure of experimental sessions, and the acute effects of MDMA. Experimental sessions occurred in a comfortable outpatient office, participants were offered the option to use eyeshades while reclining in a comfortable position, and listening to a pre-set music playlist. Experimental sessions lasted 8–10 h after which participants remained overnight with a nurse on site to ensure safety. When needed, zolpidem or lorazepam were prescribed for difficulty sleeping following experimental sessions. Integration sessions focused on emotional processing and reviewing the experimental session, as well as identifying and reflecting on new insights and perspectives related to their life and PTSD. Additional integration sessions occurred

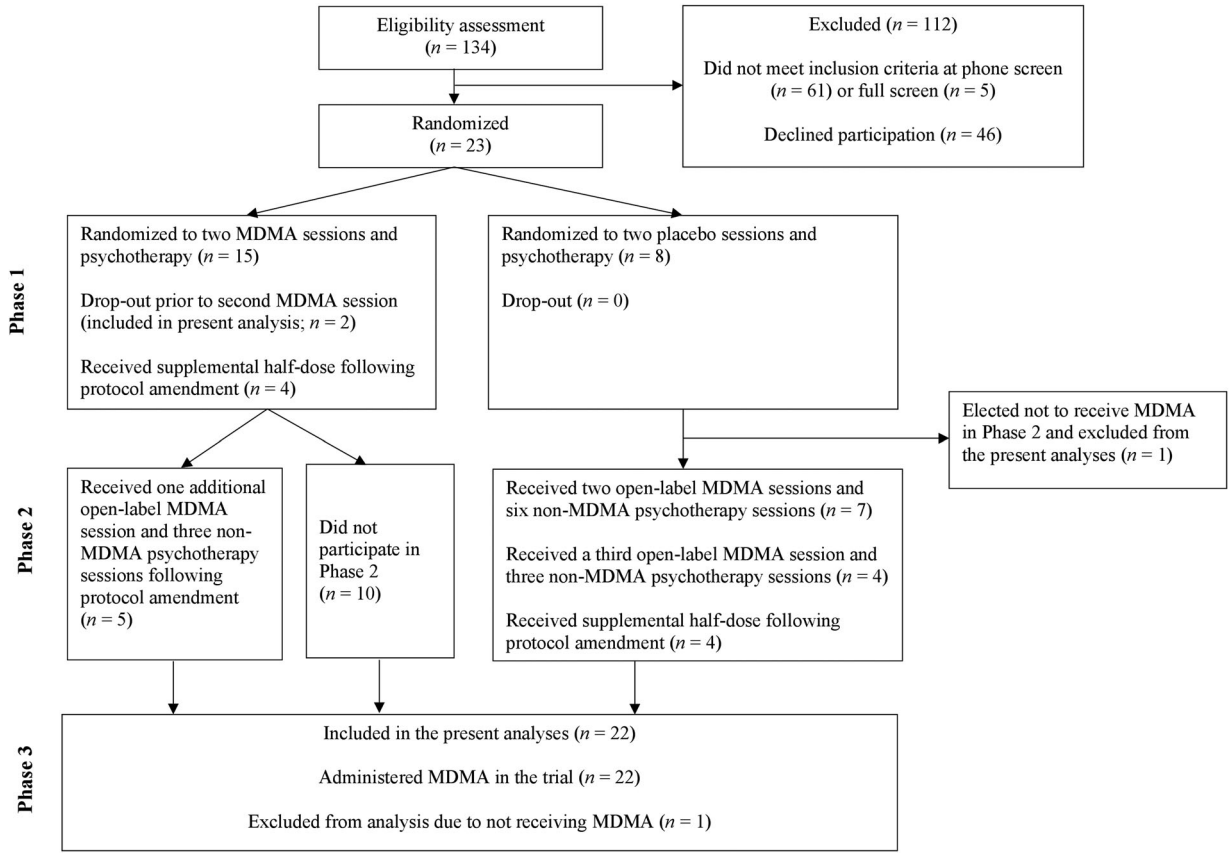

Figure 1. Study flow for the present analyses.

when judged to be necessary by the study investigators. The same male and female co-therapist team were present for all treatment sessions. For further details, see Mithoefer et al. (2011).

Subjects, investigators, nurses, and independent raters were blinded to condition during Phase 1. Outcome measures were repeated and the blind was broken two months after participants' second MDMA/placebo-assisted psychotherapy session. PTSD symptoms were measured at baseline (prior to session 3) and 3–7 days after each MDMA/placebo session, 2 months after the second experimental session, and (among individuals that were initially assigned to receive placebo and then enrolled in Phase 2) 6–8 weeks after their final MDMA session. Clinician-assessed PTSD severity ratings were completed by a blinded independent rater. PTSD symptoms at participants' final assessment (with the majority occurring after session 12 and as late as after session 24) are used as post-treatment outcomes in the present analyses. Participants completed ratings of therapeutic alliance at baseline (prior to session 3) and at sessions 4 and 9.

1.3. Measures

1.3.1. Therapeutic alliance

Therapeutic alliance was measured using the WAI (Horvath & Greenberg, 1989). The WAI is a 36 item self-report measure of the client's perception of the therapeutic alliance that includes three subscales (Tasks [agreement on the task of therapy], Goals [agreement on the goals of therapy], and Bonds [affective bond between the therapist and patient]) and a Total score. Items (e.g. 'I believe _____ is genuinely concerned for my welfare' and '___ and I trust one another') are rated on a Likert scale from 1 (never) to 7 (always). Fourteen items are reverse scored. The total WAI score is the mean of all items with higher scores representing a stronger therapeutic alliance. The WAI shows good psychometric properties, including strong internal consistency (Horvath & Greenberg, 1989). In line with previous research with co-therapists (e.g. Crowe & Grenyer, 2008; Heckman et al., 2017; Woody & Adessky, 2002), participants were instructed to complete the WAI once at each timepoint with reference to both of their co-therapists.

