Scaling Up: Multisite Open-Label Clinical Trials of MDMA-Assisted Therapy for Severe Posttraumatic Stress Disorder

Julie B. Wang1, Jessica Lin1,2, Leah Bedrosian1, Allison Coker1,3, Ilsa Jerome1, Allison Feduccia4, Alia Lilienstein5, Charlotte Harrison1, Elizabeth Heimler1, Michael Mitroeff1,3,6, Annie Mitroeff3, Marcela Ot’alora G.3,7, Bruce Poulter3,7, Shannon Carlin1,3, Rebecca Matthews1, Berra Yazar-Klosinski5, Amy Emerson1, and Rick Doblin5

Abstract

Background: Posttraumatic stress disorder (PTSD) is a debilitating mental health condition associated with serious adverse health outcomes and functional impairment. Previous MDMA-assisted therapy (MDMA-AT)

1MAPS Public Benefit Corporation (MAPS PBC), San Jose, CA, USA
2MDMA Therapy Training Program, San Jose, CA, USA
3University of California, San Francisco, CA, USA
4Psychedelic Support Inc., Santa Cruz, CA, USA
5Multidisciplinary Association for Psychedelic Studies (MAPS), San Jose, CA, USA
6Medical University of South Carolina, Charleston, SC, USA
7Aguazul-Bluewater Inc., Boulder, CO, USA

Corresponding Author:
Julie B. Wang, MPH, PhD, MAPS Public Benefit Corporation (MAPS PBC), 3141 Stevens Creek Boulevard #40547, San Jose, CA 95117, USA.
Email: juliewang@mapsbcorp.com
studies have shown promising results in single site studies. Two open-label studies tested this modality in multisite clinical trials to assess the feasibility of scaling this manualized therapy across 14 North American sites. **Method:** Cotherapist dyads were trained in the manualized MDMA-AT protocol and administered three experimental sessions 3 to 5 weeks apart among participants with severe PTSD. Cotherapist dyads were provided clinical supervision and evaluated for protocol adherence by centralized raters. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) assessed change in symptoms severity. **Results:** Adherence rating scores were high across cotherapist dyads ($M = 95.08\%$, $SD = 3.70\%$) and sites ($M = 95.23\%$, $SD = 2.20\%$). CAPS-5 scores decreased following 3 MDMA-AT sessions at 18 weeks post baseline ($\Delta M = -29.99$, $\Delta SD = 13.45$, $p < .0001$, $n = 37$, Cohen’s $d = 2.2$, confidence interval [1.97, 2.47]). MDMA was well tolerated. **Conclusions:** These findings corroborate previous results that MDMA-AT can achieve significant improvements in PTSD symptom severity and demonstrate scalability of manualized therapy across clinic sites in the United States and Canada.

**Keywords**
3,4-methylenedioxymethamphetamine, MDMA, psychotherapy, MDMA-AT, posttraumatic stress disorder, PTSD, efficacy, training

**Introduction**
Posttraumatic stress disorder (PTSD) is a serious mental health condition that can result from surviving a traumatic event and interfere with work performance, interpersonal relationships, and functioning, creating a significant burden on a person’s daily life. PTSD affects 4% to 5% of the population worldwide and between 13.5% and 17% of veterans (Dursa et al., 2014; Hoge et al., 2004; Kessler et al., 2004). People with PTSD are at greater risk of suicide and other comorbidities, including increased chronic pain and cardiovascular disease (Baker et al., 1997; Conner et al., 2014; Edmondson & Cohen, 2013). Available treatments for PTSD include various forms of trauma-focused talk therapies and two selective serotonin uptake inhibitors (paroxetine and sertraline) that are approved by the U.S. Food and Drug Administration (Bradley et al., 2005; Cloitre et al., 2012; Ipser et al., 2006; Lee et al., 2016). However, patients often do not respond to or tolerate available treatments, discontinue treatment, and/or experience relapse, which warrants further investigation into novel treatments (Goetter et al., 2015; Lee et al., 2016).
3,4-Methylenedioxymethamphetamine (MDMA) is a monoamine releasing phenethylamine which possesses unique pharmaco-therapeutic properties that may enhance traditional talk therapy by making trauma memory processing more tolerable (Feduccia et al., 2018). MDMA has been proposed to augment therapy through one or more of these processes: reducing fear in the face of emotionally distressing memories, fear-extinction learning, greater compassion for self and others, increased interpersonal affiliation, and an enhanced therapeutic alliance (Carhart-Harris et al., 2014; Gabay et al., 2019; Hysek et al., 2014; Young et al., 2015). MDMA-assisted therapy (MDMA-AT) typically consists of a cotherapist dyad who provides participants with talk therapy in preparatory sessions, followed by active MDMA-AT sessions, and each with several associated integrative sessions. Early Phase 2 trials of MDMA-AT for treatment of PTSD have shown significant and even potentially long-term reductions in PTSD symptom severity (Mithoefer et al., 2011; Mithoefer et al., 2013; Mithoefer et al., 2019; Oehen et al., 2013; O’atalora et al., 2018). Specifically, pooled analysis of participants across six Phase 2 trials indicated that nearly 67% no longer met PTSD criteria at least 12 months after their last active MDMA-AT treatment (Jerome et al., 2020). Study limitations however including variations in study design and methods require corroboration of these results.

In preparation for the Phase 3 trials, the sponsor conducted two multisite open-label lead-in studies of MDMA-AT to train and select therapists across the United States (MP16 study) and Canada (MP17 study). The studies provided new cotherapist dyads the opportunity to administer MDMA-AT under clinical supervision. To maximize treatment fidelity across multiple study sites, adherence raters systematically evaluated the new cotherapist dyads’ adherence to the therapy manual under clinical supervision by the therapy training team. Cotherapist dyads were cleared to participate in Phase 3 trials following administration and evaluation of MDMA-AT under clinical supervision. The primary aim of the present study was to examine treatment efficacy and safety across multiple clinic sites and therapy dyads. The analysis combined data from the two multisite open-label lead-in studies to assess MDMA-AT treatment adherence, PTSD symptom reduction, and treatment safety.

**Method**

**Participants and Study Design**

Across 12 U.S. study sites and 2 Canadian sites, a total of 37 unique cotherapist dyads provided MDMA-AT for treatment under clinical supervision
among participants with severe PTSD. Study sites included private practice clinics in Charleston (SC), Boulder (CO), Fort Collins (CO), Los Angeles (CA), New Orleans (LA), San Francisco (CA), New York (NY), Boston (MA), Vancouver (British Columbia, Canada), and Montreal (Quebec, Canada); and the University of California, San Francisco (UCSF, CA), University of Connecticut (UC, CT), University of Wisconsin Madison (WI), and New York University (NY). Sites ranged from one to four cotherapist dyads, and each unique dyad treated one participant. Study participants were recruited from November 2017 to March 2019 via internet advertisements, provider referrals, and by word-of-mouth. Study sites conducted telephone screenings to assess initial eligibility prior to inviting participants on-site for further screening.

Eligibility criteria included confirmation of severe PTSD, which was defined as having a CAPS-5 Total severity score of 35 or greater (Weathers et al., 2017). Participants were asked to agree to the study protocol including lifestyle modifications. Exclusionary criteria included past or present psychotic disorder, Bipolar I disorder, pregnancy or lactation, current diagnosis of a substance use disorder (except for caffeine or nicotine), uncontrolled hypertension, weighing less than 48 kg, and other medical conditions contraindicated for MDMA such as cardiac conditions or cerebrovascular disease. Participants who were at serious risk of suicide or posed a risk to others were also ineligible. Participants with controlled hypertension underwent additional screening to confirm the absence of clinically significant underlying cardiovascular disease. Participants who were enrolled into the study were asked, under the supervision of a physician, to taper off psychiatric medications and any other medications that might have interfered with the effects or metabolism of MDMA.

