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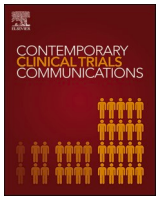

MDMA-assisted brief cognitive behavioral conjoint therapy for PTSD: Study protocol for a pilot study

L.A. Morland [a,b,c,*], D. Perivoliotis [b,c], T.R. Wachsman [b], A. Alam [b,c], K. Knopp [b,c], C. Khalifian [b,c], D. Ramanathan [b,c], B.E. Chargin [b], A.W. Bismark [b,c], S. Glynn [d,e], C. Stauffer [f,g], A.C. Wagner [h,i]

[a] Department of Veterans Affairs National Center for PTSD Women's Health Sciences Division, 150 South Huntington Street, Boston, MA, 02130, USA
[b] Veterans Affairs San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA, 92161, USA
[c] Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, La Jolla, CT, 92093, USA
[d] VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd, Los Angeles, CA, 90073, USA
[e] Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, 760 Westwood Plaza, Los Angeles, CA, 90024, USA
[f] Department of Psychiatry, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR, 97239, USA
[g] Veterans Affairs Portland Health Care System, 3710 SW US Veterans Hospital Rd, Portland, OR, 97239, USA
[h] Remedy, 703 Bloor Street West, Suite 201, Toronto, Ontario, M6G 1L5, Canada
[i] Department of Psychology, Toronto Metropolitan University, 350 Victoria St., Toronto, Ontario, M5B 2K3, Canada

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ABSTRACT

Background: Posttraumatic Stress Disorder (PTSD) impacts both individual and relational functioning. Veteran couples are at increased risk of relationship distress due to military stressors such as deployment, family reintegration, and traumatic stress. Although both Cognitive-Behavioral Conjoint Therapy (CBCT) and its brief version (bCBCT) consistently have large effects on reducing PTSD symptoms, these treatments have more variable effects on relational outcomes. Given the impact of relationship functioning on the overall health of veterans, improving the effect of PTSD treatments on relationship functioning is an essential area of research. One promising path is the role of MDMA (3,4-methylenedioxymethamphetamine)-assisted therapy in augmenting the relational impact of established therapeutic interventions such as bCBCT.

Method/Design: This is a single site, open-label study assessing the preliminary efficacy, safety, and acceptability of MDMA-assisted therapy in combination with bCBCT in 8 veterans with PTSD and their intimate partners ($N = 16$). Therapy teams trained in bCBCT and MDMA-assisted therapy will deliver bCBCT combined with two MDMA sessions and two couple emotion focused integration sessions. PTSD symptom severity and relationship functioning outcomes will be evaluated.

Conclusion: This is the first study to examine the efficacy of MDMA-assisted bCBCT for improving PTSD and relationship functioning among a sample of U.S. military veterans and their partners. This project could provide an opportunity to pilot a scalable model of treating PTSD within the Veterans Affairs healthcare system and leverage the benefits of MDMA for veterans with PTSD, as well as the downstream benefits to their partner on both individual and relationship functioning. ClinicalTrials.gov Identifier: NCT05979844.

1. Introduction

Military personnel and veterans are disproportionately impacted by PTSD, especially those who are exposed to combat or military sexual trauma [1]. PTSD is associated with a plethora of negative effects when left untreated, including other mental health problems [2], unemployment [3], and suicidality [4,5]. The negative effects of PTSD are not limited to only those who are diagnosed with the disorder. Many PTSD symptoms, especially anger, withdrawal, and avoidance, can also harm intimate relationship partners, leading to poor relationship adjustment and instability, parenting problems, and intrafamilial violence [6–8]. These negative consequences then have a cyclical effect:

* Corresponding author. Department of Veterans Affairs National Center for PTSD Women's Health Sciences Division, 150 South Huntington Street, Boston, MA, 02130, USA.
E-mail address: leslie.morland@va.gov (L.A. Morland).

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interpersonal issues cause reduced social support and higher stress, which are then associated with worse PTSD treatment results [9,10]. These issues also negatively impact the intimate partners in relationships with PTSD-positive individuals, who show increased risk of somatic symptoms, anxiety, insomnia, depression, and low self-esteem [11,12].

Current research suggests that using a couple-based approach to treat PTSD can enhance treatment impacts [13] by improving both PTSD symptoms and relationship functioning simultaneously, thereby interrupting the feedback loop between them. Cognitive-Behavioral Conjoint Therapy (CBCT) is a 15-session manualized treatment for couples that is designed to reduce PTSD symptoms and enhance relationship functioning [14]. Results from clinical trials in veteran and community samples [15] support CBCT's efficacy in reducing PTSD symptom severity and improving relationship functioning. However, retaining couples for a 15-session treatment appeared to be difficult. Subsequently, an 8-session brief form of CBCT (bCBCT) was designed to overcome logistical barriers to attendance. Current research supports the efficacy of bCBCT for improving both PTSD symptoms and relationship functioning [16].

While the effect bCBCT has on PTSD symptoms is consistently robust, relationship-focused outcomes have been less compelling [16]. Morland et al. [16] found large-sized improvements in PTSD after bCBCT treatment with only small effect sizes for relationship improvement. Given the importance of relationship functioning for veteran and partner mental health and well-being, it is imperative to examine the relational benefits of PTSD treatment and methods to augment them. Using medications that potentiate the mechanisms of action in psychotherapy is one strategy to enhance its effects. MDMA is a monoamine releaser and re-uptake inhibitor with indirect effects on neurohormone release that has been proposed as an ideal compound to enhance couple therapy for PTSD. The subjective effects of MDMA create a productive psychological state that enhances the therapeutic process, creating a significant opportunity to enhance the benefits of PTSD treatments, particularly couple-based interventions like bCBCT. MDMA-assisted interventions for dyads [17] may improve bonding and strengthen the effects of dyadic treatment interventions.

MDMA activates the serotonin (5-HT) system, elevates hormones and neurotransmitters that increase feelings of connection, safety, and love (e.g., oxytocin, vasopressin, dopamine, and serotonin), decreases the fear response via the amygdala, and decreases attachment to and rigidity of memories via the hippocampus [18,19]. The combination of these effects creates an environment where couples can process trauma and share the relational hurt that has resulted from PTSD (e.g., conflict, emotional numbing, stonewalling). The mindset shift and relational closeness facilitated by MDMA enhances a couple's ability to be present and support one another through the challenging work of addressing trauma and relationship distress.