1.3.2. PTSD symptoms

Clinician-assessed PTSD symptoms were measured using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1990). The CAPS assesses the 17 PTSD symptoms in the DSM-IV, including identification of a criterion A trauma, symptoms of re-experiencing, avoidance, and hyperarousal, symptom duration, and level of distress/impairment. For each symptom, the CAPS includes measures of frequency (rated on a scale 0–4) and intensity (rated on

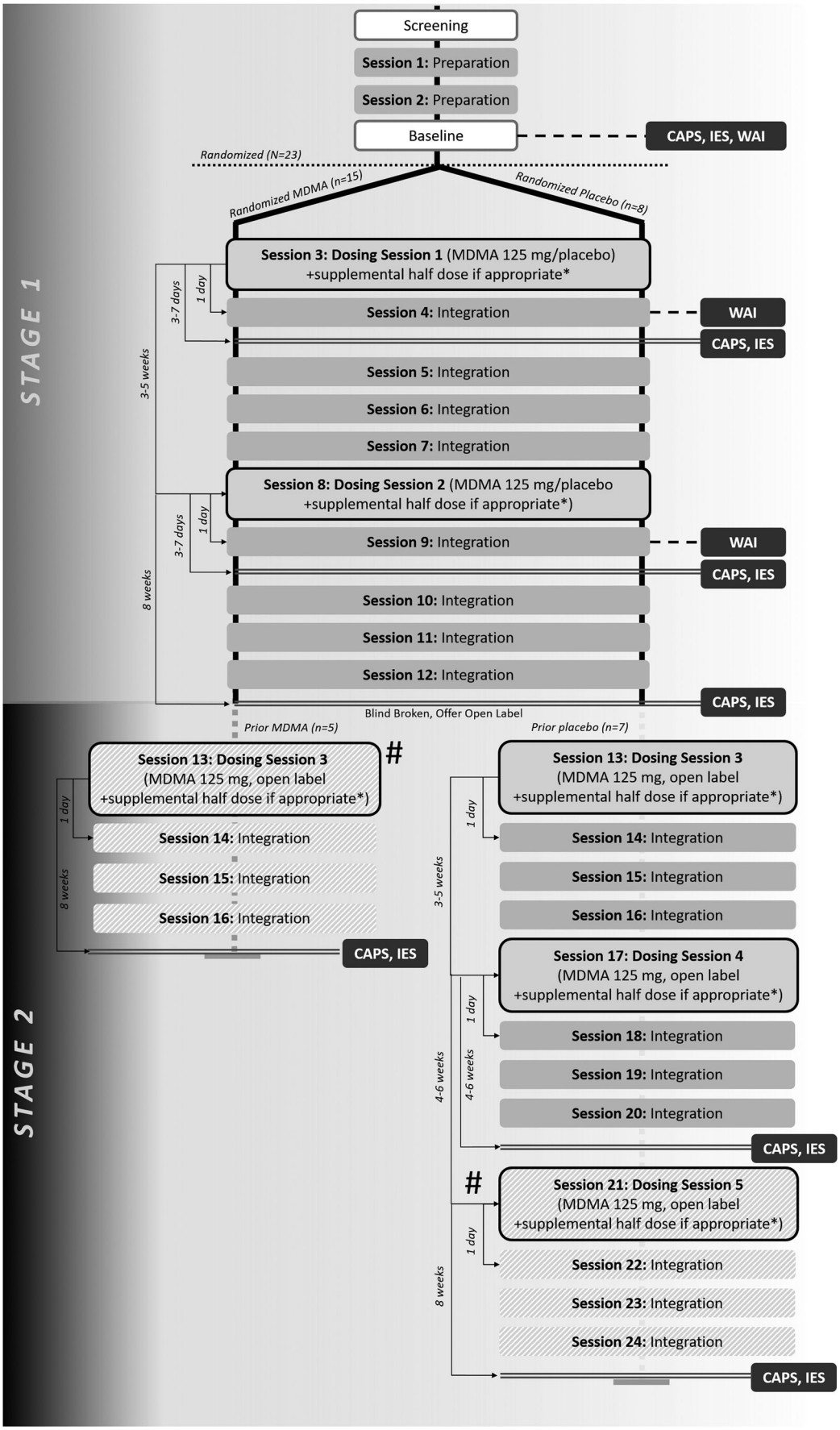

Figure 2. A timeline of patient progression through study procedures.

Note: CAPS: Clinician Administered PTSD Scale; IES: Impact of Event Scale-Revised; WAI: Working Alliance Inventory. Grey dashed lines (▪ ▪ ▪) indicates that not all patients entered Stage 2. The solid double line (═══) indicates a visit with assessments but no therapy sessions occurred. Sessions with striped backgrounds (▨) represent those added following protocol amendments. *Supplemental half doses were available after a protocol amendment, and the final nine participants enrolled were allowed this supplement. Four patients in the MDMA group and four in the placebo group received supplemental doses. #A protocol amendment allowed four participants initially in the placebo condition and five participants initially in the MDMA condition to receive an additional (i.e. a third) MDMA session and three integration sessions.

a scale 0–4), which are then summed to calculate the severity for each symptom (ranging from 0 to 8). A total PTSD severity is then calculated by summing each of the 17 severity scores. The CAPS was considered a gold-standard measure of PTSD at the time the parent trial was conducted and has excellent psychometric properties (Weathers et al., 2001).

