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RESEARCH ARTICLE

Healing together: Results from a pilot trial of 3,4-Methylenedioxymethamphetamine-enhanced cognitive-behavioral conjoint therapy for posttraumatic stress disorder

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Abstract

Posttraumatic stress disorder (PTSD) disrupts individual well-being and relationship health, particularly among veteran/military couples with heightened risks due to deployment, family reintegration, and traumatic stress. Although cognitive-behavioral conjoint therapy (CBCT) and brief CBCT (bCBCT) have demonstrated strong efficacy in reducing PTSD symptoms, their impact on relational outcomes is less compelling. Given the importance of relationship functioning for veterans' overall health, enhancing interpersonal outcomes of PTSD treatment remains a research priority. One promising approach is the integration of 3,4-methylenedioxymethamphetamine (MDMA)–assisted therapy to augment the relational benefits of established PTSD interventions. This single-site, open-label pilot study evaluated the preliminary benefit, safety, and acceptability of MDMA-assisted bCBCT in eight U.S. military veterans with PTSD and their intimate partners ($N = 16$). An eight-session MDMA-assisted bCBCT protocol with two MDMA administration sessions and dyadic integration

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sessions incorporating elements of integrative behavioral couples therapy was delivered. Outcomes included PTSD symptom severity, relationship functioning, and safety. Veterans exhibited large pre–post PTSD symptom reductions, $d = 1.25$, which were generally maintained during follow-up. Both veterans and partners experienced large improvements in relationship functioning, ds = 1.83 and 1.29, respectively, with moderate rebound during follow-up. No serious adverse events were reported. This first trial of MDMA-assisted bCBCT in U.S. veterans and their partners provides preliminary evidence of potential improvements in PTSD and relational outcomes, with no identified serious safety concerns. This model has potential for future evaluation in large health care systems, leveraging the hypothesized therapeutic effects of MDMA for individuals with PTSD and their families.

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric condition with a lifetime prevalence of approximately 6% in the general population (Goldstein et al., 2016) and 29% in military veterans (Holder et al., 2023; Lehavot et al., 2018; Na et al., 2023). The impacts of PTSD extend beyond the individual, disrupting mental, emotional, and physical health as well as straining close relationships by undermining intimacy, communication, and safety (Campbell & Renshaw, 2018). Individuals living with PTSD and their intimate partners experience elevated rates of depression, anxiety, and relationship distress, with relational challenges serving as strong predictors of suicidality (Carter et al., 2024; Kazan et al., 2016). The far-reaching effects of PTSD underscore a need for interventions that address both PTSD symptoms and relational functioning (Sijercic et al., 2022).

Cognitive-behavioral conjoint therapy (CBCT) for PTSD was developed to simultaneously address trauma-related symptoms and relationship health (Monson & Fredman, 2012; Monson et al., 2021). Although CBCT has demonstrated large reductions in PTSD symptoms (e.g., gs = 1.28–1.71; Monson et al., 2024), improvements in relationship satisfaction have been more moderate (gs = 0.48 – 0.65), with some studies finding no significant impact on relationship functioning or reporting mixed results (Liebman et al., 2020; Morland et al., 2022). Morland and colleagues (2022) developed and tested an eight-session brief CBCT (bCBCT) protocol with a veteran sample, and though the results for PTSD symptom reduction were on par with the full 15-session protocol (ds = 1.05–1.12), improvements in relationship functioning were smaller, did not show a significant benefit compared to an active control condition (within-group ds = 0.19–0.38), and were similar to those observed in individual PTSD treatment that does not directly target interpersonal functioning (Sijercic et al., 2022). One reason for these small relationship functioning gains may be that CBCT (and bCBCT) is fundamentally a PTSD treatment that incorporates relational context and skills rather than a couple therapy that directly targets persistent relational dynamics outside of PTSD.

Given the persistent gap in relational outcomes (Sijercic et al., 2022), researchers have explored integrating adjunctive interventions to enhance the efficacy of CBCT (Sippel et al., 2023). The nonclassic psychedelic 3,4-methylenedioxymethamphetamine (MDMA; Stocker & Liechti, 2024) has garnered considerable clinical, research, and public attention for its potential to facilitate improvements in relationship functioning (Wagner, 2021). MDMA-assisted psychotherapy (MDMA-AT) is being studied as a breakthrough individual treatment for PTSD (Smith et al., 2022). MDMA's therapeutic effects, believed to result from its empathogenic (Hysek et al., 2014), prosocial (Bershad et al., 2016; Hysek et al., 2014), and fear-reducing properties (Young et al., 2015), may make it ideally suited to augment relational and PTSD outcomes in CBCT.

Monson and colleagues (2020) conducted the first study combining MDMA with CBCT. In this uncontrolled trial, six couples received CBCT with two MDMA sessions, in which both the PTSD-diagnosed and PTSD-negative partners received MDMA. Following each MDMA session, couples engaged in integration sessions to help them process insights, emotions, and trauma-related material that emerged from the MDMA sessions. MDMA dosing and integration sessions utilized the inner-directed therapeutic approach evaluated in Phase 2 and Phase 3 MDMA-assisted individual therapy trials, in which the patients' inner process guides the session (Alpert et al., 2026; Mitchell et al., 2021, 2023; Mithoefer et al., 2018). Results showed large and sustained improvements in PTSD symptoms (ds = 1.85–3.59) and moderate-to-large gains in relationship satisfaction (ds = 0.64–1.22), depression, emotion regulation, and trauma-related beliefs. These findings suggest that MDMA may amplify the relational mechanisms of CBCT (see Lyubomirsky, 2022).

