ORIGINAL INVESTIGATION

Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials

Lisa Jerome[1] · Allison A. Feduccia[1] · Julie B. Wang[1] · Scott Hamilton[2] · Berra Yazar-Klosinski[3] · Amy Emerson[1] · Michael C. Mithoefer[4] · Rick Doblin[3]

Abstract

Rationale Posttraumatic stress disorder (PTSD) is a chronic condition that has wide-ranging negative effects on an individual's health and interpersonal relationships. Treatments with long-term benefits are needed to promote the safety and well-being of those suffering from PTSD.

Objectives To examine long-term change in PTSD symptoms and additional benefits/harms after 3,4-methylenedioxy-methamphetamine (MDMA)-assisted psychotherapy for treatment of PTSD.

Methods Participants received two to three active doses of MDMA (75–125 mg) during blinded or open-label psychotherapy sessions with additional non-drug therapy sessions. PTSD symptoms were assessed using the Clinician-Administered PTSD Scale for DSM IV (CAPS-IV) at baseline, 1 to 2 months after the last active MDMA session (treatment exit), and at least 12 months post final MDMA session (LTFU). A mixed-effect repeated-measures (MMRM) analysis assessed changes in CAPS-IV total severity scores. The number of participants who met PTSD diagnostic criteria was summarized at each time point. Participants completed a long-term follow-up questionnaire.

Results There was a significant reduction in CAPS-IV total severity scores from baseline to treatment exit (LS mean (SE) = − 44.8 (2.82), $p < .0001$), with a Cohen's d effect size of 1.58 (95% CI = 1.24, 1.91). CAPS-IV scores continued to decrease from treatment exit to LTFU (LS mean (SE) = − 5.2 (2.29), $p < .05$), with a Cohen's d effect size of 0.23 (95% CI = 0.04, 0.43). The number of participants who no longer met PTSD criteria increased from treatment exit (56.0%) to LTFU (67.0%). The majority of participants reported benefits, including improved relationships and well-being, and a minority reported harms from study participation.

Conclusions PTSD symptoms were reduced 1 to 2 months after MDMA-assisted psychotherapy, and symptom improvement continued at least 12 months post-treatment. Phase 3 trials are investigating this novel treatment approach in a larger sample of participants with chronic PTSD.

Trial registration clinicaltrials.gov Identifier: NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610

✉ Lisa Jerome
  Ilsa@mapsbcorp.com

[1] MAPS Public Benefit Corporations, 1115 Mission St., Santa Cruz, CA 95060, USA

[2] Stanford School of Medicine, Stanford University, Stanford, CA, USA

[3] Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA, USA

[4] Medical University of South Carolina, Charleston, SC, USA

Introduction

Posttraumatic stress disorder (PTSD) is a chronic mental illness that affects approximately 3% to 4% of the general population, 17% of US war veterans who served in Iraq or Afghanistan (Hoge et al. 2004; Kessler et al. 2004), and 32% of emergency personnel and first responders (Hoge et al. 2004; Javidi and Yadollahie 2012). Symptoms of PTSD include avoiding places, activities associated with the trauma, negative effects on mood and cognition, hypervigilance, and intrusive thoughts or memories, sometimes to the extent of re-experiencing the traumatic event (Koenen et al. 2017). Although treatments are available, patients often either do not respond or discontinue their prescribed treatment and experience relapse. Novel treatments are therefore needed to produce long-term benefits in those who suffer from PTSD.

Evidence-based treatments for PTSD include pharmacotherapies and/or psychotherapies (Cipriani et al. 2018; Lee et al. 2016), which appear to perform moderately well when compared with placebo. Pharmacological treatments for PTSD typically require daily administration of medications, and symptoms often return when patients discontinue their medications (Batelaan et al. 2017). Psychotherapies for PTSD, compared to pharmacotherapies, have greater effects with more enduring benefits (Kline et al. 2018; Lee et al. 2016; Merz et al. 2019) and typically have lower dropout rates. This is particularly true of trauma-focused therapies, which are considered first-line treatment for PTSD, that require participants to engage with trauma-related thoughts, feelings, and responses (Lee et al. 2016; Steenkamp et al. 2015). However, many people with PTSD still fail to adequately respond to or tolerate available pharmacological or psychotherapeutic interventions with common reasons for treatment dropout to include worsening of psychiatric symptoms, hospitalization, disengagement from treatment, and side effects from medications (Eftekhari et al. 2013; Goetter et al. 2015; Mott et al. 2014; Resick et al. 2002; Schnurr 2007). Novel treatments for chronic PTSD are needed, especially among individuals who do not respond to conventional treatment.