Self-reported PTSD symptoms were measured using the revised Impact of Event Scale-Revised (IES-R; Weiss, 2007). The IES-R is a 22-item self-report measure developed to assess PTSD symptoms based on the DSM-IV. It includes three subscales (intrusion [8 items], avoidance [8 items], and hyperarousal [6 items]), and a total score. Participants identify a stressful life event and rate event-related items (e.g. 'I tried not to think about it' and 'I had waves of strong feelings about it') based on the amount of distress they caused them over the previous 7 days. Items are rated on a scale from 0 (not at all) to 4 (extremely). The IES-R has shown good psychometric properties, including good internal consistency and test-retest reliability (Weiss, 2007; Weiss & Marmar, 1997).

1.4. Data analysis

Independent samples t-tests examined potential differences in therapeutic alliance based on participant sex. Correlation coefficients were calculated for therapeutic alliance (baseline and sessions 4 and 9) and self-reported and clinician-assessed PTSD severity (baseline and post-treatment). Hierarchical regression was used to examine the contribution of therapeutic alliance in explaining the variance in post-treatment PTSD severity (controlling for baseline PTSD severity and the number of days since baseline that post-treatment PTSD severity was measured at). Separate analyses were run for self-reported (IES-R) and clinician-assessed (CAPS) PTSD treatment outcomes. In the first stage, pre-treatment PTSD severity and days since baseline were entered as independent variables. Post-treatment PTSD severity was entered as the dependent variable. For the second stage, therapeutic alliance was entered as an independent variable with separate analyses conducted for therapeutic alliance at baseline (Stage 2a) and sessions 4 (Stage 2b) and 9 (Stage 2c). We set the alpha level for significance as $p < .05$ (two-tailed) and further examined statistical significance following FDR correction for multiple comparisons using the Benjamini and Hochberg method (p-FDR $< .05$). Analyses were conducted using SPSS version 28. Sensitivity analyses were conducted to confirm results were consistent when excluding the three participants excluded from the primary outcomes paper (due to not having treatment-resistant PTSD [$n = 1$] or only receiving single dose of MDMA [$n = 2$]).

The above frequentist hierarchical regression analyses were supplemented with Bayesian generalised linear modelling, which is known to produce less biased results compared to maximum likelihood estimation methods when sample sizes are small (McNeish, 2016). The Region of Practical Equivalence (ROPE) was defined as the range from −0.1–0.1 (Kruschke, 2015), corresponding to a negligible effect size according to Cohen (1988) after z-standardization of the outcome (CAPS and IES-R) and predictor (WAI at stage 2a, 2b, and 2c) variables (to achieve scale-invariance of the posterior coefficient estimates in relation to the ROPE; Makowski, Ben-Shachar, Chen, et al., 2019). Significance of an effect was defined as <2.5% of the posterior distribution falling into the ROPE. Bayesian analyses were conducted in R using the rstanarm (Gabry & Goodrich, 2017) and bayestestR packages (Makowski, Ben-Shachar, and Lüdecke, 2019).

Following reporting guidelines recommended by Makowski, Ben-Shachar, Chen, et al. (2019), three indices are provided for each model: (1) existence of effect, indicated by the probability of direction (pd; i.e. the percentage probability that an effect of the predictor on the outcome exists in a given direction); (2) significance of the effect, indicated by the percentage of the full posterior distribution within the ROPE; and (3) effect size, indicated by the standardised median coefficient.

2. Results

2.1. Descriptive statistics and preliminary analyses

The sample (Mean age = 57.50; $SD = 7.51$) was exclusively Caucasian (100%) and predominantly female (77.3%). There were no statistically significant differences between males and females in therapeutic alliance at baseline (female mean = 220.94, $SD = 27.99$; male mean = 224.20, $SD = 19.69$; $t(20) = .24$, $p = .812$), session 4 (female mean = 226.75, $SD = 24.46$; male mean = 227.00, $SD = 19.60$; $t(18) = .02$, $p = .985$), or session 9 (female mean = 227.59, $SD = 22.19$; male mean = 223.20, $SD = 11.65$; $t(20) = -.42$, $p = .679$). The mean duration of participants' PTSD was 18.2 years with a baseline clinician-assessed PTSD severity of 82.9 ($SD = 21.77$). Twenty individuals (90.9%) had a crime-related index trauma and two individuals (9.1%) had a military-related index trauma. All individuals had at least one unsuccessful PTSD treatment with an SSRI or SNRI. Twenty-one individuals (95.5%) had previously received at least one course of psychotherapy. For means, standard deviations, and correlations for therapeutic alliance and PTSD severity measures, see Table 1.

2.2. Primary analysis

2.2.1. Therapeutic alliance and clinician-assessed PTSD severity

In Stage 1, baseline clinician-assessed PTSD severity and days since baseline were not significantly associated with post-treatment clinician-assessed PTSD severity ($F[2, 19] = .14$, $p = .869$, $R^2 = .12$) and accounted for 1% of the variance. At Stage 2(a), adding therapeutic alliance at baseline to the model did not result in a significant change in explained variance ($R^2 = .13$; $F_{change} = 2.42$, $p = .137$, p-FDR = .137; $r^2_{change} = .11$). At Stage 2(b), adding therapeutic alliance at session 4 to the model resulted in a significant increase in explained variance ($R^2 = .29$; $F_{change} = 6.77$, $p = .019$, p-FDR = .038) and accounted for an additional 29% of the variation in post-treatment PTSD severity, above and beyond baseline PTSD severity and days since baseline. At Stage 2(c), adding therapeutic alliance at session 9 to the model resulted in a significant increase in explained variance ($R^2 = .26$; $F_{change} = 5.89$, $p = .026$, p-FDR = .039) and accounted for an additional 24% of the variation in post-treatment PTSD severity, above and beyond baseline PTSD severity and days since baseline. Bayesian analyses were consistent with frequentist analyses, with therapeutic alliance at baseline not resulting in a significant change in explained variance (12.3% in ROPE), while therapeutic alliance at sessions 4 and 9 accounted for a significant amount of variance (both 0% in ROPE) above and beyond baseline clinician-assessed PTSD severity and days since baseline. See Supplementary Materials for further details.