Phase 3 clinical trials of individual MDMA-assisted therapy (MDMA-AT) using a model of treatment developed by the Multidisciplinary Association for Psychedelic Studies (MAPS) were recently completed, with numerous studies worldwide currently pursuing research of MDMA-AT for PTSD. Two multi-site, placebo-controlled phase 3 trials showed large improvements in PTSD symptoms relative to placebo following three MDMA sessions combined with nine integration sessions, ($d = 0.91$ [20]; $d = 0.70$ [21]). At the end of the treatment phase, 67 % [20] and 71.2 % [21] of MDMA condition participants no longer met diagnostic criteria for PTSD and 33 % [20] and 46.2 % [21] met criteria for remission. In 2020, results were published from the first preliminary open trial of MDMA-assisted CBCT [17], providing insight regarding the dyadic approach. Six community couples with one PTSD-diagnosed partner completed a 15-session CBCT protocol delivered in a condensed format combined with two MDMA treatment sessions and two corresponding integration sessions. Both partners received 75 mg or 100 mg of MDMA HCl (plus an optional supplemental half-dose) in the first and second MDMA treatment sessions, respectively. Results showed large improvements in PTSD ($d = 2.10$), with 5 out of 6 patients showing sustained remission of PTSD diagnosis for 6 months. Other measures of patient and partner mental health and relationship functioning also showed medium to large improvements ($ds = 0.64$ to 3.59). A follow-up paper also reported improvements in secondary outcomes including post-traumatic growth, intimacy, and reduced accommodation to PTSD by patients' partners [22].

The current study extends the prior MDMA-assisted CBCT study by using a sample of U.S. military veterans and the shorter 8-session bCBCT version, as well as by developing a protocol for administering MDMA only to the PTSD-diagnosed partner while retaining the dyadic focus and structure of treatment. The Department of Veterans Affairs (VA) is the largest PTSD treatment provider system in the world [23], and previous research has indicated the need to study the efficacy of PTSD treatments specifically within the unique population of U.S. veterans [24]. It is critical to develop a protocol for MDMA-assisted couple-based PTSD treatment that can be implemented in accordance with VA regulations, which prohibit providing medicine to non-veteran partners. There may also be cases outside of the VA setting in which partners of patients with PTSD want to be involved with the treatment, but are unable to take MDMA (e.g., pregnant partners, lack of interest, etc.). Therefore, this protocol tests the benefits of a dyadic MDMA-AT model that may provide a more flexible and scalable pathway for implementation in VA and elsewhere.

The overall objective of this study is to evaluate the preliminary efficacy, safety, tolerability, and acceptability of enhancing bCBCT with two MDMA administrations and two emotion focused integration sessions in a sample of U.S. veterans and their intimate partners seeking PTSD treatment at the VA San Diego Healthcare System (VASDHS). MDMA-assisted bCBCT is not an FDA approved intervention and the safety and efficacy has not been demonstrated. This study will be testing two main hypotheses: (1) PTSD-diagnosed (PTSD+) veterans will demonstrate statistically significant improvement in PTSD symptoms as measured with the Clinician Administered PTSD Scale for DSM-5 (CAPS-5 [25]) and (2) PTSD + veterans and their partners will report statistically significant improvements in couple satisfaction as measured with the Couples Satisfaction Index-32 (CSI-32 [26]).

2. Materials and methods

2.1. Research design

This single site, open-label study assesses the preliminary efficacy, safety, and acceptability of MDMA-assisted bCBCT in a sample of 8 veterans diagnosed with PTSD (PTSD + veteran) and their intimate partners ($N = 16$) within the VASDHS. First, referred veterans undergo a pre-screening, screening, and enrollment period prior to treatment. During pre-screening, a medical chart review for the PTSD + veteran and a phone screen with both the PTSD + veteran and intimate partner are completed. If no exclusion criteria are identified during the phone screen, the dyad is scheduled for the informed consent appointment. After informed consent is collected, eligibility assessments are administered to both the PTSD + veteran and intimate partner. If both are eligible at this stage, the PTSD + veteran is scheduled for medical labs. When medical eligibility is confirmed by the study physician, if necessary, PTSD + veterans start a taper of any prohibited concomitant medications. Once full eligibility has been confirmed, a baseline assessment is completed for both partners and the initial therapy treatment sessions and first MDMA session are scheduled.

Teams of two co-therapists deliver the MDMA-assisted bCBCT intervention, with both therapists facilitating two full-day MDMA sessions for the PTSD + veteran and one therapist facilitating 8 bCBCT sessions with the dyad. The PTSD + veteran is given 80 mg of MDMA HCl with an optional 40 mg supplemental dose in the first session and 100 mg of MDMA HCl with an optional 40 mg supplemental dose in the second session (see Table 1). Similar MDMA HCl doses to those used in

Table 1
Dose regimen of MDMA HCl.

MDMA Session	Initial Dose of MDMA HCl	Supplemental Dose of MDMA HCl[a]	Min-Max Cumulative Dose
1	80 mg MDMA HCl (~68 mg MDMA)	40 mg MDMA HCl (~34 mg MDMA)	80 mg MDMA HCl to 120 mg MDMA HCl (~68 mg–~102 mg MDMA)
2	100 mg MDMA HCl (~84 mg MDMA)	40 mg MDMA HCl (~34 mg MDMA)	100 mg MDMA HCl to 140 mg MDMA HCl (~84 mg–~118 mg MDMA)
Total Cumulative Dose			180–260 mg MDMA HCl (~152 mg–220 mg MDMA)

[a] Unless tolerability issues emerge with the initial dose or the participant declines.

this study have been safely used in a previous pilot CBCT study with a community sample [17]. The intimate partner is invited to be present for part of the MDMA session (unless they decline or it is clinically contraindicated) but does not receive MDMA. The PTSD + veteran receives telephone check-in calls from a clinician every other business day for one week following each MDMA session. In addition to the bCBCT and MDMA sessions, the co-therapists facilitate one preparatory session as well as two emotion-focused integration sessions, one following each MDMA session with the dyad. Outcomes examining PTSD symptom severity and relationship functioning are evaluated at baseline, mid-treatment, post-treatment, 3-months post-treatment, and 6-months post-treatment (see Fig. 1).