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Despite these promising results, there are practical and clinical limitations to utilizing the full CBCT protocol and providing MDMA to both partners. The current pilot trial evaluated the feasibility, safety, and preliminary clinical benefit of an MDMA-enhanced bCBCT protocol dosing only the veteran diagnosed with PTSD in couples within the U.S. Department of Veterans Affairs (VA) health care system, offering several novel extensions to prior work.

First, this study evaluated a model in which only the patient with PTSD received MDMA; the partner participated in all therapy sessions except those in which MDMA was administered. Pending U.S. Food and Drug Administration (FDA) approval, insurance coverage and reimbursement guidelines may limit MDMA prescriptions to only individuals diagnosed with PTSD. Within the VA, medications are prescribed to the identified veteran patient. Further, in broader health care settings, partners may not be able or willing to participate in MDMA sessions (e.g., due to high blood pressure, pregnancy, and/or breastfeeding). Notably, no clinical studies of MDMA-assisted individual therapy for PTSD have reported impacts on relationship outcomes, leaving an open question regarding whether couple-based MDMA-enhanced PTSD treatment can still have relational benefit when only the PTSD-diagnosed patient receives MDMA.

Second, this is the first study to examine eight-session bCBCT, rather than the full 15-session CBCT protocol, combined with MDMA-enhanced therapy. Engagement in CBCT can be challenging, with data indicating that couples complete only eight sessions on average (Glynn et al., 2025; Pukay-Martin et al., 2022). A briefer model may expand access, accommodate individual or systemic barriers, and offer more flexibility.

Third, the current study implemented a novel approach to dyadic integration following MDMA dosing sessions by incorporating aspects of *integrative behavioral couple therapy* (IBCT; Roddy et al., 2016) along with bCBCT principles. Although the bCBCT intervention teaches couples relationship skills and concepts such as healthy communication and conflict management, it may not directly address underlying relationship dynamics outside the scope of PTSD symptoms. The unique emphasis on couple therapy–informed integration was intended to boost the relational impact of MDMA-enhanced bCBCT by directly addressing relational processes that underlie global relationship functioning and satisfaction.

METHOD

Participants

Participants were recruited from September 2023 to March 2025. Veterans and their partners were referred from mental health clinics or were self-referred from within the Veterans Affairs San Diego Healthcare System (VASDHS). Participants were 18 years of age or older and included (a) veterans who met the criteria for PTSD (PTSD+) as outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013) and assessed using the Clinician Administered PTSD Scale for *DSM-5* (CAPS-5; Weathers, Blake, et al., 2013), with at least moderate severity based on a total severity score of at least 28 and (b) the veteran's intimate partner in a committed relationship who was willing to participate in the intervention and did not meet the screening criteria for possible PTSD as assessed using the PTSD Checklist for *DSM-5* (PCL-5; Weathers, Litz, et al., 2013) and defined as a total score of 30 or lower. Additionally, dyads had to agree to required lifestyle modifications (e.g., medication guidelines for the PTSD+ veteran, restrictions on other trauma-focused or couples-focused therapy).

Psychiatric exclusions included, but were not limited to: panic disorder; bipolar disorders; psychotic disorders; current serious suicide risk (Columbia–Suicide Severity Rating Scale [C-SSRS; Posner et al., 2011] score of 4 or higher at a frequency of once a week or more, or any suicidal behavior within 6 months of screening); intimate partner violence; severe relationship aggression; or current alcohol or substance use at a level involving withdrawal, requiring detox, or that the study team determined to be a safety concern or that could interfere with participation. Full abstinence during the study was not required, but the participants must have had a plan agreed upon by the investigator, therapy team, and study physician to reduce the use of alcohol and substances and manage symptoms without self-medicating. Medical exclusions included uncontrolled hypertension, cardiovascular or neurovascular disease, or other unstable medical conditions. For the complete list of psychiatric and medical eligibility criteria and lifestyle modifications, see Morland et al. (2024; Trial Registration NCT05979844).

Demographic characteristics are reported without individual-level specificity to avoid inadvertently deidentifying participants in this small study. Veterans were 45.57 years old on average (range: 28–60 years). Five of the eight veterans were male, and seven were heterosexual. In terms of race, five veterans were White, and the remaining veterans reported Asian or another nonspecified race; in terms of ethnicity, two veterans were Hispanic or Latino. Median educational attainment was college graduate, and veterans reported a range of employment statuses, including unemployed, intermittent work, part-time work, full-time work, and retired. Three veterans reported taking psychoactive medication(s), and six veterans met the criteria for one or more past or current comorbidities, including major depressive disorder and substance use

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disorders, per the Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND; Tolin et al., 2016). Partners were 42.50 years old on average (range: 30–55). Three partners were male, and all eight were heterosexual. In terms of race, six partners were White; in terms of ethnicity, two were Hispanic or Latino. Median educational attainment was professional or graduate degree, and employment statuses included unemployed, intermittent work, part-time, full-time, and retired. The majority of couples were married, with an average reported relationship length of 14.88 years (range: 2–34), and couples reported a median household income of more than $105,000.

Procedure

The study protocol was approved by the VA San Diego Institutional Review Board (H220067). The study design was preregistered (Trial Registration NCT05979844), and the hypotheses, methods, and analytic plan were previously published (Morland et al., 2024). This was a single-site, open-label study assessing the preliminary clinical benefit, safety, feasibility, and acceptability of MDMA-enhanced therapy in combination with bCBCT in a sample of eight PTSD+ veterans and their intimate partners ($N = 16$) within the VASDHS. The study was conducted according to ethical standards, and all participants completed informed consent prior to being enrolled in the study.