2.2.2. Therapeutic alliance and self-reported PTSD severity

At Stage 1, baseline self-reported PTSD severity was not significantly associated with post-treatment self-reported PTSD severity ($R^2 = .03$; $F[1, 19] = .27$, $p = .767$) and accounted for 3% of the variance. At Stage 2(a), adding therapeutic alliance at baseline to the model resulted in a significant increase in explained variance ($R^2 = .22$; $F_{change} = 4.54$, $p = .047$), although this increase did not survive correction (p-FDR = .056), and accounted for an additional 20% of the variation in post-treatment PTSD severity, above and beyond baseline PTSD severity and days since baseline. At Stage 2(b), adding therapeutic alliance at session 4 to the model resulted in a significant increase in explained variance ($R^2 = .40$; $F_{change} = 10.56$, $p = .005$, p-FDR = .030) and accounted for an additional 40% of the variation in post-treatment PTSD severity, above and beyond baseline PTSD severity and days since baseline. At Stage 2(c), adding therapeutic alliance at session 9 to the model resulted in a significant increase in explained variance ($R^2 = .29$; $F_{change} = 6.70$, $p = .019$, p-FDR = .038) and accounted for an additional 26% of the variation in post-treatment PTSD severity, above and beyond baseline PTSD severity and days since baseline. Bayesian analyses were consistent with frequentist analyses, with therapeutic alliance at baseline not resulting in a significant change in explained variance (3.1% in ROPE), while therapeutic alliance at sessions 4 and 9 accounted for a significant amount of variance (0% and 0.01% in ROPE, respectively) above and beyond baseline self-reported PTSD severity and days since baseline. See Supplementary Materials for further details.

2.3. Sensitivity analyses

Supplementary frequentist and Bayesian analyses confirmed that the above results were consistent when excluding the three participants who had been excluded from the primary outcomes paper (see Supplementary Material).

3. Discussion

In this examination of therapeutic alliance as a putative mechanism underlying MDMA-AP's therapeutic effect on PTSD, therapeutic alliance at baseline (pre-session 3) and sessions 4 and 9 significantly predicted self-reported PTSD outcomes. Notably, the relationship between therapeutic alliance at baseline and self-report PTSD outcomes did not survive correction for multiple comparisons. Additionally, therapeutic alliance at sessions 4 and 9 (but not baseline) significantly predicted clinician-assessed PTSD outcomes. The relationship between therapeutic alliance and treatment was fairly strong with therapeutic alliance accounting for 11–40% of the variance in PTSD treatment outcomes, above and beyond baseline PTSD and days since baseline. Therapeutic alliance at baseline accounted for 11% of the variance in clinician-assessed PTSD outcome, which is a medium sized effect that is consistent with previous research on the relationship between therapeutic alliance and PTSD treatment outcomes (for a meta-analysis, see Howard et al., 2022). Importantly however, this effect was not statistically significant and should therefore be interpreted with strong caution. All results were consistent when examined in the full sample of individuals that had received at least one MDMA session, as well as among those that had received at least two MDMA sessions and had a history of both failed psychotherapeutic and pharmacological PTSD treatment. These findings provide the first preliminary empirical support for the importance of therapeutic alliance within MDMA-AP or the relationship between therapeutic factors and MDMA-AP treatment outcomes. These findings are generally consistent with research indicating the therapeutic alliance is predictive of treatment outcomes across psychotherapeutic interventions

Table 1. Means, standard deviations and correlation coefficients.

	Mean	*SD*	Range	1.	2	3.	4.	5.	6.
1. Therapeutic Alliance$_{\text{-Baseline}}$	6.16	.72	4.00–7.00	–	–	–	–	–	–
2. Therapeutic Alliance$_{\text{-Session 4}}$	6.30	.64	4.67–7.00	.69^{+}	–	–	–	–	–
3. Therapeutic Alliance$_{\text{-Session 9}}$	6.29	.56	5.14–7.00	.68^{+}	.89^{+}	–	–	–	–
4. PTSD Severity (CAPS)$_{\text{-Baseline}}$	82.86	21.77	43.00–113.00	−.01	.19	.07	–	–	–
5. PTSD Severity (CAPS)$_{\text{-Post-Treatment}}$	25.14	19.05	.00–79.00	−.33	−.52*	−.50*	.04	–	–
6. PTSD Severity (IES-R)$_{\text{-Baseline}}$	47.68	14.40	13.00–72.00	.09	.04	.15	.59$^{\#}$	−.08	–
7. PTSD Severity (IES-R)$_{\text{-Post-Treatment}}$	16.73	14.84	.00–51.00	−.43*	−.62$^{\#}$	−.48*	.10	.70^{+}	.16

Note: *$p < .05$. $^{\#}p < .01$. $^{+}p < .001$.

(Flückiger et al., 2018), including treatments for PTSD (Howard et al., 2022), and suggest that the importance of therapeutic alliance may extend to MDMA-AP.