In 2017, the Food and Drug Administration (FDA) designated 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy as a Breakthrough Therapy after their assessment of preliminary results from phase 2 clinical trials. MDMA-assisted psychotherapy combines MDMA, a monoamine releaser with a unique pharmacodynamic profile (Bershad et al. 2016; Kirkpatrick et al. 2014), that when administered in a therapeutic setting, appears to increase the tolerability and effectiveness of psychotherapy (Bershad et al. 2016; Feduccia et al. 2018; Kamilar-Britt and Bedi 2015). MDMA-assisted psychotherapy is a drug-assisted psychotherapy similar to psychedelic-assisted psychotherapies, such as those using psilocybin or LSD (Feduccia et al. 2018; Feduccia et al. 2019; Mithoefer et al. 2016). MDMA is administered in a setting designed to enhance and support the therapeutic effects of the compound. Modern formulations of psychedelic-assisted psychotherapy retain attention to set, or immediate mental and emotional state, and setting, or treatment environment featured in early clinical use of classic psychedelics (Grof 2008; Mithoefer et al. 2016). Similar phase 2 clinical trials of LSD and psilocybin have been conducted to treat anxiety in people with a cancer diagnosis (Gasser et al. 2014; Griffiths et al. 2016; Grob et al. 2011).

Potential mechanisms underlying the observed therapeutic effects of MDMA-assisted psychotherapy include acute changes in brain activity associated with emotional memory processing (Carhart-Harris et al. 2015; Gamma et al. 2000), which may reduce distress when facing traumatic memories, an increase in emotional empathy for self and others, and greater self-compassion (Baggott et al. 2015, 2016; Bedi et al. 2010, 2014; Schmid et al. 2014). Another proposed mechanism is enhancement of fear extinction (Feduccia and Mithoefer 2018) suggested by nonclinical studies indicating that MDMA can enhance this process in rodents (Young et al. 2015; Young et al. 2017).

The present analysis extends the follow-up of participants across six phase 2 clinical trials who had participated in a treatment protocol consisting of two or three 8-h psychotherapy sessions combined with MDMA for treatment of PTSD. Initial findings from these and other trials published elsewhere (Mithoefer et al. 2018, 2019, 2011; Oehen et al. 2013; Ot'alora et al. 2018) have shown MDMA-assisted psychotherapy was both safe and efficacious with medium to large effect sizes (Feduccia et al. 2019). Pooled analyses from the six double-blind randomized controlled studies ($n = 103$) found participants who received 75 to 125 mg MDMA (active dose) in two blinded experimental sessions, spaced a month apart, had significant reductions in Clinician-Administered PTSD Scale for DSM IV (CAPS-IV) total severity scores at the 1- to 2-month follow-up compared with participants who received 0–40 mg MDMA (placebo/control dose), with a large between-group effect size (Cohen's $d = 0.8$) (Mithoefer et al. 2019). Active dose participants also experienced additional benefits including reduced depression symptoms after MDMA-assisted psychotherapy. Overall, active treatment was well-tolerated throughout the study period with a dropout rate of 7.6% (Mithoefer et al. 2019).

The long-term benefit of MDMA-assisted psychotherapy was supported by preliminary evidence from the first phase 2 trial. In a longitudinal study, reductions in PTSD symptoms were stable up to 17 months after MDMA-assisted psychotherapy (mean 45.4 months) (Mithoefer et al. 2013). The primary aim of this analysis was to expand upon the initial

findings by pooling data from all six phase 2 trials to examine long-term effects of MDMA-assisted psychotherapy on PTSD symptoms and other benefits/harms. Participants in all six trials underwent a long-term follow-up assessment at least 1 year post-treatment to assess PTSD symptom severity and complete a long-term follow-up questionnaire (LTFUQ), which assessed both benefits and harms from participation in the phase 2 clinical trials. Available data were pooled to achieve a larger sample size to examine the LTFU data and to inform the design of long-term assessment of treatment outcomes in phase 3 trials.