2.2. Regulatory

This study protocol was approved by the Institutional Review Board (IRB) and Research and Development Committee of the VASDHS, Food and Drug Administration (FDA), Research Advisory Panel of California (RAPC), and Drug Enforcement Agency (DEA). Due to MDMA's status as a Schedule I substance, an Investigational New Drug (IND) application was required by the FDA and all of these approvals were required before study launch (see Fig. 2).

2.3. Participants

A sample of 8 Veteran patients eligible to receive services from the VASDHS and their intimate partners will be referred to this study by VASDHS providers. The PTSD + veteran receives MDMA-assisted bCBCT in this study and the non-PTSD partner does not receive study medication but is involved in all therapy sessions. Participants must be a) a veteran who meets criteria for PTSD on the CAPS-5, or b) an intimate partner in a committed relationship with such a veteran who is willing to participate in the intervention and who does not meet criteria for PTSD on the PTSD Checklist for DSM-5 (PCL-5 [27]). At the completion of the Screening period, participants must meet all eligibility requirements and the PTSD + veteran must agree to all requested lifestyle modifications (e.g., limits on medications, post-MDMA driving, restrictions on other mental healthcare, etc.) to proceed to the baseline assessment. A couple's enrollment is confirmed once the PTSD + veteran has completed medication tapering (if applicable), continues to agree to all requested lifestyle modifications, and the dyad meets all eligibility criteria (see Table 2 for a complete list).

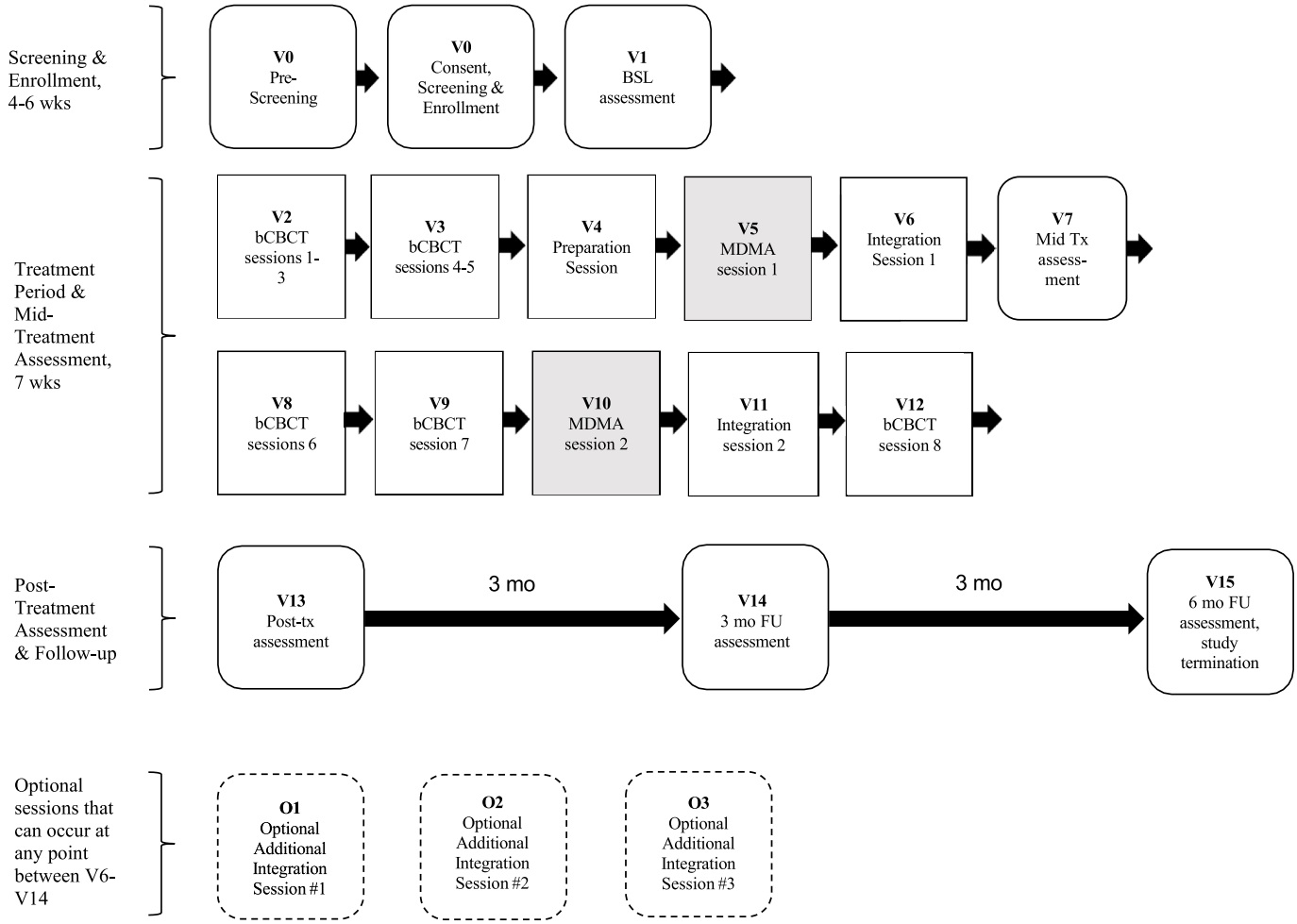
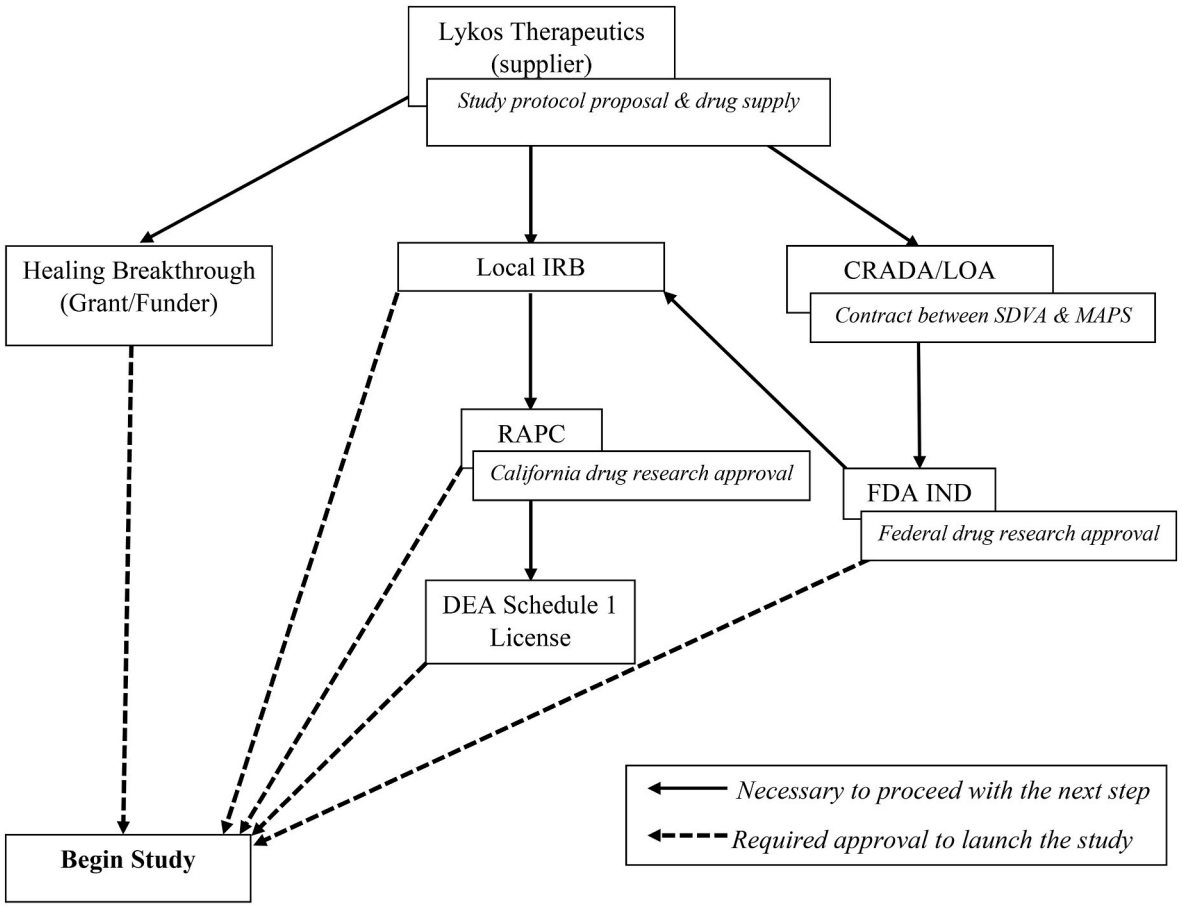