There is a growing debate regarding the importance of psychotherapy in MDMA-AP and interventions with related pharmacological properties (e.g. psilocybin therapy; Carhart-Harris et al., 2018). The results of the present study provide preliminary support for the importance of the psychotherapeutic component of MDMA-AP and against MDMA being a traditional stand-alone pharmacological intervention. They also provide early support for suggestions that such pharmacologically-enhanced interventions lead to change via common factors of psychotherapy, including the therapeutic alliance (Gukasyan & Nayak, 2022). While further research remains necessary due to the limited sample size and correlational nature of present findings, several studies have similarly found support for a relationship between the therapeutic alliance and one's bond with individuals present during one's acute experience and subsequent improvements in mental health (Haijen et al., 2018; Kettner et al., 2021; Murphy et al., 2022). For instance, a recent study found that therapeutic alliance was predictive of reductions in depressive symptoms following psilocybin therapy for major depressive disorder (Murphy et al., 2022).

Although further replication remains necessary to draw strong conclusions, the present findings have several potentially important clinical implications. First, they suggest that it is worthwhile to pay specific attention to developing and enhancing therapeutic alliance prior to providing MDMA sessions. It may therefore be worthwhile for MDMA-AP training manuals and treatment development provide specific guidance on enhancing the therapeutic alliance (e.g. Pinto et al., 2012), resolving ruptures in the alliance (Eubanks et al., 2018), and to draw more explicitly from common factor techniques (Solomonov et al., 2018). Additionally, the present results suggest that if MDMA-AP is extended to samples of individuals that exhibit complex comorbidities or greater difficulties with establishing a strong therapeutic alliance or where the strength of the therapeutic alliance plays an especially important role (e.g. individuals with borderline personality disorder [BPD]; Boritz et al., 2018; Zeifman et al., 2021), further attention may be needed to ensure that a strong therapeutic alliance is established (Traynor et al., 2022; Zeifman & Wagner, 2020).

The present study has several important limitations. The sample was fairly small and non-diverse (i.e. mostly female and exclusively Caucasian), which is a key issue in MDMA-AP research to date (Williams et al., 2019). Further research in larger samples with greater diversity will be necessary to identify the generalizability of these findings. Therapeutic alliance was only measured via patient-rated self-report. Therefore, additional research that includes therapist and observer-rated therapeutic alliance (Horvath & Greenberg, 1989) will help to further elucidate the role of therapeutic alliance within MDMA-AP. The PTSD symptom measures used in the present study were based on DSM-IV PTSD symptoms. Therefore, it will be important for future research to examine the relationship between therapeutic alliance and measures of DSM-5-TR PTSD symptoms (e.g. the CAPS-5; Weathers et al., 2018). The present findings were only examined in the context of MDMA-AP for PTSD. As research begins to expand the application of MDMA-AP, including to alcohol use disorder (Sessa et al., 2021),, distress related to life-threatening illness (Wolfson et al., 2020), and couples-based therapy (Wagner, 2021), it will be necessary to examine whether the role of therapeutic alliance within MDMA-AP extends across clinical samples. It will also be important to examine the relationships between therapeutic alliance and outcomes including: (a) experiences during MDMA sessions (e.g. cognitive reappraisal [Agin-Liebes et al., 2022], insight [Davis et al., 2021], and acceptance/avoidance [Wolff et al., 2022]); (b) trait-level changes (e.g. insight [Peill et al., 2022] and avoidance [Zeifman, Wagner et al., 2023]); and (c) treatment outcomes that extend beyond PTSD severity (e.g. quality of life and relational improvements [e.g. see Wagner et al., 2021]).

Although the therapy model used in the present study is the most commonly researched MDMA treatment model, there remains a need for examining the role of therapeutic alliance within alternative MDMA-AP models (e.g. MDMA-assisted cognitive behavioural conjoint therapy or exposure therapy; Monson et al., 2020). Additionally, a single therapist dyad provided MDMA-AP for all participants in the present study. Further research will therefore be necessary to determine the generalizability of the

present findings across MDMA-AP providers. Finally, the present study only assessed therapeutic alliance at three timepoints, had a small sample (particularly within the placebo condition), and was not designed to establish a unique causal role of therapeutic alliance or the effect of MDMA-AP on therapeutic alliance itself. Given research suggesting that MDMA may enhance feelings of closeness and alters processing of physiological and behavioural responses to social stimuli (Bedi et al., 2009; Bershad et al., 2019; Molla et al., 2023; Schmid et al., 2014; Wardle & de Wit, 2014; Zeifman, Kettner et al., 2023), larger studies that measure therapeutic alliance at each session (including during MDMA sessions) will be important for examining the effect of MDMA on therapeutic alliance, differences with therapy that does not include MDMA, and the potential causal role of therapeutic alliance within MDMA-AP.

Acknowledgements

We thank MAPS for sharing these data, as well as the study participants, coordinators, and therapists for their contribution to this research.

Author contributions

MCM and ATM conducted the clinical trial. RJZ and AW contributed the conceptualisation of the manuscript. RJZ and HK conducted the statistical analyses. RJZ wrote the original draft of the manuscript. All authors reviewed and edited the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Canadian Institutes of Health Research [grant number 202110MFE-472921-HTB-272687]; MAPS Public Benefit Corporation.

Data availability statement

The data that support the findings of this study are available from the sponsor (MAPS). However, restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of MAPS at http://maps.org/datause. All requests for raw and analysed data are promptly reviewed by the sponsor delegate and trial organiser, MAPS PBC, to verify if the request is subject to any confidentiality obligations. Patient-related data not included in the paper were generated as part of clinical trials and may be subject to patient confidentiality. Any data that can be shared will be released via a data use agreement.

References

Agin-Liebes, G., Zeifman, R. J., Luoma, J. B., Garland, E. L., Campbell, W. K., & Weiss, B. (2022). Prospective examination of the therapeutic role of psychological flexibility and cognitive reappraisal in the ceremonial use of ayahuasca. *Journal of Psychopharmacology*, *36*(3), 295–308. https://doi.org/10.1177/02698811221080165

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association.