Treatment

The MDMA-AT therapeutic approach is detailed in the “Manual for MDMA-Assisted Therapy in the Treatment of PTSD,” published by MAPS (MDMA Treatment Manual, available at maps.org/treatment-manual). MDMA-AT was conducted over a duration of 9 to 15 weeks. Treatment periods consisted of three preparatory sessions before the first administration of MDMA and three MDMA experimental sessions, in which each session was followed by three integrative sessions. In preparatory sessions, participants met with their cotherapist dyad to develop therapeutic rapport, discuss their PTSD symptoms, and the upcoming MDMA-AT session. Therapists provided information on what to expect during the MDMA-AT sessions, including drug effects and strategies to manage any challenging experiences that may emerge.
Participants were offered a total of three open-label MDMA-AT sessions that were scheduled 3 to 5 weeks apart. In the first experimental session, participants were administered a divided dose of 80 mg MDMA initial + 40 mg MDMA supplemental (United States) or 100 mg MDMA initial + 50 mg MDMA supplemental (Canada). Supplemental doses were administered 1.5 to 2 hours after the initial dose. The purpose of the supplemental dose was to enable a longer period to process trauma during MDMA-AT sessions without significantly impacting the intensity of pharmacodynamic effects. The second and third experimental sessions utilized slightly higher divided doses of 120 mg MDMA + 60 mg MDMA (United States) and 125 mg MDMA + 62.5 mg MDMA (Canada). The nominal difference in MDMA doses between countries was due to drug availability, where U.S. participants received racemic MDMA synthesized by David Nichols, PhD (Purdue University) and Canadian participants received racemic MDMA from Lipomed AG Switzerland.

Therapy during MDMA-AT sessions consisted of periods of introspection alternating with periods of communication between the participant and the cotherapist dyad. Participants were encouraged to remain with trauma-related memories, feelings, and/or thoughts as the cotherapist dyad provided support. MDMA-AT sessions lasted 6 to 8 hours and ended after drug effects returned to baseline. Participants remained overnight at the site with a night attendant, except for four participants who did not stay overnight as part of a safety substudy. After each MDMA-AT session, participants received several follow-up visits, including three integrative sessions, where therapists facilitated participants’ continued emotional processing, addressed any difficulties following the MDMA-AT session, and helped participants to apply any benefits gained in the MDMA-AT sessions to daily life. Participants worked with the same cotherapist dyad throughout the entire treatment period. The therapeutic approach is detailed in the MDMA Treatment Manual.

Therapy Training and Adherence Rating

As part of the open-label lead-in studies, therapy trainees completed the MDMA Therapy Training Program, which included approximately 120 hours of both online and in-person courses and experiential learning (details about the current MDMA Training Program curriculum available at mapspublicbenefit.com/training). Trainees were recruited from mental health and medical professions and were required to demonstrate experience providing therapy or counseling services to adults affected by trauma. Trainees were paired in cotherapist dyads according to professional training and experience, so that every cotherapist dyad had at least one psychotherapist with extensive
clinical experience. Clinical supervisors evaluated each therapy trainee working on the open-label studies to deliver MDMA treatment under clinical supervision. Cotherapist dyads were systematically assessed on their treatment fidelity using an adherence rating checklist that was developed by experienced therapists and trainers.

The aim of the adherence ratings was to measure consistency of MDMA-AT that was delivered across all of the study sites using adherence criteria described in the “Manual for Adherence Ratings of MDMA-Assisted Psychotherapy for Treatment of Posttraumatic Stress Disorder” published by MAPS (available at maps.org/treatment-manual). Raters were graduate-level professionals in psychology, social work, or psychiatry who had a minimum of 1-year experience working with adults affected by trauma and had completed a 50-hour Adherence Training Program and interrater reliability testing. Raters and supervisors reviewed cotherapist dyads’ session videos and evaluated them against the “Manual for Adherence Ratings for Treatment Fidelity.” Dichotomous Adherence Criteria (Yes/No) covered a range of factors, from communicating treatment expectations to nurturing the therapeutic alliance and building trust, across each of the preparatory, experimental, and integrative sessions. For each cotherapist dyad, adherence ratings were performed on at least their first 10 study visits. Each rated session was reviewed in full and rated independently. In the present study, adherence rating percentage scores were calculated as follows: for preparatory sessions, each of the 24 adherence criterion were expected to be met at least once across their three rated preparatory sessions; for experimental sessions, scores were calculated independently, with each of the 20 adherence criterion expected to be met in each rated experimental session; and for integrative sessions, each of the 12 adherence criterion were expected to be met at least once across each set of three integrative sessions that took place after an experimental session. In addition to adherence ratings, raters provided qualitative comments on sessions for clinical supervisors’ review.

**PTSD Measure**

The primary outcome measure of PTSD symptoms was change in Total Severity scores from the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). The CAPS-5 is a semistructured 30-item interview to assess past-month presence and severity of PTSD through diagnostic and symptom severity scores, with good internal consistency, concurrent validity, and test/retest reliability (Weathers et al., 2013). CAPS-5 Total Severity scores range from 0 to 80, with higher values indicating greater symptom severity. The CAPS-5 interviews were administered remotely via live video conferencing.
by a centralized pool of trained independent raters (IRs). IRs were not present during any therapy sessions, remained blinded to the study design, and were scheduled on the basis of their availability. CAPS-5 was assessed at baseline and within three weeks after each MDMA-AT session (visit 8, visit 13, and primary endpoint visit 19). All CAPS-5 assessments for each participant were performed by different IRs.

**Safety Measures**

Vitals including systolic blood pressure, diastolic blood pressure, heart rate, and body temperature were measured during each experimental session, with measurements occurring once prior to drug administration, at least once 1.5 to 2 hours after initial MDMA dose administration and prior to supplemental dose, and once approximately 6 to 7 hours after initial dose of MDMA.

Adverse events (AEs) were collected throughout the study and gathered during face-to-face visits, telephone calls, and/or correspondence with therapists or site staff. AEs were rated by the site physician as mild (causing no limitations on daily activities), moderate (some limitation in daily activities), or severe (preventing performance of daily activities). The site investigators also assessed for “serious” AEs, which is defined as “fatal, life-threatening, requires or prolongs inpatient hospitalization, or produces persistent and significant disability.” AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA 20.0) and overseen by a medical monitor. In the present analysis, AEs were counted at the participant-level across an aggregate of the three experimental sessions for day of, 1 day postexperimental, and 2 days postexperimental session.

Suicidal ideation and behavior were measured with the Columbia Suicide Severity Rating Scale (C-SSRS) and were assessed at baseline and during visits and select phone calls throughout the study. The C-SSRS is a clinician-administered structured interview that measures presence and intensity of suicidal ideation and behavior during the assessment period (lifetime or since last assessment; Posner et al., 2007).

**Statistical Analysis**

All outcome analyses were based on participants who received MDMA in at least one experimental session and had at least one follow-up CAPS-5 assessment. Nominal variables were described in terms of frequencies and percentages. Ordinal and nonnormal continuous variables were described using the sample mean and range and were analyzed by nonparametric statistical tests. Approximately normal variables were described using sample mean and
standard deviations, presented as $M (SD)$ throughout, and analyzed by parametric statistical tests. Treatment efficacy was used to estimate the mean change in CAPS-5 Total Severity scores from baseline (Visit 3) to primary endpoint (Visit 19), which was 18 weeks postbaseline. Least-squares means from a restricted maximum likelihood-based model for repeated measures was used to estimate the change in CAPS-5 across timepoints. All analyses were carried out with SAS Version 9.4 (SAS Institute, Cary NC).

Results

Participant Sample

A total of 308 people were screened for study eligibility between November 2017 and March 2019, and 37 participants were enrolled. Across the 14 investigative sites, 37 cotherapist dyads each treated one participant. Only one participant did not complete the primary endpoint assessment; before the start of the second MDMA-AT session, the participant withdrew from the study due to an AE of increased nightmares which was reported as mild. The sample consisted of 15 men (40.5%) and 22 women (59.5%), mean age was 35.6 (10.8) years, and the majority of participants were White (73.0%) and not Hispanic or Latino (94.6%). Five veterans were enrolled, with three (8.1%) having index traumas related to combat. Mean baseline CAPS-5 Total scores were 45.4 (7.2). Many participants reported a history of having had multiple traumas (81.1%) or developmental trauma (78.4%). The mean (SD) duration of PTSD was 10.3 (11.0) years. C-SSRS indicated 89.2% of participants reported a history of lifetime suicidal ideation and 40.5% a lifetime history of suicidal behavior. See Table 1 for demographics and baseline characteristics. The MDMA supplemental dose was withheld by the investigator in two instances for two participants due to occurrence of tachycardia and elevated blood pressure following the initial dose, though neither required any medical intervention or further medical evaluation.