Methods

To examine long-term changes in PTSD symptoms after MDMA-assisted psychotherapy, secondary treatment endpoints, and long-term follow-up data across six phase 2 trials were pooled for analysis. The six studies were similar in study design and treatment protocol and were conducted between April 2004 and March 2017 at five study sites, including the USA (two sites; MP-1, MP-8, and MP-12), Canada (MP-4), Switzerland (MP-2), and Israel (MP-9). Eligibility criteria included 18 years of age or older, chronic PTSD (6 months or longer), a CAPS-IV score of ≥ 50 (all studies except MP-4) or ≥ 60 (MP-4), and inadequate response to previous psychotherapy and/or medication for PTSD. Participants were recruited through Internet advertisements, referrals by healthcare professionals, and word of mouth.

In these trials, the study design consisted of a blinded study segment, an open-label crossover, and long-term follow-up (LTFU). Participants who met the study inclusion criteria after screening were randomized to either (i) a control group (inactive placebo; 25 mg, 30 mg, or 40 mg MDMA) or (ii) active dose group (75 mg, 100 mg, or 125 mg). Control participants received active MDMA (100–125 mg) doses during the open-label crossover. By treatment exit, all participants received active doses of MDMA in either blinded or open-label sessions. In the present study, baseline, treatment exit after active MDMA doses, and LTFU data were included for secondary analyses. MDMA used for treatment in US sites was synthesized by David Nichols at Purdue University, and by Lipomed AG, Arlesheim, Switzerland, for non-US studies. Gelatin capsules were compounded with lactose to produce equivalent-weight capsules across dose groups. All studies were approved by Institutional Review Boards, and all study participants provided written consent for participation. Details of the specific study designs, inclusion/exclusion criteria, therapeutic methods, and the primary analysis results of group differences during the blinded segment are available in previous publications (Mithoefer et al. 2018, 2019, 2011, 2013; Oehen et al. 2013; Ot'alora et al. 2018).
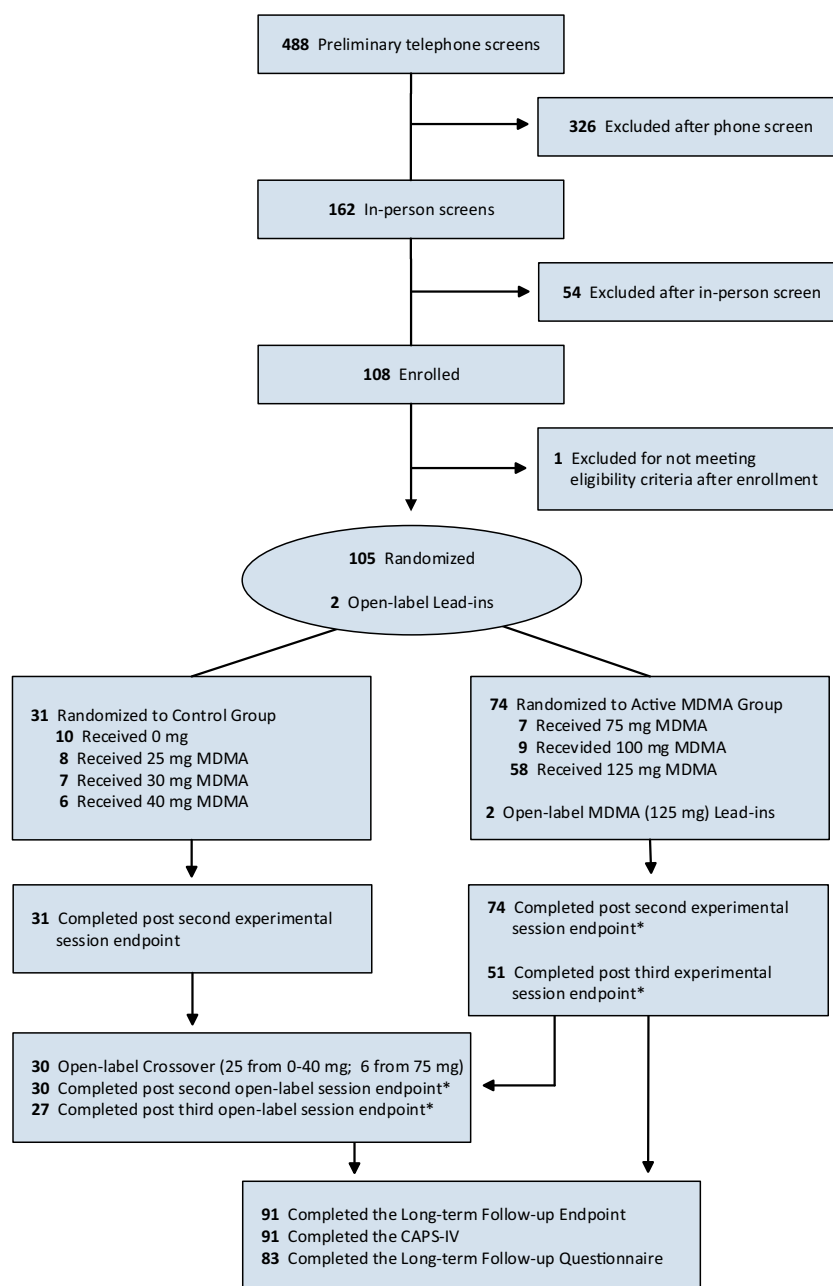
MDMA treatment