American Psychological Association. (2017). *Clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults*. http://www.apa.org/about/offices/directorates/guidelines/ptsd.pdf

Bedi, G., Phan, K. L., Angstadt, M., & De Wit, H. (2009). Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology*, *207*(1), 73–83. https://doi.org/10.1007/s00213-009-1635-z

Bershad, A. K., Mayo, L. M., Van Hedger, K., McGlone, F., Walker, S. C., & de Wit, H. (2019). Effects of MDMA on attention to positive social cues and pleasantness of affective touch. *Neuropsychopharmacology*, *44*(10), 1698–1705. https://doi.org/10.1038/s41386-019-0402-z

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Klauminzer, G., Charney, D. S., & Keane, T. M. (1990). A clinician rating scale for assessing current and lifetime PTSD: The CAPS-1. *Behavior Therapist*, *13*, 187–188.

Bordin, E. S. (1979). The generalizability of the psychoanalytic concept of the working alliance. *Psychotherapy: Theory, Research & Practice*, *16*(3), 252–260. https://doi.org/10.1037/h0085885

Boritz, T. Z., Zeifman, R. J., & McMain, S. F. (2018). Mechanisms of change in dialectical behavior therapy. In M. Swales (Ed.), *The Oxford handbook of dialectical behaviour therapy* (pp. 515–532). Oxford University Press.

Bryant, R. A. (2019). Post-traumatic stress disorder: A state-of-the-art review of evidence and challenges. *World Psychiatry*, *18*(3), 259–269. https://doi.org/10.1002/wps.20656

Carhart-Harris, R. L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., Branchi, I., & Kaelen, M. (2018). Psychedelics and the essential importance of context. *Journal of Psychopharmacology*, *32*(7), 725–731. https://doi.org/10.1177/0269881118754710

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Lawrence Erlbaum Associates Inc.

Crowe, T. P., & Grenyer, B. F. S. (2008). Is therapist alliance or whole group cohesion more influential in group psychotherapy outcomes? *Clinical Psychology & Psychotherapy*, *15*(4), 239–246. https://doi.org/10.1002/cpp.583

Davis, A. K., Barrett, F. S., So, S., Gukasyan, N., Swift, T. C., & Griffiths, R. R. (2021). Development of the Psychological Insight Questionnaire among a sample of people who have consumed psilocybin or LSD. *Journal of Psychopharmacology*, *35*(4), 437–446. https://doi.org/10.1177/0269881120967878

Eubanks, C. F., Burckell, L. A., & Goldfried, M. R. (2018). Clinical consensus strategies to repair ruptures in the therapeutic alliance. *Journal of Psychotherapy Integration*, *28*(1), 60–76. https://doi.org/10.1037/int0000097

Feduccia, A. A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2019). Breakthrough for trauma treatment: Safety and efficacy

of MDMA-assisted psychotherapy compared to paroxetine and sertraline. *Frontiers in Psychiatry*, *10*, 650. https://doi.org/10.3389/fpsyt.2019.00650

Flückiger, C., Del Re, A. C., Wampold, B. E., & Horvath, A. O. (2018). The alliance in adult psychotherapy: A meta-analytic synthesis. *Psychotherapy*, *55*(4), 316–340. https://doi.org/10.1037/pst0000172

Gabry, J., & Goodrich, B. (2017). *rstanarm: Bayesian Applied Regression Modeling via Stan*. R package version 2.15.3. https://CRAN.R-project.org/package=rstanarm

Gukasyan, N., & Nayak, S. M. (2022). Psychedelics, placebo effects, and set and setting: Insights from common factors theory of psychotherapy. *Transcultural Psychiatry*, *59*(5), 652–664. https://doi.org/10.1177/13634615209833684

Haijen, E. C., Kaelen, M., Roseman, L., Timmermann, C., Kettner, H., Russ, S., Nutt, D., Daws, R. E., Hampshire, A. D. G., Lorenz, R., & Carhart-Harris, R. L. (2018). Predicting responses to psychedelics: A prospective study. *Frontiers in Pharmacology*, *9*, 897. https://doi.org/10.3389/fphar.2018.00897

Heckman, T. G., Heckman, B. D., Anderson, T., Bianco, J. A., Sutton, M., & Lovejoy, T. I. (2017). Common factors and depressive symptom relief trajectories in group teletherapy for persons ageing with HIV. *Clinical Psychology & Psychotherapy*, *24*(1), 139–148. https://doi.org/10.1002/cpp.1989

Horvath, A. O., & Greenberg, L. S. (1989). Development and validation of the working alliance inventory. *Journal of Counseling Psychology*, *36*(2), 223–233. https://doi.org/10.1037/0022-0167.36.2.223

Howard, R., Berry, K., & Haddock, G. (2022). Therapeutic alliance in psychological therapy for posttraumatic stress disorder: A systematic review and meta-analysis. *Clinical Psychology & Psychotherapy*, *29*(2), 373–399. https://doi.org/10.1002/cpp.2642

Jardim, A. V., Jardim, D. V., Chaves, B. R., Steglich, M., Ot'alora, G. M., Mithoefer, M. C., da Silveira, D. X., Tófoli, L. F., Ribeiro, S., Matthews, R., Doblin, R., & Schenberg, E. E. (2021). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for victims of sexual abuse with severe post-traumatic stress disorder: An open label pilot study in Brazil. *Brazilian Journal of Psychiatry*, *43*(2), 181–185. https://doi.org/10.1590/1516-4446-2020-0980

Kettner, H., Rosas, F. E., Timmermann, C., Kärtner, L., Carhart-Harris, R. L., & Roseman, L. (2021). Psychedelic communitas: Intersubjective experience during psychedelic group sessions predicts enduring changes in psychological wellbeing and social connectedness. *Frontiers in Pharmacology*, *12*, 623985. https://doi.org/10.3389/fphar.2021.623985

Kruschke, J. (2015). *Doing Bayesian data analysis: A tutorial with R, JAGS, and Stan* (2nd ed.). Academic Press.