Adherence Rating Scores

Across 37 cotherapist dyads, a total of 375 study sessions were reviewed and rated for adherence. An average of 10 sessions were rated per participant (range = 9-14), which consisted of three preparatory, two experimental, and five integrative sessions per cotherapist dyad. Seven sessions that were initially assigned for adherence rating (one preparatory, three experimental, and three integrative sessions) were not included in the analysis due to missing ratings or recording errors. Thirteen additional sessions involving three dyads
Table 1. Demographics and Baseline Characteristics.

|                           | Unite States (n = 33) | Canada (n = 4) | Total (N = 37) |
|---------------------------|-----------------------|----------------|----------------|
| **Gender, n (%)**         |                       |                |                |
| Male                      | 13 (39.4)             | 2 (50.0)       | 15 (40.5)      |
| Female                    | 20 (60.6)             | 2 (50.0)       | 22 (59.5)      |
| **Age, M (SD)**           | 36.421 (11.1)         | 29.3 (5.4)     | 35.6 (10.8)    |
|                           | Min, Max              | 18.6, 62.3     | 24.1, 34.7     | 18.6, 62.3   |
| **Ethnicity, n (%)**      |                       |                |                |
| Hispanic or Latino        | 1 (3.0)               | 1 (25.0)       | 2 (5.4)        |
| Not Hispanic or Latino    | 32 (96.9)             | 3 (75.0)       | 35 (94.6)      |
| **Race, n (%)**           |                       |                |                |
| American Indian or Alaskan native | 1 (3.0) | 0 | 1 (2.7) |
| Asian                     | 5 (15.2)              | 1 (25.0)       | 6 (16.2)       |
| Black or African American | 1 (3.0)               | 0              | 1 (2.7)        |
| Native Hawaiian or Pacific Islander | 0 | 0 | 0 (0) |
| White                     | 24 (72.7)             | 3 (75.0)       | 27 (73.0)      |
| Multiple                  | 2 (6.1)               | 0              | 2 (5.4)        |
| **Baseline BMI categories, n (%)** |         |                |                |
| Underweight               | 2 (6.06)              | 0              | 2 (5.4)        |
| Normal                    | 16 (48.5)             | 3 (75.0)       | 19 (51.4)      |
| Overweight/obese          | 15 (45.5)             | 1 (25.0)       | 16 (43.2)      |
| **Duration of PTSD in years, M (SD)** | 10.6 (11.5) | 7.9 (6.2) | 10.33 (11.02) |
| **Trauma history, n (%)** |                       |                |                |
| Developmental trauma      | 26 (78.8)             | 3 (75.0)       | 29 (78.4)      |
| Veteran                   | 5 (15.2)              | 0              | 5 (13.5)       |
| Combat exposure           | 3 (9.1)               | 0              | 3 (8.1)        |
| Multiple trauma           | 27 (81.8)             | 3 (75.0)       | 30 (81.1)      |
(continued)
|                              | Unite States ($n = 33$) | Canada ($n = 4$) | Total ($N = 37$) |
|------------------------------|-------------------------|-----------------|-----------------|
| Dissociative subtype of PTSD, $n$ (%) | 13 (39.4)               | 1 (25.0)        | 14 (37.8)       |
| Disabled from work, $n$ (%)   |                         |                 |                 |
| No                           | 27 (81.8)               | 3 (75.0)        | 30 (81.1)       |
| Yes                          | 6 (18.2)                | 1 (25.0)        | 7 (18.9)        |
| Prestudy psychiatric medications, $n$ (%) |                     |                 |                 |
| Antidepressants              | 24 (72.7)               | 3 (75.0)        | 27 (73.0)       |
| Anxiolytics                  | 17 (51.5)               | 2 (50.0)        | 19 (51.4)       |
| Hypnotics/Sedatives          | 9 (27.3)                | 1 (25.0)        | 10 (27.0)       |
| Psychostimulants             | 9 (27.3)                | 1 (25.0)        | 10 (27.0)       |
| Prestudy therapy, $n$ (%)     |                         |                 |                 |
| None                         | 1 (3.0)                 | 0               | 1 (2.7)         |
| EMDR                         | 12 (36.4)               | 1 (25.0)        | 13 (35.1)       |
| Group psychotherapy          | 3 (9.1)                 | 0               | 3 (8.1)         |
| Other cognitive behavioral therapy | 18 (54.5)           | 1 (25.0)        | 19 (51.4)       |
| Psychodynamic                | 14 (42.4)               | 0               | 14 (37.8)       |
| Interpersonal therapy (IPT)  | 0                       | 2 (50.0)        | 2 (5.4)         |
| Prolonged exposure           | 0                       | 1 (25.0)        | 1 (2.7)         |
| Other                        | 25 (75.8)               | 4 (100)         | 29 (78.4)       |
| Baseline CAPS-5 total severity score, $M$ (SD) | 45.42 (6.7)         | 45.25 (11.8)    | 45.41 (7.2)     |
| Lifetime C-SSRS, $n$ (%)      |                         |                 |                 |
| Positive ideation            | 29 (87.9)               | 4 (100)         | 33 (89.2)       |
| Serious ideation             | 14 (42.4)               | 1 (25.0)        | 15 (40.5)       |
| Positive behavior            | 14 (42.4)               | 1 (25.0)        | 15 (40.5)       |

Note: BMI = body mass index; PTSD = posttraumatic stress disorder; CBT = cognitive-behavioral therapy; EMDR = eye movement desensitization and reprocessing therapy; C-SSRS = Columbia Suicide Severity Rating Scale; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5.
were rated for adherence in replacement of sessions that were unable to be rated or as requested by a supervisor for further assessment. Overall, adherence ratings were high; cotherapist dyads scored a mean of 95.1% ($SD = 3.7\%$, range $= 84.6\%$ to 100%). Across session type, cotherapist dyads scored a mean adherence rating of 92.0% ($SD = 7.2\%$; range $= 75.0\%$ to 100%) for preparatory sessions, 98.0% ($SD = 3.3\%$; range $= 85.0\%$ to 100%) for experimental sessions, and 93.1% ($SD = 9.8\%$; range $= 58.3\%$ to 100%) for integrative sessions. Table 2 presents overall adherence rating scores by site and by country.

**Efficacy Outcome**

The primary efficacy analysis was change in CAPS-5 Total Severity scores from baseline ($M = 45.41$, $SD = 7.18$) to the primary endpoint ($M = 15.56$, $SD = 10.87$). At the primary endpoint, there was a significant mean change in CAPS-5 scores of $-29.89$ ($SD = 13.45$, $p < .0001$) indicating improvement in PTSD symptoms (Cohen’s $d = 2.2$; confidence interval $[1.97, 2.47]$). Figure 1 presents CAPS-5 scores by visit. The primary aim of the open-label studies was to train new cotherapist dyads to lead into the sponsor’s larger Phase 3 trials. In general, efficacy of MDMA-AT was comparable between the United States (mean change $= -30.5$, $SD = 14.1$) and Canada (mean change $= -25.0$ ($SD = 2.58$). Across all sites, the mean change in CAPS-5 scores ranged from $-7.00$ ($9.90$) to $-47.00$ ($1.46$). Table 2 presents CAPS-5 scores by country and site. At the primary endpoint (Visit 19), 91.89% ($n = 34$) of all participants had a clinically meaningful reduction (10 points or greater) in their CAPS-5 scores ($p < .0001$) and 75.68% ($n = 28$) no longer met PTSD criteria ($p < .001$).