Initial prescreening involved a medical chart review for the PTSD+ veteran and a phone screen with both the PTSD+ veteran and their intimate partner. Dyads then provided informed consent and were enrolled in the study. Additional psychiatric and medical assessments were conducted to determine eligibility. After the PTSD+ veteran's medical eligibility was confirmed via in-person medical laboratory tests, PTSD+ veterans who were on prohibited concomitant medications (e.g., antidepressants, prohibited opiates) completed a study physician–guided medication taper. Next, dyads completed the baseline assessment and initiated treatment, with additional assessments at midtreatment, end of treatment, and 3- and 6-months posttreatment. See Figures 1 and 2 for participant flow and the sequence of the procedures, and Morland et al. (2024) for the full list of screening measures.

Treatment

Therapists delivered the eight-session bCBCT intervention combined with an MDMA-focused preparation session, two full-day MDMA sessions for the PTSD+ veteran, and at least one integration session with the veteran and partner following each MDMA session (see Figure 1). The bCBCT for PTSD protocol includes psychoeducation about trauma and its impact on relationship functioning, building emotional and physical safety in the relationship, listening and communication skills, in vivo exposure (called *approach*), and conjoint thought challenging. MDMA sessions were scheduled following bCBCT content on sharing thoughts and feelings and cognitive processing. Sessions 1–3 of bCBCT were delivered in a massed format (one 4-hr session), followed by Sessions 4–5 in a massed format (one 3-hr session). The MDMA preparation session (1.5 hr) was delivered the business day before the first MDMA session (6–8 hr), followed by the first integration session (1.5 hr) the day following the MDMA session. Sessions 6 and 7 (1.5 hr each) were delivered over the next 2 weeks. The second MDMA session (6–8 hr) was delivered the week after bCBCT Session 7, followed by the second integration session (1.5 hr) the following morning and the final bCBCT session (1.5 hr) approximately 1 week later. Treatment duration averaged 7 weeks. Each dyad had a primary therapist who was present for all sessions, with a cotherapist present for the preparation, MDMA, and integration sessions.

During the MDMA sessions, the PTSD+ veteran was given 80 mg of MDMA HCl (~68 mg MDMA) with an optional 40 mg MDMA HCl (~34 mg MDMA) supplemental dose in the first session and 100 mg of MDMA HCl (~84 mg MDMA) with an optional 40 mg MDMA HCl supplemental dose in the second. The intimate partner was invited to be present for the last 1–2 hr of the MDMA sessions to share and connect but did not receive MDMA. A study clinician or member of the team conducted one to three phone check-ins with the PTSD+ veteran to assess potential side effects and suicidality during the week following each MDMA session.

Dyadic integration occurred the day after each MDMA dosing session, with up to three additional integration sessions offered according to participants' preferences and therapists' clinical judgment. During integration, veterans were invited to share their experiences from the MDMA session and trauma- or relationship-related insights that occurred during or since the MDMA session. Partners were invited to share their feelings related to both the relationship and veterans' experiences. Although the structure of the integration sessions remained participant-led rather than guided by a therapist's agenda, the protocol prompted therapists to look for naturally arising opportunities to use evidence-based couple therapy strategies from IBCT (e.g., unified detachment, empathic joining) to deepen vulnerability, promote understanding and empathy, reinforce shifts from rigid patterns to more flexibility, and enhance

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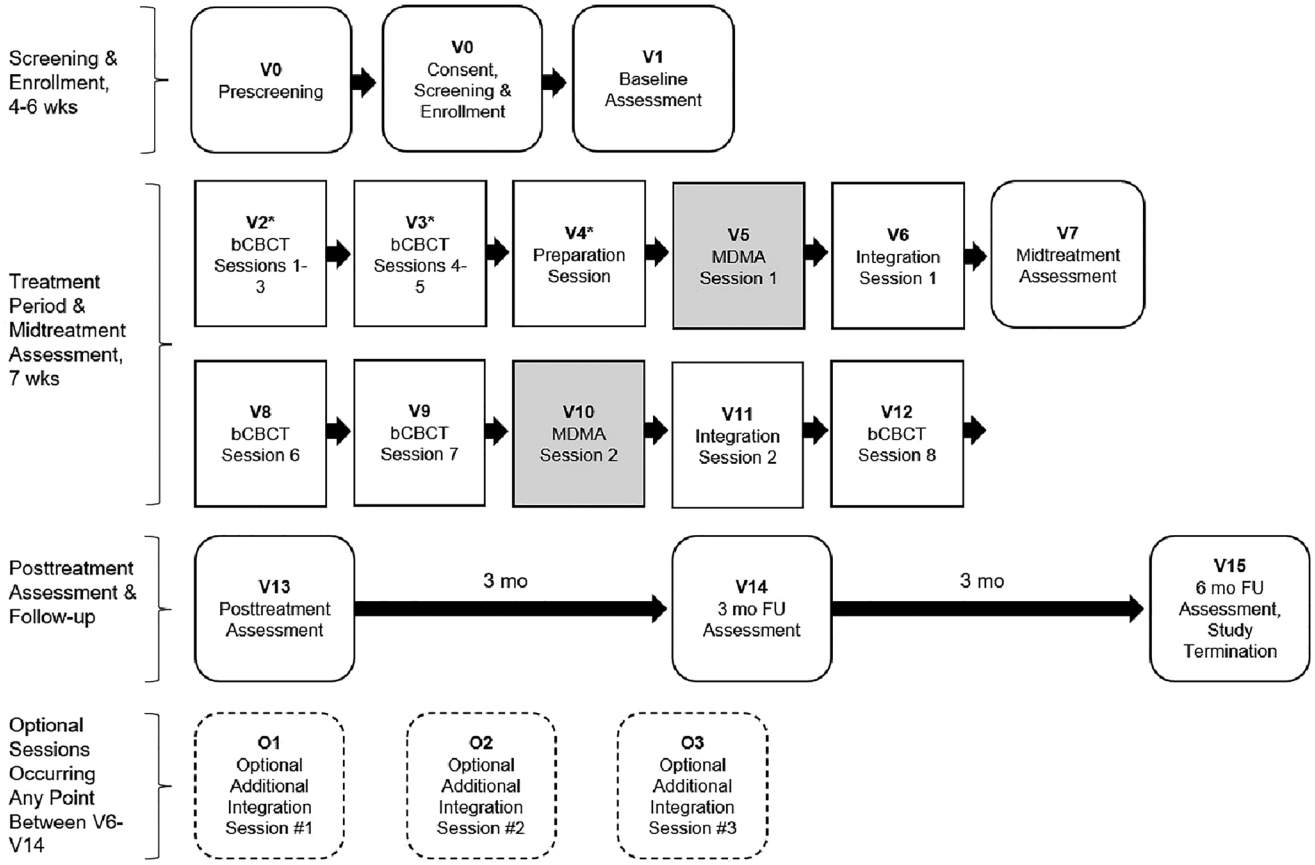