Krystal, J. H., Davis, L. L., Neylan, T. C., Raskind, M. A., Schnurr, P. P., Stein, M. B., Vessicchio, J., Shiner, B., Gleason, T. D., & Huang, G. D. (2017). It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: A consensus statement of the PTSD psychopharmacology working group. *Biological Psychiatry*, *82*(7), e51–e59. https://doi.org/10.1016/j.biopsych.2017.03.007

Makowski, D., Ben-Shachar, M. S., Chen, S. A., & Lüdecke, D. (2019). Indices of effect existence and significance in the Bayesian framework. *Frontiers in Psychology*, *10*, 2767. https://doi.org/10.3389/fpsyg.2019.02767

Makowski, D., Ben-Shachar, M. S., & Lüdecke, D. (2019). bayestestR: Describing effects and their uncertainty, existence and significance within the Bayesian framework. *Journal of Open Source Software*, *4*(40), 1541. https://doi.org/10.21105/joss.01541

McNeish, D. (2016). On using Bayesian methods to address small sample problems. *Structural Equation Modeling: A Multidisciplinary Journal*, *23*(5), 750–773. https://doi.org/10.1080/10705511.2016.1186549

Mitchell, J. M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora, M., Garas, W., Paleos, C., Gorman, I., Nicholas, C., Mithoefer, M., Carlin, S., Poulter, B., Mitoefer, A., Quevedo, S., Wells, G., Klaire, S. S., van der Kolk, B., … Doblin, R. (2021). MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study. *Nature Medicine*, *27*(6), 1025–1033. https://doi.org/10.1038/s41591-021-01336-3

Mithoefer, M. C., Grob, C. S., & Brewerton, T. D. (2016). Novel psychopharmacological therapies for psychiatric disorders: Psilocybin and MDMA. *The Lancet Psychiatry*, *3*(5), 481–488. https://doi.org/10.1016/S2215-0366(15)00576-3

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., Holland, J., Hamilton, S., Yazzar Klosinski, B., Emerson, A., & Doblin, R. (2018). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *The Lancet Psychiatry*, *5*(6), 486–497. https://doi.org/10.1016/S2215-0366(18)30135-4

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., & Doblin, R. (2011). The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: The first randomized controlled pilot study. *Journal of Psychopharmacology*, *25*(4), 439–452. https://doi.org/10.1177/0269881110378371

Molla, H., Lee, R., Lyubomirsky, S., & de Wit, H. (2023). Drug-induced social connection: Both MDMA and methamphetamine increase feelings of connectedness during controlled dyadic conversations. *Scientific Reports*, *13*(1), 15846. https://doi.org/10.1038/s41598-023-43156-0

Monson, C. M., Wagner, A. C., Mithoefer, A. T., Liebman, R. E., Feduccia, A. A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Doblin, R., & Mithoefer, M. C. (2020). MDMA-facilitated cognitive-behavioural conjoint therapy for posttraumatic stress disorder: An uncontrolled trial. *European Journal of Psychotraumatology*, *11*(1), 1840123. https://doi.org/10.1080/20008198.2020.1840123

Murphy, R., Kettner, H., Zeifman, R., Giribaldi, B., Kaertner, L., Martell, J., Read, T., Murphy-Beiner, A., Baker-Jones, M., Nutt, D., Erritzoe, D., Watts, R., & Carhart-Harris, R. L. (2022). Therapeutic alliance and rapport modulate responses to psilocybin assisted therapy for depression. *Frontiers in Pharmacology*, *12*, 788155. https://doi.org/10.3389/fphar.2021.788155

Oehen, P., Traber, R., Widmer, V., & Schnyder, U. (2013). A randomized, controlled pilot study of MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of Psychopharmacology*, *27*(1), 40–52. https://doi.org/10.1177/0269881112464827

Ot'alora, G. M., Grigsby, J., Poulter, B., Van Derveer, J. W., III, Giron, S. G., Jerome, L., Feduccia, A. A., Hamilton, S., Yazar-Klonsinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2018). 3,4-Methylenedioxymethamphetamine-

assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. *Journal of Psychopharmacology*, *32*(12), 1295–1307. https://doi.org/10.1177/0269881118806297

Peill, J. M., Trinci, K. E., Kettner, H., Mertens, L. J., Roseman, L., Timmermann, C., Rosas, F. E., Lyons, T., & Carhart-Harris, R. L. (2022). Validation of the Psychological Insight Scale: A new scale to assess psychological insight following a psychedelic experience. *Journal of Psychopharmacology*, *36*(1), 31–45. https://doi.org/10.1177/02698811211066709

Pinto, R. Z., Ferreira, M. L., Oliveira, V. C., Franco, M. R., Adams, R., Maher, C. G., & Ferreira, P. H. (2012). Patient-centred communication is associated with positive therapeutic alliance: A systematic review. *Journal of Physiotherapy*, *58*(2), 77–87. https://doi.org/10.1016/S1836-9553(12)70087-5

Schmid, Y., Hysek, C. M., Simmler, L. D., Crockett, M. J., Quednow, B. B., & Liechti, M. E. (2014). Differential effects of MDMA and methylphenidate on social cognition. *Journal of Psychopharmacology*, *28*(9), 847–856. https://doi.org/10.1177/0269881114542454