**Safety Outcomes**

During MDMA-AT sessions, there were transient increases in blood pressure and pulse that returned to normal levels by the end of the sessions.

The most common AEs following treatment at the participant-level were headache (68%), muscle tightness (49%), insomnia (35%), anxiety (32%), nausea (30%), fatigue (27%), and suicidal ideation (27%). On the day of the MDMA-AT sessions, the most frequently reported AEs were muscle tightness (73%), headache (62%), insomnia (49%), nystagmus (30%), and nausea (27%). Two days posttreatment, there was one report of headache and three reports of insomnia. Other AEs at two days posttreatment ranged from one to two reports of anxiety, fatigue, pain in jaw, and suicidal ideation. Table 3 presents AEs from days 0, 1, and 2 with an overall prevalence of 10% or greater.
Table 2. CAPS-5 Total Severity Scores by Site.

|                      | N   | Overall adherence score, % (SD) | CAPS-5, baseline (n = 37), M (SD) | CAPS-5, Visit 19 (n = 36), M (SD) | Change in CAPS-5, baseline to Visit 19 (n = 36), M (SD) |
|----------------------|-----|--------------------------------|----------------------------------|----------------------------------|-----------------------------------------------------|
| All                  | 37  | 95.23 (2.20)                   | 45.41 (7.18)                     | 15.56 (10.87)                    | -29.89 (13.45)                                      |
| Total United States  | 33  | 94.75 (7.69)                   | 45.42 (6.70)                     | 14.84 (10.76)                    | -30.5 (14.10)                                       |
| US Site 1            | 3   | 96.30 (8.56)                   | 48.33 (6.11)                     | 14.00 (9.00)                     | -34.33 (12.42)                                      |
| US Site 2            | 1   | 93.75 (9.77)                   | 36.00                            | 28.00                            | -8.00                                               |
| US Site 3            | 3   | 97.08 (4.21)                   | 47.67 (4.04)                     | 18.00 (19.29)                    | -29.67 (22.90)                                      |
| US Site 4            | 4   | 91.84 (8.37)                   | 40.75 (3.77)                     | 14.50 (7.23)                     | -26.25 (6.08)                                       |
| US Site 5            | 3   | 93.29 (6.09)                   | 41.67 (4.73)                     | 11.00 (14.93)                    | -30.67 (17.62)                                      |
| US Site 6            | 3   | 94.99 (5.48)                   | 51.00 (14.20)                    | 4.00 (6.93)                      | -47.00 (1.46)                                       |
| US Site 7            | 4   | 96.94 (6.01)                   | 47.25 (3.86)                     | 14.50 (8.89)                     | -32.75 (8.54)                                       |
| US Site 8            | 1   | 93.06 (6.27)                   | 51.00                            | 10.00                            | -41.00                                              |
| US Site 9            | 1   | 95.83 (6.97)                   | 41.00                            | 13.00                            | -28.00                                              |
| US Site 10           | 3   | 92.55 (12.41)                  | 44.33 (10.12)                    | 13.33 (7.09)                     | -31.00 (13.00)                                      |
| US Site 11           | 4   | 94.85 (8.15)                   | 48.50 (3.11)                     | 15.75 (11.76)                    | -32.75 (13.28)                                      |
| US Site 12           | 3   | 96.48 (6.60)                   | 42.00 (5.29)                     | 32.00                            | -7.00 (9.90)                                        |
| Total Canada         | 4   | 98.12 (5.81)                   | 45.25 (11.84)                    | 20.25 (9.98)                     | -25.00 (2.58)                                       |
| CA Site 1            | 3   | 96.23 (6.50)                   | 47.33 (13.58)                    | 22.67 (10.69)                    | -24.67 (3.06)                                       |
| CA Site 2            | 1   | 100.00 (0.00)                  | 39.00                            | 13.00                            | -26.00                                              |

Note. Two of the three participants at U.S. Site 12 completed the primary endpoint. CAPS-5 Repeated Measures: F(3) = 58.37; p < .0001. CAPS-5 at least 10-point reduction at Visit 19: 91.89% (n = 36); \( \chi^2 \) p < .0001. CAPS-5 = Clinician-Administered PTSD Scale for DSM-5.
Most participants reported AEs that were rated as either mild or moderate. Five participants each experienced an AE posttreatment that was rated as severe; however, these AEs did not occur on the day of experimental sessions or 2 days after. All five severe AEs (syncope, headache, anal fissure, exacerbation of suicidal ideation, and suicide attempt) occurred between 5 and 78 days post experimental session. There was one serious AE (SAE) of an aborted suicide attempt in a participant 28 days after their third experimental session. The attempt was aborted by the participant, who was later evaluated at the ER without being admitted and discharged 3 hours after presentation. The study investigator determined that this particular SAE was unrelated to treatment, given that it occurred 28 days after last treatment and MDMA has an elimination half-life of 7 to 9 hours. This participant had a prior history of suicidality due to underlying PTSD, with two previously reported suicide attempts in their lifetime.

At baseline, 51.4% of participants reported the presence of current suicidal ideation (see Table 4). During the study, there were 10 participants who reported suicidal ideation AEs, ranging from one to 20 days postexperimental session. In Table 4, suicidality was counted at the participant-level and, within each experimental session, counts were aggregated across three integration sessions. In general, after the day of experimental sessions, there were transient increases in suicidal ideation and serious ideation during the integrative sessions. At study termination, five participants reported the presence of suicidal ideation, of whom four had a history of suicidal ideation; no participants reported serious suicidal ideation or suicidal behavior. At study
Table 3. Adverse Events With Prevalence of ≥10% Aggregated Across Three Sessions for Day of experimental, 1 Day Postexperimental, and 2 Days Postexperimental Session.

| Event                      | N | % | n (% | n (%) | n (%) |
|----------------------------|---|---|------|-------|-------|
| Headache                   | 25 | 68 | 23 (62) | 13 (35) | 1 (3) |
| Muscle tightness           | 18 | 49 | 27 (73) | 0 | 0 |
| Insomnia                   | 13 | 35 | 18 (49) | 2 (5) | 3 (8) |
| Anxiety                    | 12 | 32 | 7 (19) | 1 (3) | 2 (5) |
| Nausea                     | 11 | 30 | 10 (27) | 3 (8) | 0 |
| Fatigue                    | 10 | 27 | 5 (14) | 3 (8) | 2 (5) |
| Suicidal ideation          | 10 | 27 | 1 (3) | 2 (5) | 1 (3) |
| Nystagmus                  | 8  | 22 | 11 (30) | 0 | 0 |
| Dizziness                  | 7  | 19 | 9 (24) | 3 (8) | 0 |
| Palpitations               | 5  | 14 | 3 (8) | 1 (3) | 0 |
| Abdominal discomfort       | 5  | 14 | 2 (5) | 1 (3) | 0 |
| Decreased appetite         | 5  | 14 | 7 (19) | 1 (3) | 0 |
| Vision blurred             | 4  | 11 | 2 (5) | 0 | 0 |
| Vision impairment          | 4  | 11 | 0 | 0 | 0 |
| Pain in jaw                | 4  | 11 | 3 (8) | 1 (3) | 1 (3) |
| Paraesthesia               | 4  | 11 | 3 (8) | 0 | 0 |
| Hyperhidrosis              | 4  | 11 | 4 (11) | 0 | 0 |

aAE (adverse event) counted once per participant across three separate “Day of experimental” sessions. bAE counted once per participant across three separate “1 Day postexperimental” sessions. cAE counted once per participant across three separate “2 Days postexperimental” sessions.
Table 4. Suicidal Ideation and Behavior as Measured by Columbia Suicide Severity Rating Scale (C-SSRS), N = 37.