FIGURE 1 Study procedures.

Note: MDMA = 3,4-Methylenedioxymethamphetamine; bCBCT = brief cognitive-behavioral conjoint therapy; V = visit; mo = month; FU = follow-up; O = optional session.

connection, as well as to reinforce relational skills from CBCT.

Treatment delivery

Treatment modality

All bCBCT sessions were delivered virtually by a therapist in a VA office, with the couple connecting via their personal device from a private and quiet location. During the initial therapy session, couples received bCBCT handouts, reminders for MDMA session procedures and requirements, and post-MDMA session guidance for the partner. Treatment sessions were audio- and video-recorded for fidelity assessment and clinical supervision.

The MDMA sessions were held in person at the VASDHS. PTSD+ veterans arrived at the VA hospital for screening, conducted by the study coordinator and study physician, which included a breathalyzer, urine pregnancy test (if applicable), urine drug test, and measurement of vital signs (blood pressure, heart rate, temperature). Participants were then escorted to a private room to join their study therapists and begin the MDMA session. The physical setting in which the MDMA sessions occurred was designed to accommodate the unique nature of MDMA-AT (Perivoliotis et al., 2025). Partners were invited to join for the final 1–2 hr of the session, and all partners in the current study chose to do so.

Treatment and assessment fidelity and reliability monitoring

Therapists included four doctoral-level licensed clinicians trained in MDMA-AT and CBCT. Weekly consultation and tape review were provided to maximize therapist fidelity to bCBCT, preparation, MDMA, and integration session protocols. A subset of 10% of the CBCT sessions was randomly selected for review by an independent CBCT therapist, which demonstrated a 92% adherence to the modified condensed bCBCT treatment manual.

Assessments were conducted virtually. CAPS-5 assessors included trained bachelor's- and graduate-level assessors supervised by a doctoral-level clinician. Experts in the diagnosis and assessment of PTSD using the CAPS-5 served as study assessment trainers, supervisors, and reli-

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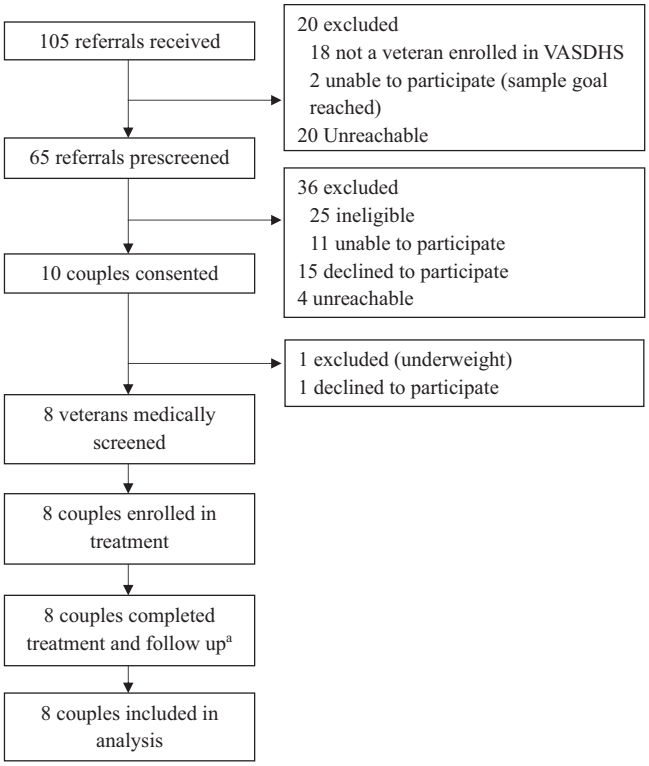


FIGURE 2 Participant flow.
Note: The 105 total referrals included 59 provider referrals and 46 self-referrals. [a]Two non–posttraumatic stress disorder (PTSD) partners did not complete the 3-month follow-up, but all participants completed the 6-month follow-up.

ability raters. Approximately one third (35%) of CAPS-5 assessments were randomly selected for reliability rating, including at least one from every participant. Interrater reliability was excellent, severity score absolute agreement intraclass correlation coefficient (ICC) = .99.