Fig. 1. Study overview.



Note. Lykos Therapeutics was formerly known as MAPS Public Benefit Corporation (PBC). IRB = Institutional Review Board; CRADA = Cooperative Research and Development Agreement; LOA = Letter of Agreement; RAPC = Research Advisory Panel of California; FDA IND = Food and Drug Administration Investigational New Drug; DEA = Drug Enforcement Agency.

Fig. 2. Regulatory overview.

2.4. Intervention

bCBCT. bCBCT is comprised of eight 75-min sessions arranged into two phases. Exercises for skill acquisition and maintenance are included both within and outside of sessions. Phase 1 (sessions 1–2) focuses on the rationale for the therapy and establishing safety within the relationship. Phase 2 (sessions 3–7) focuses on increasing relational satisfaction and undermining PTSD-related distress. Session 8 terminates treatment and prepares the couple for relapse prevention. In this study, bCBCT sessions 1–3 and sessions 4-5 are massed (i.e., the content of the initial three sessions is combined into one longer session and the content of sessions four and five are combined into one longer session) while the remaining sessions are conducted on a weekly basis.[1]

Preparatory session content. Following bCBCT massed sessions 4-5, a 90-min preparation session is provided consistent with the MAPS/Lykos adherence protocol, which includes psychoeducation about MDMA and space for the couple to ask questions about the treatment protocol in the presence of both therapy providers. During this session, in addition to establishing a therapeutic alliance and trust, the therapists provide both partners guidance on what to expect during the MDMA sessions, how to respond to the memories and feelings that could arise during treatment, as well as how the non-dosed partner can be involved in the sessions.

MDMA sessions. MDMA sessions occur within the sleep clinic space of the Jennifer Moreno VA Medical Center. This space is equipped with a bed or space for a reclining chair and access to medical support if needed. The PTSD + veteran's drug tox screen and blood alcohol level (before session only), temperature, blood pressure, and pulse are collected and confirmed to be in safe ranges before, during, and at the end of the MDMA sessions. A study physician is on call for consultation and intervention if needed. Administration of MDMA occurs in the morning and the PTSD + veteran is required to stay on site (approx. 8 h) and then have planned transportation home with a prearranged driver, typically the intimate partner. Consistent with the Lykos Therapeutics model [28], during MDMA sessions, the therapists create a sense of safety and support to facilitate an unfolding of the veteran's innate

[1] Previously only bCBCT sessions 1-3 were massed and bCBCT sessions four and five were conducted on a weekly basis following the first MDMA and Integration sessions. Based on the investigators' judgement and feedback from initial study participants, the order of the treatment sessions was modified.

Table 2
Eligibility criteria.