|                          | Positive ideation<sup>a</sup> | Serious ideation<sup>b</sup> | Positive behavior<sup>c</sup> |
|--------------------------|-------------------------------|-------------------------------|-------------------------------|
|                          | n/N (%)                       | n/N (%)                       | n/N (%)                       |
| Lifetime<sup>d</sup>     | 33/37 (89.2)                  | 15/37 (40.5)                  | 15/37 (40.5)                  |
| Baseline<sup>e</sup>     | 19/37 (51.4)                  | 0/37                          | 0/37                          |
| Experimental Session 1  |                               |                               |                               |
| Predose (Visit 5)        | 9/37 (24.3)                   | 0/37                          | 0/37                          |
| Postdose (Visit 5)       | 2/37 (5.4)                    | 0/37                          | 0/37                          |
| Integrative Sessions (Visits 6, 7, 9)<sup>f</sup> | 15/37 (40.5)                  | 1/37 (2.7)                    | 0/37                          |
| Experimental Session 2  |                               |                               |                               |
| Predose (Visit 10)       | 4/37 (10.8)                   | 0/37                          | 0/37                          |
| Postdose (Visit 10)      | 2/37 (5.4)                    | 0/37                          | 0/37                          |
| Integrative Sessions (Visits 11, 12, 14)<sup>f</sup> | 16/37 (43.2)                  | 2/37 (5.4)                    | 0/37                          |
| Experimental Session 3  |                               |                               |                               |
| Predose (Visit 15)       | 2/36 (5.6)                    | 0/36                          | 0/36                          |
| Postdose (Visit 15)      | 1/36 (2.8)                    | 0/36                          | 0/36                          |
| Integrative Sessions (Visit 16-18)<sup>f</sup> | 16/36 (44.4)                  | 2/36 (5.6)                    | 1/36 (2.8)                    |
| Study Termination (Visit 20) | 5/37 (13.5)                  | 0/37                          | 0/37                          |

<sup>a</sup>Positive ideation was defined as a score of 1 or greater on the C-SSRS assessment. <sup>b</sup>Serious ideation was defined as a score of 4 or 5 on the C-SSRS assessment. <sup>c</sup>Positive behavior was defined as a response of “yes” to any of the suicidal behavior questions on the C-SSRS. One participant reported positive behavior during the study which was an SAE of suicide attempt. <sup>d</sup>Lifetime C-SSRS assessed at screening. <sup>e</sup>Baseline C-SSRS assessed at Preparatory Session 3 (Visit 4). <sup>f</sup>Participant-level events across integrative sessions.
termination, participants were provided with an exit plan that included the ability to request referral for further therapy or medical care as needed.

**Discussion**

These two open-label lead-in studies show that a large treatment response to MDMA-AT can be scaled and replicated by newly trained cotherapist dyads across multiple sites. Further, consistent with earlier Phase 2 studies, MDMA was well tolerated by participants and AEs were generally mild to moderate.

Adherence ratings from these trials demonstrated high levels of fidelity to the treatment manual across new cotherapist dyads, new sites, and session type, and suggest that this treatment modality was reproducible. Importantly, adherence was high in MDMA-AT sessions, which were considered particularly challenging due to their content, length, and novel modality. Ongoing supervision and evaluation were essential components in ensuring that newly trained cotherapist dyads were supported in delivering competent and compassionate therapy in alignment with the treatment model. In addition to supporting ongoing quality assurance, adherence ratings and qualitative comments from adherence raters provided valuable insights into areas where new cotherapist dyads required additional clinical supervision. The benefits of video-recorded sessions in clinical supervision have been well documented (American Psychological Association, 2015; Haggerty & Hilsenroth, 2011; Huhra et al., 2008; Nelson, 2014). Reviewing video-recorded sessions allowed supervisors to more objectively assess therapists’ skills than they might through a supervision discussion or review of session notes; it also provided therapists with opportunities for self-review and reflection, and to more objectively identify their own skills and areas for improvement (Alpert, 1996). Access to session videos for both their own review as well as for formal supervision and adherence ratings and comments from third-party observers allowed supervisors to provide detailed, timely feedback, and guidance to cotherapist dyads as they conducted treatment.

Three sessions of MDMA-AT significantly improved participants’ PTSD symptom severity from baseline to the primary endpoint, which was consistent with previous MDMA-AT studies (Mithoefer et al., 2019). In the present study, participants had a CAPS-5 score reduction of −29.89, which was comparable to a reduction of -26.35 (converted from CAPS-IV score of −44.8) among participants who were in the sponsor’s previous Phase 2 studies across five study sites. Therapists in the prior Phase 2 studies received
approximately 50 hours of in-person training, expanded to 120 hours of online and in-person training for the present studies. Across each site, there was a significant reduction in participant’s CAPS-5 scores, ranging from a mean change of $-7.00$ ($SD = 9.90$) to $-47.00$ ($SD = 1.46$). At the primary endpoint, all but two participants (91.89%) had a clinically meaningful reduction in CAPS-5 scores (10-point reduction or greater), and the majority of participants (75.68%) no longer met criteria for PTSD diagnosis. These results demonstrate that MDMA-AT can be scaled to multiple sites across different countries while maintaining significant efficacy in reducing participant’s PTSD symptom severity.

Overall, MDMA-AT was well-tolerated, with participants experiencing transient increases in blood pressure and pulse that returned to baseline levels posttreatment. Additionally, the type and duration of AEs that were reported in these two open-label lead-in studies were expected and consistent with reports from previous Phase 2 studies (Mithoefer et al., 2018; Ot’alora et al., 2018). Prevalence of AEs occurring during the day of experimental sessions were greatly reduced 2 days posttreatment. Frequently reported AEs on the day of experimental sessions included muscle tightness, headache, insomnia, nystagmus, and nausea, which at 2 days posttreatment were reduced to only one report of headache and three reports of insomnia. Other AEs at 2 days posttreatment ranged from one to two reports of anxiety, fatigue, pain in jaw, and suicidal ideation. These AEs were consistent with AEs reported in a non-sponsor MDMA-AT open-label pilot study, including anxiety, fatigue, insomnia, and headache (Jardim et al., 2020).

A history of suicidality was common in this study sample, where enrollment criteria included a diagnosis of having severe PTSD. Lifetime history and posttreatment prevalence rates for positive ideation, serious ideation, and positive behavior were comparable against an analysis of pooled C-SSRS data from four previous Phase 2 studies that included a total of 68 participants. The previous Phase 2 studies had 15 (24.2%) reports of positive ideation and 1 (1.6%) report of serious ideation at long-term follow-up (Jerome et al., 2019). In the present study, at study termination, there were five (13.5%) reports of positive ideation and no reports of either serious ideation or suicidal behavior.

There was one instance of an SAE, an unsuccessful suicide attempt, self-aborted by the participant, that occurred 28 days following the final experimental session (between Visit 16 and 18), which was resolved by the next day. The participant had a lifetime history of ongoing suicidal ideation and two previous suicide attempts. The study investigator determined that this particular SAE was unrelated to treatment given that it occurred nearly a
month after the last MDMA-AT session. Furthermore, clinic notes indicated that the event was likely triggered by a stressful life event. The participant reported PTSD symptoms improvement 47 days after the SAE. Specifically, their baseline CAPS-5 score was 44, which decreased to 23 following the three MDMA-AT session, indicating a clinically meaningful improvement in PTSD symptom severity (Jerome et al., 2019).

MDMA is described as enhancing emotional memory processing of traumatic memories with greater tolerability in therapeutic settings (Carhart-Harris et al., 2014; Mithoefer et al., 2013). After experimental sessions, participants continue to work with their therapists to process these memories during their nondrug integrative sessions. As with other types of therapy that involve extensive review of past trauma, it is possible that recall of such memories can temporarily trigger PTSD symptoms or negative emotions. This phenomenon likely explains increased reports of suicidal ideation several days after the experimental sessions and during the integrative sessions. Future studies should closely monitor suicidality due to the high risk for suicidal ideation and behavior in this population. Overall, prevalence of suicidality was low across all Phase 2 studies, including the present lead-in studies, to suggest that MDMA-AT treatment has a favorable risk/benefit ratio among those with severe PTSD.

**Limitations**

Although this study reproduced previously reported Phase 2 efficacy findings across multiple sites, there were between one to four participants per site and only four participants in Canada, which limited country- and site-level comparisons. Additionally, the single-arm study design limited the interpretation of the safety and efficacy data, since outcomes may have occurred due to other factors outside of treatment.