Measures

Primary endpoints

Clinician-assessed PTSD symptoms and diagnosis

The CAPS-5 (Weathers, Blake, et al., 2013) is a 30-item interview that is used to evaluate the 20 *DSM-5* PTSD symptom criteria (APA, 2013). Each symptom is rated on a 5-point severity scale from 0 (*absent*) to 4 (*extreme/incapacitating*), with total scores ranging from 0 to 80. Reliable and clinically significant change was defined in three nested categories: *treatment response*, defined as a symptom severity reduction of 12 points or more (Marx et al., 2022); *loss of diagnosis*, defined as a treatment response plus no longer meeting the *DSM-5* criteria for PTSD; and *remission*, defined as a loss of diagnosis plus a total end-of-treatment symptom severity score of less than 12. The CAPS-5 has demonstrated good reliability and validity (Weathers, Blake, et al., 2013) and had good internal consistency in this sample, Cronbach's $\alpha = .86$.

Secondary endpoints

Couple satisfaction

The Couple Satisfaction Index (CSI-32; Funk & Rogge, 2007) is a 32-item, self-report survey measuring romantic relationship satisfaction. The first item measures the overall happiness of the relationship on a 7-point scale, and other items capture satisfaction, quality, and happiness of the relationship on 6-point scales (range: 0–5), with varying response options. Scores are summed, and higher total scores indicate higher relationship satisfaction; scores below 104.5 indicate clinically significant relationship distress. Reliable change was calculated using sample-specific dispersion parameters as described by Jacobson and Truax (1991) and the reliable change index tool created by Evans (2023). Reliable change on the CSI-32 was operationalized in this sample as a change of 13.61 points or more. Clinically significant improvement was defined as moving from the relationally distressed category (i.e., a satisfaction score less than 104.5) to the nondistressed category; clinically significant deterioration was defined as the converse. In this sample, internal consistency was excellent among veterans, Cronbach's $\alpha = .97$, and their partners, Cronbach's $\alpha = .98$.

Self-report PTSD symptoms

The PCL-5 (Weathers, Litz, et al., 2013) is a 20-item, self-report survey measuring PTSD symptom severity. Participants were asked to rate how much distress they experienced due to each symptom over a specified timeframe. Items were rated on a 5-point scale ranging from 0 (*not at all*) to 4 (*extremely*), with scores summed and total scores ranging from 0 to 80. Higher scores indicate higher levels of PTSD symptom severity. The PCL-5 has demonstrated good validity and reliability in veterans (Cronbach's $\alpha = .96$; Bovin et al., 2016). Partners completed the collateral version of the PCL-5 (PCL-C) to measure their perceptions of the veterans' PTSD symptoms. In the current sample, Cronbach's alpha was .88.

Client satisfaction

The Client Satisfaction Questionnaire (CSQ-8; Larsen et al., 1979) is an eight-item, self-report survey measuring patient satisfaction with treatment. Items are rated on 4-point scales with varying response options. A mean score is generated, with higher mean scores indicating higher satisfaction. The measure also includes an open-ended item to capture any other feedback. The measure has demon-

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strated high internal consistency (Cronbach's α = .93; Larsen et al., 1979). In the current sample, Cronbach's alpha was .96.

Safety endpoints

Adverse event tracking

Study staff assessed the severity, incidence, and frequency of adverse events (AEs); AEs of special interest (AESIs), a subset of AEs involving cardiac function, suicide risk, and signals of abuse potential; treatment-emergent AEs (TEAEs), AEs occurring during and within 2 days after MDMA administration); serious adverse events (SAEs), AEs resulting in death, life-threatening experience, hospitalization, persistent significant disability, concomitant medication use, and suicidal ideation and behavior throughout the study. Vital signs (blood pressure, heart rate, and temperature) were assessed during each MDMA session before the initial dose, before the supplemental dose, at the end, and additionally as needed.

Suicidal ideation and behavior

Prior to each therapy session at every study visit, a study clinician or clinical coordinator administered the C-SSRS (Posner et al., 2011) to assess suicidal ideation, ideation intensity, and suicidal behavior. The C-SSRS uses a series of yes or no screening questions that are administered to identify the respondent's risk level as low, moderate, or high based on the presence of ideation (Questions 1 [passive] and 2 [active]), method (Question 3), plan (Question 4), intent (Question 5), and suicidal and/or self-injurious behavior (four or more subsequent questions depending on responses).

Data analysis

The primary statistics of interest were effect sizes, calculated as Cohen's *d* (standardized mean differences), as well as reliable and clinically significant change as defined for each outcome measure. Consistent with standards, we interpret *d* values of 0.2 as a small effect, 0.5 as a medium effect, and 0.8 or greater as a large effect. Effect size calculations utilized estimated marginal means derived from piecewise linear models (Segment 1: baseline, midtreatment, and end of treatment; Segment 2: end of treatment, 3-month follow-up, and 6-month follow-up) that controlled for baseline levels of the outcome variables. PTSD effect sizes were calculated using PTSD+ veteran data. Relationship satisfaction effect sizes were derived using models that included data from both partners and were structured as two-intercept dyadic models that accounted for interdependence.

Effect size calculations were based on the full enrolled sample using intention-to-treat principles. There were two sources of missing data. First, three participants inadvertently skipped a single item on one of their questionnaires; given the small sample size and small proportion of missing item-level data, mean substitution was used for these items prior to calculating each participant's measure scores. Second, two intimate partners did not complete the 3-month follow-up assessment, although they did complete the 6-month follow-up assessment. Maximum likelihood estimation of marginal means was used to reduce bias due to missing assessment data for partners' relationship satisfaction. Data were analyzed using SPSS (Version 31.0) and R (Version 4.5.2).