Criterion	Participant	
Inclusion	Veteran	Partner
Age 18 or older	X	X
Be in a committed relationship and cohabitating for at least 12 months	X	X
Fluent in speaking and reading English	X	X
Willing to commit to medication dosing, therapy sessions, follow-up sessions, completing evaluation instruments, and all necessary telephone contact.	X	X
Able to swallow pills	X	
Agree to have study visits recorded, including MDMA and bCBCT sessions, and be aware that Independent Rater assessments for all sessions will occur	X	X
Provide a contact (relative, spouse, close friend, or other support person) who is willing and able to be reached by the investigators in the event of a participant becoming suicidal or unreachable	X	
Agree to inform the investigators within 48 h of any new medical conditions or procedures	X	X
If able to become pregnant (i.e., assigned female at birth, fertile, following menarche and until becoming post-menopausal unless permanently sterile), must have a highly sensitive negative pregnancy test at study entry and prior to each MDMA session, and must agree to use adequate birth control through 10 days after the last MDMA session. Adequate birth control methods include intrauterine device (IUD), injected, implanted, intravaginal, or transdermal hormonal methods, abstinence, oral hormones plus a barrier contraception, vasectomized sole partner, or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (i.e., condom plus diaphragm, condom or diaphragm plus spermicide, oral hormonal contraceptives plus spermicide or condom)	X	
Agree to lifestyle modifications and comply with requirements for fasting and refraining from certain medications prior to MDMA sessions	X	
At Pre-Screening, have at least moderate PTSD symptoms in the last month based on PCL-5 total score of 40 or greater (index)	X	
May have well-controlled hypertension that has been successfully treated with anti- hypertensive medicines if they pass additional screening to rule out underlying cardiovascular disease	X	
May have asymptomatic Hepatitis C virus (HCV) that has previously undergone evaluation and treatment as needed	X	
At Screening, have at least moderate PTSD per CAPS-5 and symptoms in the last month constituting a CAPS-5 Total Severity Score of 28 or greater (index)	X	
May have alcohol or substance use disorder if participant is not in withdrawal or requiring detox. Participants/couples must have a plan, agreed upon by investigator, therapy team, and study physician, to reduce use of alcohol or other substances and to manage symptoms without self-medicating. Enrollment will require that, in the judgment of the investigator, therapy team, and study physician, the plan for decreasing substance use is realistic and has a good chance of succeeding to prevent substance use from impacting the safety or effectiveness of the investigational treatment	X	X
May have a history of or current Diabetes Mellitus (Type 2) if additional screening measures rule out underlying cardiovascular disease, if the condition is judged to be stable on effective management, and with approval by the study physician	X	
May have hypothyroidism if taking adequate and stable thyroid replacement medication	X	
May have a history of, or current, glaucoma if approval for study participation is received from an ophthalmologist	X	
Not enroll in any other interventional clinical trials during the duration of the study, and commit to medication dosing, therapy, and study procedures	X	X
Exclusion	Veteran	Partner
Not able to give adequate informed consent	X	X
Currently engaged in compensation and pension (C&P) litigation whereby financial gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorders	X	X
Likely, in the investigator's opinion and via assessment period, to be re-exposed to their index trauma or other significant trauma, lack social support, or lack a stable living situation	X	X
Have used Ecstasy (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the first MDMA session	X	
Have any current problem which, in the opinion of the investigator or study physician, might interfere with participation due to it impacting the participant's safety and/or ability to participate in the protocol	X	X
Have hypersensitivity to any ingredient of the MDMA HCl	X	
Have received Electroconvulsive Therapy (ECT) within 12 weeks of enrollment	X	
Have a history of or a current primary psychotic disorder assessed via the DIAMOND and clinical interview	X	X
Have a history of or current Bipolar 1 disorder, Bipolar 2 disorder, or manic episode assessed via the DIAMOND and clinical interview	X	
Have a current eating disorder with active purging assessed via DIAMOND and clinical interview	X	
Have current major depressive disorder with psychotic features assessed via DIAMOND	X	X
Have current panic disorder assessed via DIAMOND	X	
Have a current alcohol or substance use disorder other than caffeine or nicotine that the investigators, therapy team, and/or study physician judge to be a safety concern for enrollment in the study or that could interfere with the therapeutic process or with other aspects of study participation. Any participant who is not able to agree or adhere to a plan to reduce use and manage symptoms will not be enrolled.	X	X
Present with current serious suicide risk, as determined through psychiatric interview, responses to C-SSRS (scores of 4 or greater), and clinical judgment of the investigator; however, history of suicide attempts is not an exclusion. Any participant who is likely to require hospitalization related to suicidal ideation and behavior, in the judgment of the investigator, will not be enrolled. Any participant presenting with the following on the pre-screen C-SSRS will be excluded: a. Suicidal ideation score of 4 or greater within the last 6 months of the assessment at a frequency of once a week or more b. Any suicidal behavior, including suicide attempts or preparatory acts, within the last 6 months of the assessment. Participants with non-suicidal self-injurious behavior may be included if approved by the study physician	X	X
Report intimate partner violence or severe relationship aggression, as defined by meeting either of the following criteria, that the investigators and/or therapy team judge to be a safety concern for enrollment in the study of that could interfere with the therapeutic process or with other aspects of study participation: a. A score of $\geq$7 on the E-HITS screening tool b. A score of "severe" on the Psychological Aggression scale of the Revised Conflict Tactics Inventory (CTS-2)	X	X
Would present a serious risk to others as established through clinical interview and if necessary, discussion with treating psychiatrist	X	X
Require ongoing concomitant therapy with a psychiatric medication other than the exceptions described in protocol section on Concomitant Therapy	X	
Have a history of any medical condition that could make receiving a sympathomimetic drug harmful because of increases in blood pressure and heart rate. This includes, but is not limited to, a history of myocardial infarction, cerebrovascular accident, or aneurysm. Participants with other mild, stable chronic medical problems may be enrolled if the study physician and PI agree the condition would not significantly increase the risk of MDMA administration or be likely to produce significant symptoms during the study that could interfere with study participation or be confused with side effects of the MDMA. Examples of stable medical conditions that could be allowed include, but are not limited to Diabetes Mellitus (Type 2), Human Immunodeficiency Virus (HIV) infection, Gastroesophageal Reflux Disease (GERD), etc. Any medical disorder judged by the investigator to significantly increase the risk of MDMA administration by any mechanism would require exclusion.	X	
Have a diagnosis of uncontrolled hypertension defined by the American Heart Association as repeated readings of $\geq$140 mm of Mercury [mmHg] systolic or $\geq$ 90 mmHg diastolic	X	
Have a history of ventricular arrhythmia at any time, other than occasional premature ventricular contractions (PVCs) in the absence of ischemic heart disease	X	

(*continued on next page*)

Table 2 (*continued*)

Criterion	Participant
Have Wolff-Parkinson-White syndrome or any other accessory pathway that has not been successfully eliminated by ablation	X
Have a history of arrhythmia, other than premature atrial contractions (PACs) or occasional PVCs in the absence of ischemic heart disease, within 12 months of screening. Participants with a history of atrial fibrillation, atrial tachycardia, atrial flutter or paroxysmal supraventricular tachycardia or any other arrhythmia associated with a bypass tract may be enrolled only if they have been successfully treated with ablation and have not had recurrent arrhythmia for at least one year off all antiarrhythmic drugs and confirmed by a cardiologist	X
Have a marked Baseline prolongation of QT/QTc interval. For purposes of eligibility, this is defined as repeated demonstration of a QT interval corrected using Fridericia's formula [QTcF] >450 ms [ms].	X
Have a history of additional risk factors for Torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)	X
Require use of concomitant medications that prolong the QT/QTc interval during Sessions. Refer to protocol section on Concomitant Medications	X
Have symptomatic liver disease or have significant liver enzyme elevations	X
Have history of hyponatremia or hyperthermia	X
Weigh less than 48 kg (kg)	X
Are pregnant or nursing or are able to become pregnant and are not able/willing to practice an effective means of birth control	X
Have engaged in ketamine-assisted therapy or used ketamine within 12 weeks of enrollment	X
Have any preexisting conditions that can affect renal functioning	X