Participants began treatment with three 90-min preparatory therapy sessions, followed by two 8-h psychotherapy sessions, spaced a month apart, with administration of active MDMA (75–125 mg) or a comparator/placebo dose (0–40 mg). Participants and the co-therapy team (male/female) were blinded to group assignments. During all experimental sessions, 1.5-2.5 hours after the initial dose administration, participants were offered an optional supplemental dose equal to half of the initial dose. Participants stayed overnight with a night attendant after drug administration sessions. Three 90-min integrative sessions followed each experimental session, with the first occurring the morning after an experimental session. Participants received brief telephone calls for 7 days after the experimental sessions by one of the therapists for safety monitoring. The same co-therapy team met with a participant for all sessions. The manualized treatment approach is detailed in the MDMA Treatment Manual (Mithoefer 2017).

Most participants who received 100 mg or 125 mg in a blinded segment had a third active dose session (blinded or open-label depending on the study), with the exception of participants enrolled in the first US study (MP-1, prior to the amendment permitting an open-label session) and one study that had only two sessions (MP-9). Nearly all participants assigned to the control group (0–40 mg) had two blinded sessions, except for (i) one study (MP-8), where one participant in the 75 mg group and two participants in the 30 mg group had three blinded sessions (a study amendment later permitted entry into the cross-over segment after two rather than three sessions) and (ii) another study (MP-2) that enrolled active and control dose participants in three blinded sessions. Across the six studies, the control group (0–40 mg) and six participants in the 75 mg group crossed over to receive two to three open-label sessions with full dose MDMA (100–125 mg) and associated integrative sessions. Two participants in one study (MP-9, Israel) served as open-label lead-ins during supervision of new therapy teams, where they received two open-label MDMA (125 mg) sessions. Treatment exit was designated as the last endpoint where CAPS-IV was assessed after the last full active dose (100–125 mg) MDMA session, either blinded or open-label (Fig. 1).

Long-term follow-up assessment occurred at least 12 months after the final active dose MDMA session for each participant and included completion of the CAPS-IV (all studies) and a LTFUQ (all studies except MP-2). The long-term follow-up consisted of two visits, one with the independent rater who conducted the CAPS-IV and a meeting with the therapists. In some cases, visits occurred via telephone or video call. In study MP-1, LTFU occurred on average over 3.8 years after the study because it was added later as part of a study amendment. For all other studies, the LTFU assessment occurred approximately 12 months after the last active MDMA session.

Fig. 1 Study consort flow
diagram

*Treatment Exit (n=100) was the last endpoint after two or three active dose MDMA
sessions in either the blinded or open-label segment

Assessments

Outcome measures were administered at baseline, 1 to
2 months post two or three experimental sessions (including
blinded and open-label segments), and at long-term follow-up.
Treatment exit was defined as data from the last endpoint after
the final full active dose MDMA session prior to the LTFU
assessment. Available time points were included in the present
analysis to compare changes up to long-term follow-up.

The Clinician-Administered PTSD Scale for DSM IV
(CAPS-IV) is a structured interview designed to assess
PTSD symptom severity and diagnosis, using the recognized symptom clusters provided in DSM-IV (Blake et al.
1995; Nagy et al. 1993). It is a semi-structured interview to
assess the frequency and duration of three symptom clusters (i.e., avoidance, intrusion, and hyper-arousal), along
with overall distress. The CAPS-IV yields one total severity score, our primary outcome measure, and a diagnostic
score based on whether PTSD criteria were met (versus not
met). In all six studies, the CAPS-IV was conducted by an
independent rater who was not present during any of the
therapy sessions.