RESULTS

PTSD symptom severity

At baseline, veterans' mean CAPS-5 severity score was 39.13 (*SD* = 10.56), with a range of 29 to 55. PTSD+ veterans' CAPS-5 severity scores showed a large improvement during the treatment period (from baseline to end-of-treatment, controlling for baseline levels), $d = -1.25$. Average change during the treatment period was a 16.1-point decrease on CAPS-5 severity (range: 3–34-point decrease; *SD* = 11.4). Of the eight veteran participants, five (62.5%) demonstrated a clinically significant treatment response, three of whom (37.5%) showed a loss of diagnosis and two of whom (25.0%) showed remission. During the follow-up period, CAPS-5 severity scores showed a small rebound ($M = 6.3$ points, $d = 0.29$). See Figure 3 for the change in PTSD symptoms over the course of the study.

Relationship satisfaction

Both veterans, $d = 1.83$, and partners, $d = 1.29$, showed a large improvement in relationship satisfaction during the treatment period. Veteran, $d = -0.68$, and partner, $d = -0.47$, relationship satisfaction scores also showed a moderate rebound during the follow-up period. Average change on the CSI-32 during the treatment period was an increase of 27.9 points (*SD* = 31.8) for veterans and 19.8 (*SD* = 23.1) for partners. Five veterans and five partners (62.5% of the total sample) showed reliable improvement in relationship satisfaction, and one partner (6.3%) showed reliable deterioration (i.e., a decrease of 16 points); the remaining participants (31.3%) showed score increases smaller than the reliable change index. Of the six veterans and six partners who were relationally distressed at baseline, four veterans and four partners (66.7%) showed

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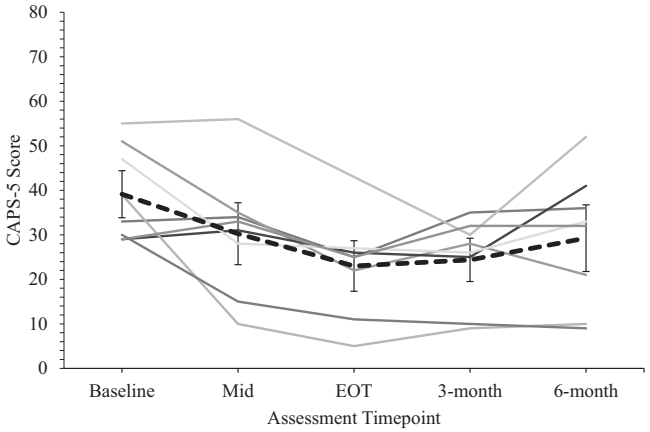


FIGURE 3 Change in posttraumatic stress disorder (PTSD) symptoms among veterans with PTSD (PTSD+).
Note: Solid lines represent raw scores for individual PTSD+ veteran participants, and the dashed line represents mean scores; error bars represent 1 standard deviation above and below the mean.
Baseline–end-of-treatment (EOT) effect size: $d = -1.25$; EOT to 6-month follow-up effect size: $d = 0.29$.
CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*.

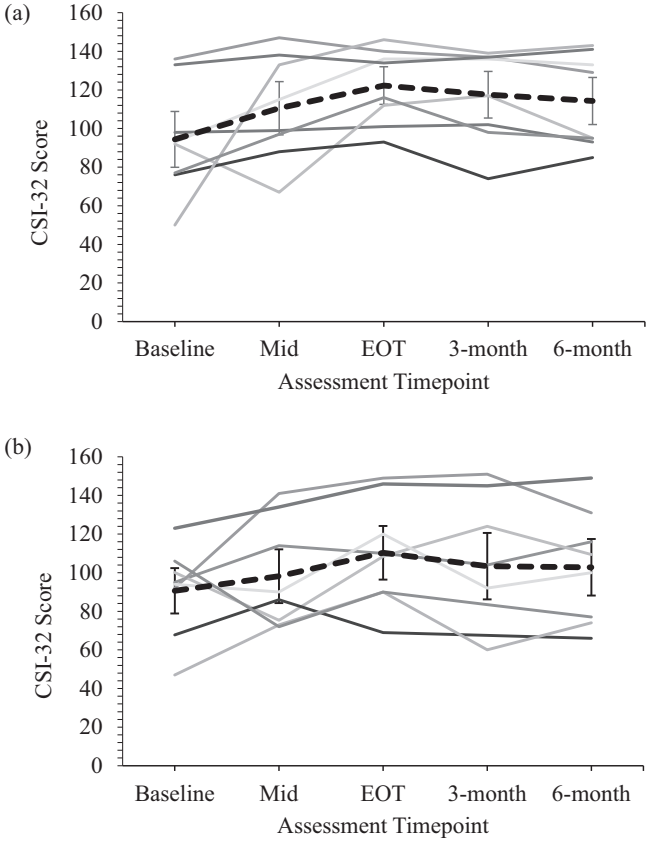


FIGURE 4 Change in relationship satisfaction for (a) veterans and (b) partners.
Note: Solid lines represent scores of individual participants, and the dashed line represents mean scores; error bars indicate 1 standard deviation above and below the mean. Veterans: baseline–end-of-treatment (EOT) effect size: $d = 1.83$; veteran EOT–6-month effect size: $d = -0.68$. Partners: baseline–EOT effect size: $d = 1.29$; EOT –6-month effect size: $d = -0.47$. CSI-32 = Couples Satisfaction Index.

clinically significant improvement. The remaining two veterans and one of the remaining partners began with and maintained nondistressed satisfaction scores. The final partner showed clinically significant deterioration, beginning in the nondistressed range and ending in the distressed range. See Figure 4 for changes in veteran and partner relationship satisfaction.