The adherence ratings collected in the study provided a valuable standardized method for ensuring consistency of care across teams; however, they could not provide a full picture of how capably a cotherapist dyad provided treatment due to limitations in the binary rating assessment. For example, an adherence criterion such as “therapists described the likely effects of MDMA” could have been rated as unmet because it was not addressed in the session, or because the therapists shared erroneous information—reflecting distinct issues from a quality and supervisory standpoint. Therefore, the quantitative measures summarized here provide only a limited assessment of the therapy adherence that must be paired with an adherence rater’s qualitative comments to fully identify specific areas of deviation from the treatment manual or
Another limitation of this analysis is that only a subset of integrative sessions was used for adherence rating (two of the three sessions following the second experimental session). While this was sufficient for clinical supervision, inclusion of these incomplete sets of integrative sessions in the analysis of integrative sessions’ adherence scores would attenuate adherence rating scores. Indeed, when excluding entire sets where an integrative session was unrated due to the initial adherence rating plan or lack of data, overall ratings rose from 93.07% ($SD = 9.79%$; range = 58.33% to 100%) to 96.49% ($SD = 6.32%$, range = 75.00% to 100%).

Although adherence raters were trained to review study sessions in an unbiased manner, there was a possibility of leniency bias if raters had a desire for MDMA-AT to be positively evaluated and/or confirmation bias leading raters to score unmet items as complete. Adherence raters completed inter-rater reliability testing as part of their training, and across the pool of 13 adherence raters, average adherence scores were consistent to one another ($M = 94.47%$, $SD = 24.33%$, range = 90.06% to 100%). However, interrater reliability was not tested within the present studies.

Due to the nature of how adherence criteria were evaluated, this study was not designed to be able to examine if fidelity to specific adherence criteria impacted participants’ PTSD improvement. Future studies would be needed to identify which criteria from the training manual may be most important for therapy efficacy and assess correlations between these criteria and participants’ outcomes.

**Conclusion**

These multisite studies demonstrate that newly trained therapists can achieve efficacy in reducing PTSD symptom severity and safety. MDMA-AT is a scalable treatment and can be successfully delivered by trained therapists across various locations.

**Acknowledgments**

The authors would like to thank the MAPS PBC adherence raters (Adrian Scharfetter, Audrey Redfield, Darrick May, Fabrice Nye, Jen Clark, Justin Forman, Linnae Ponte, Lucille Khoury, Marc L’Ecluse, Meghan Kennedy, Richard Knowles, Ryan Stevenson, and Sara Ouimette); therapy teams who worked on the MP16 and MP17 clinical trials for their dedication, expertise, and care; and Terence Ching for his manuscript review.
Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JW, JL, LB, AC, IJ, AF, CH, EH, SC, RM, AE received salary support for full-time employment with MAPS PBC for this study and other work. AL, BYK, and RD received salary support for full-time employment with MAPS for this study and other work. MM, AM, MOG, and BP received support as a contractor from MAPS PBC for training and supervision of research psychotherapists for this study and other work.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This Clinical Trial was sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)(3) nonprofit organization. MAPS provided the MDMA and fully funded this study from private donations. MAPS Public Benefit Corporation (MAPS PBC), wholly owned by MAPS, was the trial organizer.

Ethical Approval

The study protocol was reviewed by Western Copernicus Group Independent IRB (Research Triangle, NC), University of California San Francisco Human Resource Protection Program IRB, University of Madison Wisconsin Health Sciences IRB, Western IRB (Puyallup, WA), and University of British Columbia Providence Health Care Research Ethics Board. Studies were designed and conducted in accordance with Good Clinical Practice guidelines. All participants provided written informed consent.

ORCID iDs

Julie B. Wang https://orcid.org/0000-0001-7039-6061
Jessica Lin https://orcid.org/0000-0002-6533-666X

References

Alpert, M. C. (1996). Videotaping psychotherapy. *Journal of Psychotherapy Practice and Research, 5*(2), 93-105. https://www.ncbi.nlm.nih.gov/pubmed/22700270

American Psychological Association. (2015). Guidelines for clinical supervision in health service psychology. *American Psychologist, 70*(1), 33-46. https://doi.org/10.1037/a0038112

Baker, D. G., Mendenhall, C. L., Simbartl, L. A., Magan, L. K., & Steinberg, J. L. (1997). Relationship between posttraumatic stress disorder and self-reported physical symptoms in Persian Gulf War veterans. *Archives of Internal Medicine, 157*(18), 2076-2078. https://pubmed.ncbi.nlm.nih.gov/9382663/
Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta-analysis of psychotherapy for PTSD. *American Journal of Psychiatry, 162*(2), 214-227. https://doi.org/10.1176/appi.ajp.162.2.214

Carhart-Harris, R. L., Wall, M. B., Erritzoe, D., Kaelen, M., Ferguson, B., De Meer, I., Tanner, M., Bloomfield, M., Williams, T. M., Bolstridge, M., Stewart, L., Morgan, C. J., Newbould, R. D., Feilding, A., Curran, H. V., & Nutt, D. J. (2014). The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *International Journal of Neuropsychopharmacology, 17*(4), 527-540. https://doi.org/10.1017/S1461145713001405

Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., & Van der Hart, O. (2012). The ISTSS expert consensus treatment guidelines for complex PTSD in adults. https://www.scienceopen.com/document?vid=467f1783-b3f7-4a63-9ef1-02423eced639

Conner, K. R., Bossarte, R. M., He, H., Arora, J., Lu, N., Tu, X. M., & Katz, I. R. (2014). Posttraumatic stress disorder and suicide in 5.9 million individuals receiving care in the veterans health administration health system. *Journal of Affect Disorder, 166*(September), 1-5. https://doi.org/10.1016/j.jad.2014.04.067

Dursa, E. K., Reinhard, M. J., Barth, S. K., & Schneiderman, A. I. (2014). Prevalence of a positive screen for PTSD among OEF/OIF and OEF/OIF-era veterans in a large population-based cohort. *Journal of Traumatic Stress, 27*(5), 542-549. https://doi.org/10.1002/jts.21956

Edmondson, D., & Cohen, B. E. (2013). Posttraumatic stress disorder and cardiovascular disease. *Progress in Cardiovascular Diseases, 55*(6), 548-556. https://doi.org/10.1016/j.pcad.2013.03.004

Feduccia, A. A., Holland, J., & Mithoefer, M. C. (2018). Progress and promise for the MDMA drug development program. *Psychopharmacology, 235*(2), 561-571. https://doi.org/10.1007/s00213-017-4779-2

Gabay, A. S., Kempton, M. J., Gilleen, J., & Mehta, M. A. (2019). MDMA increases cooperation and recruitment of social brain areas when playing trustworthy players in an iterated prisoner’s dilemma. *Journal of Neuroscience, 39*(2), 307-320. https://doi.org/10.1523/JNEUROSCI.1276-18.2018

Goetter, E. M., Bui, E., Ojserkis, R. A., Zakarian, R. J., Brendel, R. W., & Simon, N. M. (2015). A systematic review of dropout from psychotherapy for posttraumatic stress disorder among Iraq and Afghanistan combat veterans. *Journal of Trauma Stress, 28*(5), 401-409. https://doi.org/10.1002/jts.22038

Haggerty, G., & Hilsenroth, M. J. (2011). The use of video in psychotherapy supervision. *British Journal of Psychotherapy, 27*(2), 193-210. https://doi.org/10.1111/j.1752-0118.2011.01232.x

Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I., & Koffman, R. L. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *New England Journal of Medicine, 351*(1), 13-22. https://doi.org/10.1056/NEJMoa040603
Huhra, R. L., Yamokoski-Maynhart, C. A., & Prieto, L. R. (2008). Reviewing videotape in supervision: A developmental approach. *Journal of Counseling & Development, 86*(4), 412-418. https://doi.org/10.1002/j.1556-6678.2008.tb00529.x

Hysek, C. M., Schmid, Y., Simmler, L. D., Domesc, G., Heinrichs, M., Eisenegger, C., Preller, K. H., Quednow, B. B., & Liechti, M. E. (2014). MDMA enhances emotional empathy and prosocial behavior. *Social Cognitive and Affective Neuroscience, 9*(11), 1645-1652. https://doi.org/10.1093/scan/nst161

Ipser, J. C., Carey, P., Dhansay, Y., Fakier, N., Seedat, S., & Stein, D. J. (2006). Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. *Cochrane Database System Review, 4*, Article CD005473. https://doi.org/10.1002/14651858.CD005473.pub2

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

Jerome, L., Feduccia, A., & Mithoefer, M. (2019, May 21). *MDMA-assisted psychotherapy reduces PTSD symptoms: Pooled analysis across randomized, controlled blinded trials*. American Psychiatric Association 175th Annual Meeting, Moscone Center, San Francisco, CA.