Clinical investigators and sponsor staff designed the LTFUQ to determine whether participants perceived any benefits or harms from study participation and to track elements of recovery that were not included in measures of PTSD symptoms, such as changes in interpersonal relationships, personal growth, and spirituality (see LTFUQ in the supplemental content). The sections on benefits and harms were nearly identical in structure, with language made as consistent as possible. Participants were first asked about the presence of benefits or harms and then asked about the strength of the benefit or harm on a five-point Likert scale, with 1 = slight and 5 = large or severe. An item also asked about duration: whether the benefit or harm was still apparent at 12-month follow-up and to what degree on a 1–5 Likert scale. If a benefit or harm was still present, participants were asked to rate whether it had diminished, remained the same, or had grown over time. The questionnaire also collected information about current therapy, psychiatric medications, and Ecstasy and other substance use since treatment exit.

The LTFUQ was administered in English in studies in the USA (MP-1, MP-8, and MP-12) and Canada (MP-4) and was translated into Hebrew for study MP-9. The first LTFU questionnaire (used in MP-1) contained questions about benefits and harms of study participation, the potential benefit of additional therapy soon after the last or at a later time point, current and new medications and psychotherapy, use of Ecstasy prior to enrollment and at long-term follow-up, and use of alcohol and cannabis. The questionnaire used in MP-1 asked about psychotherapy in an open-ended manner whereas later questionnaires asked whether past or current psychotherapy was for PTSD, another psychiatric condition, for personal growth, or another reason. Subsequent revisions of the LTFUQ also included items asking about occurrence of stressful life events and use of specific psychoactive substances. A hard copy of the LTFUQ was completed either at home or at the the study site.

Suicidal ideation and behavior were collected at all visits and twice during the 7 days of contact in four of the six studies (MP-4, MP-8, MP-9, and MP-12) using the clinician-administered Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al. 2007, 2011), a structured interview addressing presence and intensity of suicidal ideation and behavior.

Statistical analysis

Data from six phase 2 trials were pooled for secondary analyses of long-term effects of MDMA-assisted psychotherapy on PTSD symptoms and other benefits/harms. The modified intent-to-treat (mITT) set included participants who completed at least one active dose of MDMA (75–125 mg) treatment in blinded or open-label sessions and a follow-up assessment. A mixed-effect model repeated-measures (MMRM) analysis

was used to compare changes in CAPS-IV total severity scores at baseline, treatment exit (last follow-up 1 to 2 months after the last active dose MDMA session), and long-term follow-up (12+ months after the last MDMA session). The MMRM model included baseline CAPS-IV scores, study (six individual phase 2 studies) as a fixed effect, and participant as a random effect. Age, PTSD duration, sex, race, and prior self-reported Ecstasy use (substances assumed to contain MDMA) were added stepwise to the base model to assess relationships between each variable and the primary outcome variable. Within-subject pre-/post-treatment effect sizes were calculated with Cohen's d (Kadel and Kip 2012). Descriptive statistics were performed to summarize sample demographic and baseline characteristics, the (i) frequency and proportion of participants who no longer met CAPS-IV diagnostic criteria or had a 15-point reduction in CAPS-IV total severity scores, (ii) suicidal ideation and behavior from C-SSRS, and (iii) responses to the LTFUQ (where question stems were identical across studies and data were available). SAS software version 9.4 (SAS Institute Inc., Cary, N.C.) was used for all analyses.

Results

Sample

A total of 107 participants with moderate to severe PTSD were enrolled across the six studies. Eight participants did not complete treatment, and six of the eight participants underwent at least one experimental session prior to discontinuing study participation. Sixty-two of the participants (57.9%) were female, and 45 (42.1%) were male, with an average age (SD) of 40.5 (10.63) years. Most participants were white/Caucasian (89.7%). The average duration of PTSD at baseline was 214.1 (189.32) months. At the last endpoint after the active treatment phase (treatment exit), 100 participants had received an active dose of MDMA (75–125 mg) in two to three blinded or open-label sessions (Table 1). The long-term follow-up CAPS-IV assessment was completed by 91 participants. Eighty-three participants, who received at least one active dose of MDMA, completed the LTFUQ, and three participants from the first study (MP-1) completed the LTFUQ only, without completing the CAPS (Mithoefer et al. 2013). Thirty participants from the control group (0–40 mg) and six participants from the 75 mg group crossed over to open-label active full-dose MDMA sessions (Fig. 1; see eTable 1 for previously unpublished CAPS data from the open-label crossover). See previous publications for detailed CONSORT flow diagrams, demographics, baseline characteristics, and results from the blinded segment (Mithoefer et al. 2018, 2019, 2011, 2013; Oehen et al. 2013; Ot'alora et al. 2018).