Safety

AEs

No SAEs were reported during the study. All participants who received MDMA experienced at least one TEAE. As expected based on prior trials, participants experienced transient increases in blood pressure and pulse during MDMA sessions (see Supplementary Table S1). The most frequently experienced TEAEs (experienced by more than one participant within 7 days of an MDMA session) included headache (75.0%), feeling warm or hot (37.5%), increased blood pressure (37.5%), nausea (25.0%), decreased appetite (25.0%), and sadness (25.0%). There were no instances of high suicide risk as indicated on the C-SSRS, defined as "yes" responses to both ideation questions plus at least two of the three questions about plan, method, and intent. One participant developed active suicidal ideation (i.e., C-SSRS responses indicating both ideation and method but denying a specific plan or intent) during the pretreatment medication taper and reported passive ideation on the first C-SSRS question in the days following each MDMA session. One participant reported passive ideation at baseline that increased to active ideation during follow-up, although this participant confirmed that it was not worse than what they had previously experienced in their lifetime and concurrently reported the loss of a loved one separate from study participation. Two participants reported passive suicidal ideation at baseline and did not worsen over the course of the study. See Supplementary Table S2 for more detail on adverse events.

Medication management

Three PTSD+ veteran participants (37.5%) were prescribed antidepressant medications (duloxetine, paroxetine, desvenlafaxine) that required tapering and discon-

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tinuation prior to starting treatment; all completed the taper with no dropout due to complications related to tapering. One of these participants was also prescribed stimulant medication for attention deficit–hyperactivity disorder (ADHD), which was required to be temporarily discontinued prior to each MDMA session. One participant had an AESI of a urine drug test positive for cocaine prior to the second MDMA session, which was canceled to ensure safety. Per protocol, the principal investigator, primary therapist, and physician used clinical judgement to determine that the participant would remain in the study and the session would be rescheduled. This same participant also reported infrequent use of trazodone during treatment due to a misunderstanding of medication guidelines, though this did not contribute to any of the participant's TEAEs as determined by the study physician. One participant was prescribed antibiotics to treat a non–study-related AE during their follow-up period.

Feasibility and acceptability

All enrolled couples completed the entire course of treatment, including all MDMA and bCBCT sessions, attesting to the feasibility of the treatment. Enrollment targets were reached, although a total of 105 referrals were received, with 85 referrals being screened in some capacity (e.g., brief phone call, chart review, full phone screen). Couples were highly satisfied with treatment. Veterans reported an average score of 3.77 (out of 4) on the CSQ-8 ($SD = 0.27$, range: 3.38–4.00), and partners reported an average score of 3.81 ($SD = 0.34$, range: 3.00–4.00). Feedback captured by the open-ended item on the CSQ-8 indicated that participants were grateful for the opportunity to participate in the study and appreciated the qualities of the research team.

DISCUSSION

This pilot study is the first to provide preliminary evidence that MDMA-enhanced bCBCT is safe and can yield clinically meaningful improvements in PTSD symptom severity and relationship satisfaction when only the PTSD+ partner receives MDMA. Large reductions in clinician-rated PTSD symptoms were observed during the treatment period, accompanied by large improvements in relationship satisfaction for both members of the dyad. Examining this single-dosing approach within a couple-based framework is imperative given that pending FDA approval, MDMA would be prescribed for the patient with a PTSD diagnosis and likely not the partner. This approach provides more flexibility than dual-dosing models utilizing the full CBCT protocol and may expand access to treatment. These findings extend prior research on MDMA-enhanced psychotherapy by demonstrating the feasibility of integrating MDMA into a brief, outpatient, manualized conjoint treatment model that targets both individual and interpersonal functioning while providing MDMA only to the PTSD-diagnosed patient within a large health care system. The results have important implications for clinical scalability and public health impact, particularly for veterans and their families.

The magnitude of PTSD symptom reduction in this study appears similar to the large effect size improvements in CAPS-5 scores reported at end of treatment and follow-up in prior studies (Mitchell et al., 2021, 2023), though differences in design limit direct comparisons. Rates of loss of PTSD diagnosis and remission were lower in the current study (37.5% loss of diagnosis, 25% remission vs. 67% loss of diagnosis, 33% remission [Mitchell et al., 2021] vs. 71.2% loss of diagnosis, 46.2% remission [Mitchell et al., 2023]) and were more comparable to rates reported for non-MDMA bCBCT in this same population (Morland et al., 2022). The present study differs from the existing Phase 3 protocols in several key respects: MDMA was delivered within an evidence-based trauma-focused psychotherapy, treatment was substantially shorter regarding both the number of weeks of treatment and therapy hours, and this study treated VA-enrolled veterans. Intimate partners engaged in and benefited from this treatment. Despite potentially lower rates of remission, our findings suggest that MDMA's therapeutic effects may generalize across delivery formats and may not be limited to intensive individual therapy models in the community.