Note. PCL-5 = PTSD Checklist for DSM-5. CAPS-5 = Clinician Administered PTSD Scale for DSM-5. DIAMOND = Diagnostic Interview for Anxiety, Mood, and Obsessive Compulsive and Related Neuropsychiatric Disorders. C-SSRS = Columbia Suicide Severity Rating Scale. E-HITS = Extended - Hurt, Insulted, Threaten, Scream.

healing ability, thought to be catalyzed by MDMA. These sessions are non-directive in that the therapists do not introduce new concepts or teach new skills from bCBCT (or any other therapy). The PTSD + veteran is encouraged to alternate between periods of going inward to explore their inner experience, optionally aided using eyeshades and specially selected music, balanced with communication with the therapists and/or their partner, if present. The MDMA sessions are expected to facilitate trauma processing and yield salient trauma-related content that will be explored both within the MDMA sessions and in subsequent integration and bCBCT sessions [17]. The partner is encouraged to join the end of the MDMA sessions, unless doing so is determined to be inappropriate based on clinical judgment or couple preference. During this time, veterans may share insights or feelings related to their MDMA experience. As necessary, the therapists may assist the couple in applying communication skills they learned in bCBCT sessions to effectively share their experiences with each other during the MDMA sessions. One of the two therapists is also available to provide brief individual support for partners in a separate room if needed.

Couple-based emotion focused integration sessions. The 90-min dyadic emotion focused integration sessions occur the day after each of the MDMA sessions. Couple-based emotion focused integration sessions are informed by Integrative Behavioral Couple Therapy (IBCT), an evidence-based couple therapy in wide use throughout the VA healthcare system [29]. In particular, integration sessions use the IBCT technique of empathic joining to support couples in developing a deeper understanding of and connection with one another following the MDMA sessions. As couples process the insights experienced during the MDMA sessions, therapists use the IBCT technique of unified detachment to gently highlight and elucidate behaviors and feelings that are a result of and a reaction to PTSD, while validating each person's natural emotional reactions. The therapists specifically focus on eliciting more vulnerable emotions (e.g., sadness, fear, shame, guilt) and assist the couple in validating one another to strengthen secure attachment, which may have been injured because of PTSD-related anger, emotional numbing, or avoidance. Up to three additional couples-based integration sessions may be completed during the period between the first MDMA session and the 3-month follow-up assessment.

Training and fidelity. MDMA-assisted bCBCT is provided by clinicians who have a Master's degree or higher and a minimum of 2 years of clinical experience with couples and PTSD. Treatment providers were trained to administer both CBCT and MDMA-AT. MDMA-AT training consisted of completing the MDMA Therapy Training Program, either through the 40 h in-person retreat with the 60 h of coursework, reading, and activities completed prior to the retreat, or the 100 h fully online training program.

All treatment sessions are audio and/or videotaped to monitor continued fidelity to the protocol and for ongoing weekly consultation with a trained supervisor. Aside from weekly consultation to assure ongoing treatment fidelity, treatment adherence and competence are determined by an independent rater trained on the protocol.

2.4.1. Assessments

The PTSD + veteran and intimate partner are assessed at five timepoints throughout the study: baseline, mid-treatment, post-treatment, 3-months post-treatment, and 6-months post-treatment. In addition to the primary (PTSD) and secondary (relationship satisfaction) outcomes, the PTSD + veteran and intimate partner complete assessments for exploratory outcomes such as emotion regulation, depressive symptoms, sleep quality, and self-reported PTSD symptom severity. The post-treatment assessment also includes a qualitative interview where both the PTSD + veteran and partner have the opportunity to give feedback about their experiences in the treatment. Self-report surveys are completed in-person on paper, through Qualtrics surveys, or on fillable PDF forms, depending on participant preference. The CAPS-5 is administered at each of the main assessment timepoints by an Independent Evaluator. See Table 3 for a full breakdown of assessments.

2.4.2. Analytic plan

Treatment of missing data. Missing data will be handled using full information maximum likelihood (FIML) analyses and/or multiple imputation prior to analysis.

Power and sample size. This open-label preliminary study is not powered to detect statistically significant effects. The main purpose of the sample size of 8 couples is to establish preliminary efficacy, safety, and acceptability preceding a larger randomized controlled trial. Preliminary effectiveness will be derived primarily from estimates of within-person effect size capturing change in symptoms from baseline to mid and post, as well as maintenance of change from post through 3- and 6-month follow-up. Effect sizes will be calculated based on growth curve estimated slopes and/or model-implied estimated means and standard deviations at each assessment, using Cohen's d for within-group change (i.e., pooled standard deviations and a repeated-measures correction). A secondary source of information about preliminary effectiveness will be statistical significance of slopes in growth curve analyses, representing change in symptoms/functioning over time, using all available data from all waves; power analysis suggests the ability to detect a medium-to-large effect size (approx. $d \geq .65$) of change in PTSD symptoms during the treatment period.

Main analyses for the primary outcome (change in PTSD symptom total severity score assessed by CAPS-5) will use the modified intent-to-treat (mITT) sample of PTSD + veteran participants who completed at least one MDMA session (partners will not provide CAPS-5 data). Analysis will be conducted following the final 6-month assessment at the conclusion of the study. Reliable and clinically significant change will be

Table 3
Description of study measures.