Sessa, B., Higbed, L., O'Brien, S., Durant, C., Sakal, C., Titheradge, D., Williams, T. M., Rose-Morris, A., Brew-Girard, E., Burrows, S., Wiseman, C., Wilosn, S., Rickard, J., & Nutt, D. J. (2021). First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *Journal of Psychopharmacology*, *35*(4), 375–383. https://doi.org/10.1177/0269881121991792

Solomonov, N., McCarthy, K. S., Keefe, J. R., Gorman, B. S., Blanchard, M., & Barber, J. P. (2018). Fluctuations in alliance and use of techniques over time: A bidirectional relation between use of "common factors" techniques and the development of the working alliance. *Clinical Psychology & Psychotherapy*, *25*(1), 102–111. https://doi.org/10.1002/cpp.2143

Traynor, J. M., Roberts, D., Ross, S., Zeifman, R., & Choi-Kain, L. (2022). MDMA-assisted psychotherapy for borderline personality disorder. *Focus*, *20*(4), 358–367. https://doi.org/10.1176/appi.focus.20220056

Wagner, A. C. (2021). Couple therapy with MDMA—proposed pathways of action. *Frontiers in Psychology*, *12*, 733456. https://doi.org/10.3389/fpsyg.2021.733456

Wagner, A. C., Liebman, R. E., Mithoefer, A. T., Mithoefer, M. C., & Monson, C. M. (2021). Relational and growth outcomes following couples therapy with MDMA for PTSD. *Frontiers in Psychiatry*, *12*, 702838. https://doi.org/10.3389/fpsyt.2021.702838

Wang, J. B., Lin, J., Bedrosian, L., Coker, A., Jerome, I., Feduccia, A., Lilienstein, A., Harrison, C., Heimler, E., Mithoefer, M., Mithoefer, A., Ot'alora, M. G., Poulter, B., Carlin, S., Matthews, R., Yazar-Klonsinski, B., Emerson, A., & Doblin, R. (2021). Scaling up: Multisite open-label clinical trials of MDMA-assisted therapy for severe posttraumatic stress disorder. *Journal of Humanistic Psychology*, https://journals.sagepub.com/doi/full/10.1177/00221678211023663.

Wardle, M. C., & de Wit, H. (2014). MDMA alters emotional processing and facilitates positive social interaction. *Psychopharmacology*, *231*(21), 4219–4229. https://doi.org/10.1007/s00213-014-3570-x

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., Keane, T., & Marx, B. P. (2018). The Clinician-Administered PTSD Scale for DSM–5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment*, *30*(3), 383–395. https://doi.org/10.1037/pas0000486

Weathers, F. W., Keane, T. M., & Davidson, J. R. (2001). Clinician-administered PTSD scale: A review of the first ten years of research. *Depression and Anxiety*, *13*(3), 132–156. https://doi.org/10.1002/da.1029

Weiss, D. S. (2007). The impact of event scale: Revised. In J. P. Wilson & C. S. Tang (Eds.), *Cross-cultural assessment of psychological trauma and PTSD* (pp. 219–238). Springer.

Weiss, D. S., & Marmar, C. R. (1997). The impact of event scale–revised. In J. P. Wilson & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD: A practitioner's handbook* (pp. 399–411). Guilford Press.

Williams, M. T., Reed, S., & Aggarwal, R. (2019). Culturally informed research design issues in a study for MDMA-assisted psychotherapy for posttraumatic stress disorder. *Journal of Psychedelic Studies*, *4*(1), 40–50. https://doi.org/10.1556/2054.2019.016

Wolff, M., Mertens, L. J., Walter, M., Enge, S., & Evens, R. (2022). The Acceptance/Avoidance-Promoting Experiences Questionnaire (APEQ): A theory-based approach to psychedelic drugs' effects on psychological flexibility. *Journal of Psychopharmacology*, *36*(3), 387–408. https://doi.org/10.1177/02698811211073758

Wolfson, P. E., Andries, J., Feduccia, A. A., Jerome, L., Wang, J. B., Williams, E., Carlin, S. C., Sola, E., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M., & Doblin, R. (2020). MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: A randomized pilot study. *Scientific Reports*, *10*(1), 1–15. https://doi.org/10.1038/s41598-020-75706-1

Woody, S. R., & Adessky, R. S. (2002). Therapeutic alliance, group cohesion, and homework compliance during cognitive-behavioral group treatment of social phobia. *Behavior Therapy*, *33*(1), 5–27. https://doi.org/10.1016/S0005-7894(02)80003-X

Zeifman, R. J., Kettner, H., Pagni, B. A., Mallard, A., Roberts, D. E., Erritzoe, D., & Carhart-Harris, R. L. (2023). Co-use of MDMA with psilocybin/LSD may buffer against challenging experiences and enhance positive experiences. *Scientific Reports*, *13*(1), 13645. https://doi.org/10.1038/s41598-023-40856-5

Zeifman, R. J., Landy, M. S. H., Liebman, R., Fitzpatrick, S., & Monson, C. M. (2021). Optimizing treatment for comorbid borderline personality disorder and posttraumatic stress disorder: A systematic review of psychotherapeutic approaches and treatment efficacy. *Clinical Psychology Review*, *86*, 102030. https://doi.org/10.1016/j.cpr.2021.102030

Zeifman, R. J., & Wagner, A. C. (2020). Exploring the case for research on incorporating psychedelics within interventions for borderline personality disorder. *Journal of Contextual Behavioral Science*, *15*, 1–11. https://doi.org/10.1016/j.jcbs.2019.11.001

Zeifman, R. J., Wagner, A. C., Monson, C. M., & Carhart-Harris, R. (2023). How does psilocybin therapy work? An exploration of experiential avoidance as a putative mechanism of change. *Journal of Affective Disorders*, *334*, 100–112. doi:10.1016/j.jad.2023.04.105