Jerome, L., Feduccia, A. A., Wang, J. B., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2020). Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: A longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology, 237*(8), 2485-2497. https://doi.org/10.1007/s00213-020-05548-2

Kessler, R. C., Ames, M., Hymel, P. A., Loeppke, R., McKenas, D. K., Richling, D. E., Stang, P. E., & Ustun, T. B. (2004). Using the World Health Organization Health and Work Performance Questionnaire (HPQ) to evaluate the indirect workplace costs of illness. *Journal of Occupational Environment Medicine, 46*(6 Suppl.), S23-S37. https://doi.org/10.1097/01.jom.0000126683.75201.c5

Lee, D. J., Schnitzlein, C. W., Wolf, J. P., Vythilingam, M., Rasmusson, A. M., & Hoge, C. W. (2016). Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: Systemic review and meta-analyses to determine first-line treatments. *Depress Anxiety, 33*(9), 792-806. https://doi.org/10.1002/da.22511

Mithoefer, M. C., Feduccia, A. A., Jerome, L., Mithoefer, A., Wagner, M., Walsh, Z., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Doblin, R. (2019). MDMA-assisted psychotherapy for treatment of PTSD: Study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology, 236*(9), 2735-2745. https://doi.org/10.1007/s00213-019-05249-5

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., Holland, J., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Doblin, R.
Wang et al. (2018). 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry*, 5(6), 486-497. https://doi.org/10.1016/s2215-0366(18)30135-4

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

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., Martin, S. F., Yazar-Klosinski, B., Michel, Y., Brewerton, T. D., & Doblin, R. (2013). Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: A prospective long-term follow-up study. *Journal of Psychopharmacology*, 27(1), 28-39. https://doi.org/10.1177/026988112456611

Nelson, M. L. (2014). Using the major formats of clinical supervision. In C. E. Watkins & D. L. Milne (Eds.), *The Wiley international handbook of clinical supervision* (pp. 308-328). John Wiley & Sons. http://doi.wiley.com/10.1002/9781118846360.ch13

Oehen, P., Traber, R., Widmer, V., & Schnyder, U. (2013). A randomized, controlled pilot study of MDMA (\(+/-\) 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *Journal of Psychopharmacology*, 27(1), 40-52. https://doi.org/10.1177/0269881112464827

Ot’alora, G. M., Grigsby, J., Poulter, B., Van Derveer, J. W., III, Giron, S. G., Jerome, L., Feduccia, A. A., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2018). 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. *Journal of Psychopharmacology*, 32(12), 1295-1307. https://doi.org/10.1177/0269881118806297

Posner, K., Oquendo, M. A., Gould, M., Stanley, B., & Davies, M. (2007). Columbia classification algorithm of suicide assessment (C-CASA): Classification of suicidal events in the FDA’s pediatric suicidal risk analysis of antidepressants. *American Journal of Psychiatry*, 164(7), 1035-1043. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17606655

Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013). *The clinician-administered PTSD scale for DSM-5 (CAPS-5).* National Center for PTSD.

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., Keane, T. M., & Marx, B. P. (2017). The clinician-administered PTSD scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment*, 30(3), 383-395. https://doi.org/10.1037/pas0000486
Young, M. B., Andero, R., Ressler, K. J., & Howell, L. L. (2015). 3,4-Methylenedioxymethamphetamine facilitates fear extinction learning. *Translational Psychiatry, 5*, Article e634. https://doi.org/10.1038/tp.2015.138

**Author Biographies**

**Julie B. Wang**, MPH, PhD, is a data scientist with clinical research expertise in developing and testing public health interventions. She serves as the Senior Clinical Data Scientist at MAPS Public Benefits Corporation, where she conducts statistical analysis, interpretation, and reporting of clinical data for research development and regulatory affairs. She earned a doctorate in Public Health with a concentration in behavioral medicine at the University of California San Diego, and continued research training as a postdoctoral fellow at the University of California San Francisco and data science training at General Assembly (San Francisco).

**Jessica Lin**, MPH, is the Adherence and Supervision Program Manager at the MAPS Public Benefit Corporation (MAPS PBC), where she works to support development of systems and infrastructure for the oversight of therapists in the delivery of MDMA-assisted psychotherapy for PTSD in MAPS protocols. Prior to joining MAPS PBC, she led public health research and intervention programs in public, academic, and not-for-profit settings, including at the San Francisco Department of Public Health, University of California, Berkeley, and San Francisco AIDS Foundation. She holds a bachelor’s degree in Urban Studies and Comparative Literature from Brown University and a master’s in public health from the University of California, Berkeley.

**Leah Bedrosian**, MPH, earned her bachelor’s degree in psychology from the University of Michigan and her masters of public health in epidemiology from the University of Michigan, School of Public Health. Currently, she serves as the clinical research scientist at MAPS, primarily working on writing clinical study reports for the MDMA-assisted therapy program.
Allison Coker, PhD, is a neuroscientist with a multidisciplinary background in behavioral pharmacology studying motivation, addiction, and stress across diverse research methodologies in both preclinical and clinical research settings. She earned a bachelor’s degree in Neuroscience and Behavioral Biology from Emory University and a doctorate in Neuroscience from the University of California, San Francisco (UCSF). She is currently the Regulatory Affairs Manager at MAPS Public Benefit Corporation where she works with executive leadership and senior consultants on the development and optimization of regulatory strategy while utilizing her research background to support data-driven advancement of across the ongoing clinical development programs at MAPS. She also serves as a Clinical Research Analyst in the UCSF Department of Neurology where she previously acted as Program Manager for the Institute for Translational Neuroscience, a UCSF research consortium focused on developing novel treatment strategies for PTSD and alcohol and substance use disorders.

Ilisa Jerome earned a doctorate in psychology from the University of Maryland. She has worked for MAPS and MAPS PBC. She has worked on the creation and revision of MAPS’ Investigator’s Brochure, and has contributed to previous publications of MAPS’ research. She continues to work as an integral part of MAPS PBC’s Safety team, providing research and informational support to medical monitors and coding data using medical dictionaries.

Allison Feduccia, PhD, is a neuropharmacologist, psychedelic researcher, and a builder of virtual and in-person communities. She is the co-founder of Psychedelic.Support and a nonprofit Project New Day. In these roles, Allison facilitates the spreading of evidence-based knowledge, connection to resources, and strategies for individuals to maximize the potential therapeutic benefits of psychedelics through safe and responsible practices. In 2009, she earned a PhD in neuropharmacology from the University of Texas at Austin studying the effects of MDMA on behavior and neurochemical release. She was a postdoctoral researcher at the University of California, San Francisco and at the National Institutes of Health where she investigated treatments
for substance use disorders. Her work at MAPS Public Benefit Corporation (2015-2020) focused on MDMA protocol designs, data analyses, scientific writing, and public education and outreach.

Alia Lilienstein is a board-certified Family Medicine physician. She earned her BA in American Studies from Georgetown University in 2002, where she studied social and cultural influences on health care. Prior to medical school, she earned her Master of Public Health in epidemiology and biostatistics in 2004 from the University of California, Berkeley, and worked in clinical research and development at Chiron (later Novartis). She received her MD in 2011 from Mount Sinai School of Medicine in New York and completed residency training in Family Medicine at Cambridge Health Alliance, a Tufts- and Harvard-affiliated Accountable Care Organization. Before joining MAPS, she worked as a primary care doctor in Berkeley. She holds a certificate in psychedelic-assisted therapies and research from CIIS in San Francisco.