Domain	Measure	Description and Psychometrics	Timepoint	Veteran	Partner
Eligibility Measures					
Intimate Partner Violence	Extended Hurt, Insult, Threaten, Scream screening tool (E-HITS [40])	5-item self-report survey. Good reliability and validity. High internal consistency (.90).	Pre-eligibility	X	X
Alcohol Use	Alcohol Use Disorders Identification Test (AUDIT [41])	10-item self-report test used to detect alcohol use disorders. High internal consistency (.91).	Pre-eligibility	X	X
Drug Use	Drug Use Disorders Identification Test (DUDIT [42])	11-item self-report measure used to detect substance use disorders. High internal consistency (.80).	Pre-eligibility	X	X
Comorbid psychiatric disorders	Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND [43])	60-min semi-structured clinical interview evaluating current and lifetime DSM-5 diagnoses. Interrater and test-retest reliability range from good to excellent.	Eligibility	X	X
Suicidality	Columbia Suicide Severity Rating Scale (C-SSRS [44])	Assesses suicidal ideation, ideation intensity, and behaviors during a clinical trial. Excellent internal consistency (.93-.94). Partner completes for pre-eligibility.	Pre-eligibility, All	X	X (Pre-eligibility)
Primary Outcome Measure					
Clinician-rated PTSD symptoms	Clinician-Administered PTSD Scale for DSM-5 (CAPS-5 [25])	20-item diagnostic interview assessing severity of four PTSD-related symptom clusters: re-experiencing, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity. The evaluator rates responses on a 5-point Likert scale (0 = Absent to 4 = Extreme/Incapacitating). Total scores range from 0 to 80 with higher scores indicating greater severity.	Eligibility, All	X	
Secondary Outcome Measure					
Relationship satisfaction	Couples Satisfaction Index (CSI-32 [26])	32-item self-report survey measuring romantic relationship satisfaction. The first item measures the overall happiness of the relationship on a 7-point scale (0 = Extremely unhappy to 6 = Perfect). The other 31 items capture satisfaction, quality, and happiness of the relationship on 6-point scales (0–5) with varying response options. Total CSI-32 scores range from 0 to 161 with higher scores indicating greater relationship satisfaction. Scores below 104.5 indicate clinical relationship distress.	All	X	X
Exploratory Measures					
Self-reported PTSD symptoms	PTSD Checklist for DSM-5 (PCL-5 [27,45])	20-item self-report questionnaire assessing presence and severity of PTSD symptoms. The participant rates their distress caused by PTSD symptoms on a 5-point Likert scale (1 = Not at all to 5 = Extremely). Total scores range from 0 to 80, with higher scores indicating greater severity. High internal consistency (.96). Partners will complete the collateral version of the PCL-5 (PCL-C) starting at Baseline.	Pre-eligibility, All	X	X
Emotion regulation	Emotional Regulation Questionnaire (ERQ [46])	10-item self-report questionnaire assessing use of cognitive reappraisal and expressive suppression to alter emotion. Participants respond using a 7-point Likert scale (1 = Strongly disagree to 7 = Strongly agree). Higher scores indicate higher use of cognitive reappraisal and/or expressive suppression.	All	X	X
Adverse childhood events	Adverse Childhood Events Scale (ACES [33,34])	10-item self-report survey assessing childhood stress. Participants indicate exposure to different kinds of abuse with yes/no responses, and answer with "1" if the abuse happened often. Higher scores indicate greater exposure to childhood stressors.	Baseline	X	X
Relationship conflict	Short Form of the Revised Conflict Tactics Scale (CTS-2S [47])	Self-report inventory with 10 paired items assessing conflict and intimate partner violence across 5 domains. The participant evaluates their own actions and the partner's actions for each of the 10 items, hence 20 items total. Participants respond using an ordinal scale from 0 (This has never happened) to 6 (More than 20x in the past year). Good concurrent validity (r = .77 for respondent, r = .69 for partner).	All	X	X
Depressive symptoms	Beck Depression Inventory II (BDI-II [48])	21-item self-report measure of depression symptom severity. Participants rate the severity of each symptom on a scale of 0–3. Total scores range from 0 to 63, with higher scores indicating higher severity.	All	X	X
Sleep	Pittsburgh Sleep Quality Index (PSQI [49])	19-item self-report questionnaire assessing 7 subcategories of sleep quality over the last month. Participants respond using a combination of Likert scales (from 0 to 3) and open-ended questions that are later converted to scaled scores. Higher total scores indicate greater sleep disturbance.	All	X	X
Trauma exposure	Life Events Checklist for DSM-5 (LEC-5 [32])	17-item self-report survey assessing exposure to potentially traumatic events. Participants check off the type of exposure for each event (Happened to me, Witnessed it, Learned about it, Part of my job, Not sure, Doesn't apply).	Eligibility	X	X
Posttraumatic growth	Posttraumatic Growth Inventory (PTGI [50])	21-item self-report measure assessing level of posttraumatic growth across 5 subscales in adults who have experienced trauma. Participants respond using a 6-point Likert scale (1 = I did not experience this change as a result of my crisis, to 6 = I	All	X	

(*continued on next page*)

Table 3 (*continued*)

Domain	Measure	Description and Psychometrics	Timepoint	Veteran	Partner
		experienced this change to a very great degree as a result of my crisis). Total scores range from 1 to 126.			
Symptom accommodation	Significant Others' Response to Trauma Scale (SORTS [51])	28-item self-report measure of a partner's accommodating behaviors for a patient's PTSD symptoms. Participants rate the frequency and intensity of 14 accommodating behaviors using a scale of 0–4. Higher scores indicate greater accommodation.	All		X
Treatment expectations	Stanford Expectations of Treatment Scale [52]	10-item self-report questionnaire assessing a patient's feelings about their upcoming treatment. The first 6 items are rated on a 7-point Likert scale (1 = strongly disagree, to 7 = strongly agree). Items 7–9 are open-ended. Item 10 is a yes/no response. The scale yields a score for positive expectancy and negative expectancy.	Baseline	X	
Tolerability and Acceptability Measures					
Satisfaction with care	Client Satisfaction Questionnaire (CSQ-8 [53])	Satisfaction with healthcare and services received. Participants respond using a Likert scale from 0 to 3 with varying response options for each question. Higher scores indicate higher satisfaction.	Post-treatment	X	X
Acceptability of Care	Audiotaped Qualitative Interview	Open ended questions assessing general acceptability of participant and dyad experience. Recordings will be coded for themes.	Post-treatment	X	X

Note. "All" includes the five assessment timepoints: baseline, mid-treatment, post-treatment, 3-months post-treatment, and 6-months post-treatment. The CAPS-5 is administered for eligibility during the Screening visit, and if there is no delay of more than 30 days between the Screening visit and first treatment visit, then it will be used as the Baseline CAPS-5.

calculated for each participant using the method described by Jacobson and Truax (1991 [30]), which uses sample-specific dispersion parameters and is considered best practice in clinical psychology.