This study demonstrates that meaningful clinical and relational improvements can be achieved when only the PTSD-diagnosed partner receives MDMA, offering more flexibility and accessibility for patients wanting to engage in treatment with their partners. MDMA-facilitated changes in emotional processing and threat responding in one partner may produce downstream relational benefits for the other partner, resulting in improved relationship satisfaction for both partners. Interestingly, qualitative inquiry revealed that seven out of eight partners were either not interested in receiving MDMA ($n = 6$) or would not have been able to receive it due to work constraints ($n = 1$). The importance of having a single-dosing model for pending prescribing and legal constraints is evident; however, this study also highlights the necessity of a single-dosing model to accommodate patient preferences. Our results suggest that limiting dosing to the partner with PTSD can preserve relational benefit while potentially reducing medical risk, regulatory complexity, logistical burden, and cost.

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Improvements in relationship satisfaction during the treatment period (veterans: $d = 1.83$, partners: $d = 1.29$) were larger than the effect sizes previously reported in the Monson et al. (2020) MDMA-enhanced CBCT study (patients: $d = 0.82$, partners: $d = 0.64$, during treatment). The relational benefits in the current study may have been maximized due to the novel incorporation of evidence-based couple therapy strategies into the dyadic integration sessions. CBCT utilizes the involvement and support of the PTSD-negative partner to reduce PTSD symptoms through conjoint behavioral, emotional, and cognitive interventions; relationship functioning improves to the extent that couples learn adaptive communication and conflict management skills to manage PTSD so that PTSD symptoms no longer cause relational strain. In contrast, the strategies used in the current study specifically focused on improving broad relationship processes that underlie optimal relationship functioning, including building empathy, understanding, perspective-taking, and secure attachment between partners. Relationship outcomes have been variable across prior PTSD therapy treatment trials (Sijercic et al., 2022), including CBCT studies (Liebman et al., 2020), and relational functioning was not a treatment target in the Phase 3 MDMA studies (Mitchell et al., 2021, 2023). The large improvements in relationship satisfaction observed here suggest that integrating dyadic PTSD interventions with evidence-based couple therapy interventions may be most effective for maximizing relational benefit from MDMA-AT.

Despite large effects overall, there was substantial variability in relationship improvement across the eight dyads, with only 50.0% of veterans and 50.0% of partners showing both reliable and clinically significant improvement. One partner showed deterioration in relationship satisfaction. Given the varied nature of relationship dysfunction, more personalized treatment approaches may be needed to reliably address couples' concerns.

Both PTSD symptoms and relationship functioning also showed potentially meaningful rebound during the follow-up period. This contrasts with Monson et al. (2020), in which effect sizes from baseline through the final follow-up period were larger than effect sizes from baseline through the end of treatment. The full 15-session CBCT protocol may lead to more durable effects than a briefer eight-session protocol. Additionally, the VA-enrolled veteran sample in the current study reflects the larger VA system in terms of high medical and psychiatric complexity, which may contribute to more challenges maintaining treatment gains. Longer or more rigorous integration support may be needed for patients with more chronic and complex PTSD, such as those commonly encountered in VA. The follow-up period in our study (February 2024–November 2025) was a particularly challenging time in history for many veterans due to global conflicts and U.S. political turmoil. Such contextual challenges are known to exacerbate PTSD symptoms. More work is needed to support healthy individual and relational functioning following participation in intensive treatments like MDMA-assisted bCBCT among psychiatrically vulnerable populations.

This study is limited by its open-label design, small sample size, and lack of a comparison condition, precluding causal inference. Our sample was also predominantly heterosexual, about two thirds White, and fairly highly educated. Findings should be interpreted as preliminary. Larger randomized trials with more diverse samples are needed to isolate the incremental benefit of MDMA relative to bCBCT therapy alone, examine the durability of effects, clarify mechanisms of change, and determine generalizability.

In summary, in this uncontrolled pilot study, MDMA-enhanced bCBCT was associated with large improvements in PTSD symptoms and relationship satisfaction within a brief treatment model. The current study protocol offers innovations in the form of an individual-dosing model that allows for flexibility while retaining treatment benefit, as well as enhanced relational intervention during dyadic integration sessions. These findings support prior research showing the promise of MDMA-assisted couple therapy for PTSD to treat both PTSD symptoms and relationship distress, and encourage further rigorous investigation of MDMA-assisted couple therapies in controlled trials.

AUTHOR CONTRIBUTIONS

Leslie A. Morland: funding acquisition, writing–original draft, investigation, conceptualization, methodology, writing–review and editing, project administration, supervision. **Chandra E. Khalifian**: writing–original draft, project administration, investigation, writing–review and editing, methodology. **Dimitri Perivoliotis**: writing–original draft, writing–review and editing, project administration, investigation. **Bettye Chargin**: project administration, writing–original draft, writing–review and editing. **Al Alam**: supervision, project administration, investigation, writing–review and editing. **Tamara R. Wachsman**: writing–review and editing, project administration, writing–original draft. **Dhakshin Ramanathan**: supervision, project administration, writing–review and editing, investigation. **Andrew W. Bismark**: writing–review and editing, supervision, project administration. **Christopher Stauffer**: supervision, writing–review and editing, project administration, investigation. **Anne C. Wagner**: supervision, writing–review and editing, methodology, investigation. **Abigail C. Angkaw**: supervision, project administration, writing–review and editing.

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Kayla C. Knopp: writing–original draft, writing–review and editing, investigation, project administration, formal analysis, methodology.

AUTHOR NOTE

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OPEN PRACTICES STATEMENT

Study materials, including de-identified datasets analyzed during the current study, are available from the principal investigator (corresponding author) upon reasonable written request at Leslie.morland@va.gov. This study's design was preregistered on ClinicalTrials.gov (NCT05979844), and all study measures and hypotheses are reported in Morland et al. (2024).

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SUPPORTING INFORMATION

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