Charlotte Harrison is an experienced clinical research professional currently serving as the Clinical Program Manager for the Phase 3 MDMA-assisted psychotherapy for PTSD studies at MAPS Public Benefit Corporation, having worked at the organization for the past 5 years. Prior to joining MAPS PBC, she monitored and managed clinical trials in oncology, supportive cancer care, nephrology, dermatology, and cardiology at Clinical Assistance Programs (now AliraHealth), MedTrials, and Harvard Clinical Research Institute (now Baim Institute for Clinical Research).

Elizabeth Heimler is a devoted and experienced research professional with a background in adult and pediatric oncology. Prior to beginning her career, she earned a bachelor’s degree in psychological science and religious studies from Albion College. Since joining MPBC, she has led the Independent Rater Program. In this role, she has cultivated a dynamic, international team of Independent Raters, serving several PTSD research sites around the world, in many languages. She is committed to ensuring quality assessments while maintaining sensitive support for the “whole participant” during challenging assessment interviews. She is passionate about research ethics and innovations in mental health treatment. In her free time, she enjoys fiber arts of all kinds, hiking, and making soap.
Michael Mithoefer, MD, is a psychiatrist, and in 2000, he began collaborating with MAPS on the first U.S. Phase 2 clinical trial of MDMA-assisted psychotherapy. He and his wife Annie have since conducted two of the six MAPS-sponsored Phase 2 clinical trials testing MDMA-assisted psychotherapy for PTSD, as well a study providing MDMA-assisted sessions for therapists who have completed the MAPS-sponsored MDMA Therapy Training Program, and a pilot study treating couples with MDMA-assisted psychotherapy combined with Cognitive-Behavioral Conjoint Therapy. He is now Senior Medical Director for Medical Affairs, Training and Supervision at MAPS Public Benefit Corporation (MAPS PBC). Before going into psychiatry in 1991, he practiced emergency medicine for ten years, served as medical director of the Charleston County and Georgetown County Emergency Departments, and has held clinical faculty positions at the Medical University of South Carolina.

Annie Mithoefer, BSN, is a Registered Nurse living in Asheville, North Carolina, where she is now focused primarily on training and supervising therapists conducting MAPS-sponsored clinical trials, as well as continuing to conduct some MAPS research sessions in Charleston, South Carolina. Between 2004 and 2018, she and her husband, Michael Mithoefer, MD, completed two of the six MAPS-sponsored Phase II clinical trials testing MDMA-assisted therapy for PTSD, as well a study providing MDMA-assisted sessions for therapists who have completed the MAPS Therapist Training, and a pilot study treating couples with MDMA-assisted therapy combined with Cognitive Behavioral Conjoint Therapy. She is a Grof-certified Holotropic Breathwork Practitioner, is trained in Hakomi Therapy, and has 25 years experience working with trauma patients, with an emphasis on experiential approaches to therapy.

Marcela Ot’alora G is dedicated to the treatment and research of trauma, through art and through the use of MDMA-assisted therapy. She worked as a cotherapist in the first government approved MDMA-assisted therapy study in Madrid, Spain and is the Principal Investigator of the Phase 2 and 3 MDMA-assisted therapy trials in Boulder, Colorado. She received her MA in Transpersonal Psychology from Naropa University and MFA from University of Greensboro in North Carolina. She was born and raised in Colombia, South America and now lives in Boulder, Colorado with her husband Bruce Poulter. She is bilingual in Spanish and English. She will be leading the MDMA therapy training.
Bruce Poulter studied health planning and policy development, where he received his MPH from UC Berkeley, in the hopes of redirecting funds away from critical care units and toward programs that effectively improved the morbidity and mortality rates of the people they served. In the early 1990s, he developed and ran public health programs including a nurse-midwife based, comprehensive perinatal program, serving exclusively low-income women, as well as a program designed to prevent childhood abuse and neglect by combining public health nurses with community mental health workers focusing on at risk families. He has had the pleasure of participating in harm reduction services through Zendo, and so on, and is currently a subinvestigator, clinical supervisor and trainer with MAPS Phase 2 and Phase 3 MDMA-assisted therapy trials.

Shannon Carlin, MA, LMFT, is the director and Head of Training and Supervision at the MAPS Public Benefit Corporation (MAPS PBC), and she oversees the development and implementation of the programs that provide training and supervision to prepare mental health and medical professionals to deliver MDMA-assisted therapy in approved clinical settings. She started working with MAPS in 2011 before joining MAPS PBC in 2016. In her dedication to supporting people through growth and healing, she has served as a cotherapist on MAPS-sponsored Phase 2 trials researching MDMA-assisted therapy for anxiety associated with life-threatening illness and MDMA-assisted therapy for severe PTSD. Shannon received her master’s degree in integral counseling psychology from the California Institute of Integral Studies and a bachelor’s degree in cultural anthropology from the University of California, Santa Cruz.

Rebecca Matthews is the Chief Clinical Operations Officer (CCOO) at the MAPS Public Benefit Corporation (MAPS PBC), and she is leading the Clinical Operations teams in conducting clinical trials around the globe in all indications and clinical programs supported by MAPS PBC and MAPS. She began consulting with MAPS in 2009 and joined MAPS PBC full-time in 2015. Prior to her work at MAPS and MAPS PBC, she worked in clinical research and development at Chiron/Novartis starting in 2001 with a focus in the indications of sepsis and vaccines. She is drawn to the field of research and drug development to support the advancement of health care and to provide novel and improved treatments for the benefit of humankind. She is deeply passionate about this amazing journey and honored to be on the forefront of psychedelic medicine research. Rebecca earned her BA from UC Berkeley in 2000.
Berra Yazar-Klosinski, PhD, is a deputy director of the 501(c)(3) nonprofit Multidisciplinary Association for Psychedelic Studies (MAPS). She is responsible for development of strategic, catalytic, and capacity-building activities to facilitate research on the risk/benefit profile of psychedelics in compliance with the global regulatory landscape. She joined MAPS in 2009 to work with an organization where profit would not dictate the agenda of scientific research. Over the past 10 years, she has supported MAPS clinical research and regulatory affairs through all stages of growth. She has developed a strong track record of success with FDA, state regulatory agencies and multiple regulatory agencies outside of the United States. She earned her BS in Biology with a minor in Drama from Stanford University and her PhD in molecular, cell, and developmental biology from the University of California, Santa Cruz in 2010.

Amy Emerson is the Chief Executive Officer at the MAPS Public Benefit Corporation (MAPS PBC), a wholly owned subsidiary of the Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)(3) nonprofit organization. As the Chief Executive Officer, she has led the growth and development of this new subsidiary and is responsible for overall global regulatory strategy and implementation of research programs with a focus on the MDMA-assisted psychotherapy program within MAPS PBC. She started as a pro bono consultant at MAPS in 2003, and since then has built MAPS’ clinical department while managing the MDMA Clinical Development Program with a focus on the PTSD indication. In 2014, MAPS Public Benefit Corporation was incorporated to focus on psychedelic drug development, therapist training programs, and future sales of prescription psychedelics prioritizing public benefit above profit.

Rick Doblin, PhD, is the founder and executive director of the Multidisciplinary Association for Psychedelic Studies (MAPS). He received his doctorate in Public Policy from Harvard’s Kennedy School of Government, where he wrote his dissertation on the regulation of the medical uses of psychedelics and marijuana and his Master’s thesis on a survey of oncologists about smoked marijuana versus the oral THC pill in nausea control for cancer patients. His undergraduate thesis at New College of Florida was a 25-year follow-up to the classic Good Friday Experiment, which evaluated the potential of psychedelic drugs to catalyze religious experiences. He also conducted a 34-year follow-up study to Timothy Leary’s Concord Prison Experiment. He studied with Dr. Stanislav Grof and was among the first to be certified as a Holotropic Breathwork practitioner. He founded MAPS in 1986, and currently resides in Boston with his wife and dog.