Main analyses for the secondary outcome (relationship satisfaction assessed by the CSI-32) will use the mITT sample of both PTSD + veterans and partners. Because this outcome involves dyadic data, it will be analyzed using a two-intercept dyadic model, which provides separate estimates of intercepts and slopes for veterans and partners while also accounting for non-independence in couples' data using appropriate covariance matrices [31]. The remaining analysis methods, including sensitivity analyses, are the same as for the primary outcome.

Main and sensitivity analyses for all exploratory secondary outcomes (see Table 2) will use the same methods as the secondary outcome. Additionally, moderation analyses will explore whether the presence of secondary traumatic stressors (as assessed by the Life Events Checklist for DSM-5 [LEC- 5 [32]]) and/or adverse childhood experiences (as assessed by the Adverse Childhood Experiences [ACE] scale [33,34]) moderate the degree of improvement in CAPS-5 PTSD severity scores during the study. Following the main analyses, sensitivity analyses will be conducted with the treatment completer sample to determine whether any differences in outcomes exist as a function of treatment completion.

3. Discussion

This paper describes the protocol and methodology of a single site, open-label study evaluating the enhancement of bCBCT with two MDMA administrations and two emotion focused integration sessions in a sample of U.S. veterans and their intimate partners seeking PTSD treatment. PTSD symptoms such as anger, hypervigilance, avoidance, and emotional numbing exert a particularly deleterious effect on intimate relationship functioning, which negatively impacts overall mental and physical health, as well as quality of life, for the dyad. Veteran couples experience unique stressors, such as deployment and reintegration cycles [35] combat trauma, and military sexual trauma, that are associated with intimate partner violence [36], sexual dysfunction [37] and relationship separation [38]. Given the interpersonal nature of PTSD, veterans and their intimate partners are particularly in need of treatments that address PTSD symptoms and relationship distress simultaneously. bCBCT is one such couple-based approach which has been supported to improve both PTSD symptoms and relationship functioning while increasing treatment retention in a large clinical trial of U.S. veterans [16].

Relationship-focused outcomes still require attention in couple-based interventions such as bCBCT, beyond the established PTSD symptom improvements [16]. MDMA has the potential to reduce avoidance and emotional numbing, thus allowing veterans to share and process their trauma and understand and validate their partners' experience. MDMA may improve emotional connection, communication, and intimate bonding and strengthen the existing benefits of couple-based PTSD interventions, which in turn may improve independent and relationship functioning for the dyad.

Several aspects of this protocol were shaped specifically to fit the unique needs of the VA healthcare system. This protocol uses a patient-dosing model, in which only the PTSD + veteran is given MDMA, due to the VA only having the legislative authority to treat veterans. This is in contrast with the couple-dosing model used in the study of MDMA-assisted CBCT with a community sample in which both the PTSD+ and non-PTSD partners received MDMA [17]. A protocol that only doses the individual with PTSD but still involves their partner in the treatment would allow for regulatory compliant VA implementation and access to MDMA-bCBCT by couples for whom the intimate partner is not interested in taking MDMA or is unable to do so (e.g., pregnancy, underlying medical contraindication, use of a contraindicated medication). At present, it is unclear whether administering MDMA only to the PTSD-diagnosed partner will result in reduced effect sizes for improvements in relationship functioning relative to the couple-dosing study; data from this pilot trial will inform future head-to-head comparisons to answer this empirical question. We propose that it will be useful to have a variety of treatment models to suit different settings, populations, and individual preferences across a variety of healthcare systems.

The information gained from this study may help inform future VA clinical practice guidelines regarding the use of investigational MDMA-assisted therapy to treat PTSD in veterans, if FDA approved. Although MDMA is currently classified as a Schedule I substance by the DEA, if it is FDA approved for the treatment of PTSD, it will be reclassified to a less restrictive Schedule, potentially within the next year [39]. In the case that the Schedule I status is removed, MDMA will become more accessible for use in research and clinical practice, and the VA will need additional data on safety and effectiveness of MDMA-AT to guide implementation efforts. The MDMA-AT model studied in the Phase 3 clinical trials is comprised of three non-drug preparatory sessions, two to three MDMA sessions, and 12 non-drug integration sessions [28]. The pooled Phase 3 trials that have been conducted with the MDMA-AT

protocol included a sample of 81 % non-veterans (or 19 % veterans). Efforts are underway to examine the combination of MDMA with existing evidence-based psychotherapies for PTSD, such as CBCT, cognitive processing therapy (CPT; ClinicalTrials.gov Identifier: NCT05067244), and prolonged exposure (PE; ClinicalTrials.gov Identifier: NCT05746572). The current study will contribute to this growing body of research and help inform clinical practice guidelines, creating a foundation for future trials comparing MDMA-bCBCT with other MDMA-AT protocols.

4. Conclusion

This MDMA-assisted bCBCT protocol pilots the development of a brief treatment that addresses the cyclical relationship between PTSD symptom severity and relationship functioning. By combining MDMA-AT with a couple-based psychotherapy for PTSD, this study will provide valuable information for how relationship outcomes can be enhanced through augmentation of an established dyadic PTSD intervention. With increasing evidence supporting the clinical use of MDMA-assisted therapy for PTSD, this pilot assessing the preliminary effectiveness, safety, and acceptability of MDMA-bCBCT will inform the development of scalable models that can be implemented within the VA healthcare system.

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L.A. Morland: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft. **D. Perivoliotis:** Investigation, Supervision, Writing – original draft. **T.R. Wachsman:** Project administration, Writing – original draft. **A. Alam:** Project administration, Supervision. **K. Knopp:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **C. Khalifian:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **D. Ramanathan:** Project administration, Supervision. **B.E. Chargin:** Project administration, Writing – original draft. **A.W. Bismark:** Supervision, Writing – original draft. **S. Glynn:** Writing – original draft. **C. Stauffer:** Methodology, Writing – original draft. **A.C. Wagner:** Supervision, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Drs. Dimitri Perivoliotis and Christopher Stauffer have both been adherence raters with the Multidisciplinary Association for Psychedelic Studies (MAPS). Drs. Anne Wagner and Christopher Stauffer have been MAPS fidelity raters and MDMA-AT trainers. MAPS PBC is now known as Lykos Therapeutics.

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