Table 1 Summary of individual study designs

Study	NCT #	Location	Population	MDMA doses	Active MDMA sessions completed[b]	Long-term follow-up	Publications
MP-1	NCT00090064	Charleston, South Carolina	Crime, veterans	0 mg ($n=8$), 125 mg ($n=15$)	1 ($n=2$) 2 ($n=11$) 3 ($n=9$)	CAPS ($n=16$) LTFUQ ($n=19$)	(Mithoefer et al. 2011, 2013)
MP-2	NCT00353938	Biberist, Switzerland	Various	25 mg ($n=5$), 125 mg ($n=9$)	3 ($n=12$)	CAPS ($n=11$) LTFUQ ($n=0$)	(Mithoefer et al. 2019; Oehen et al. 2013)
MP-4	NCT01958593	Vancouver, Canada	Various	0 mg ($n=2$), 125 mg ($n=4$)	3 ($n=6$)	CAPS ($n=6$) LTFUQ ($n=6$)	(Mithoefer et al. 2019)
MP-8	NCT01211405	Charleston, South Carolina	Veterans, firefighters, police officers	30 mg ($n=7$), 75 mg ($n=7$), 125 mg ($n=12$)	1 ($n=1$) 3 ($n=18$) 5 ($n=5$) 6 ($n=1$)	CAPS ($n=24$) LTFUQ ($n=24$)	(Mithoefer et al. 2018, 2019)
MP-9	NCT01689740	Be'er Ya'aqov, Israel	Various	25 mg ($n=3$), 125 mg ($n=7$)[a]	2 ($n=9$)	CAPS ($n=9$) LTFUQ ($n=9$)	(Mithoefer et al. 2019)
MP-12	NCT01793610	Boulder, Colorado	Various	40 mg ($n=6$), 100 mg ($n=9$), 125 mg ($n=13$)	3 ($n=26$)	CAPS ($n=25$) LTFUQ ($n=25$)	(Mithoefer et al. 2019; Ot'alora et al. 2018)

NCT clinicaltrials.gov identifier, *n* number of participants

[a] The first two participants were open-label (125 mg MDMA) and were included in the efficacy analyses

[b] At treatment exit

Treatment exit and long-term follow-up CAPS

The primary efficacy evaluation on change in CAPS-IV total severity scores showed significant reductions in PTSD symptom severity at treatment exit compared to baseline (LS mean (SE) = − 44.8 (2.82), $p < .0001$). The within-subject Cohen's d effect size was 1.58 (95% CI = 1.24, 1.91). CAPS-IV total severity scores decreased further from treatment exit to LTFU (LS mean (SE) = − 5.2 (2.29), $p < .05$), with a Cohen's d effect size of 0.23 (95% CI = 0.04, 0.43), demonstrating the efficacy and stability of treatment outcomes of MDMA-assisted psychotherapy. The covariate analysis was significant for study in the MMRM to suggest changes in CAPS-IV differed across studies (eTable 2). The frequency of participants not meeting PTSD criteria according to the CAPS-IV at treatment exit was 56.0% and increased to 67.0% at the LTFU. Compared to baseline, 82.0% of participants achieved a clinically significant drop of 15 points or greater in CAPS-IV total scores at treatment exit, and 26.4% had a 15-point or greater decrease from treatment exit to LTFU. There were 11 (12.1%) participants who experienced a relapse, defined as a 15-point or greater drop in CAPS-IV scores at treatment exit but then a 15-point or greater increase in scores from treatment exit to LTFU (Table 2).

Suicidal ideation and behavior

Four of the six studies administered the C-SSRS ($n = 68$). In this study sample, which consisted of participants with chronic PTSD, 86.8% (59 participants) reported lifetime positive ideation, 36.8% (25 participants) lifetime serious ideation, and 42.6% (26 participants) lifetime positive behavior. At baseline (between enrollment and first experimental session), 60.3% (41 participants) reported positive ideation, and 1.5% (1 participant) reported positive behavior. At LTFU, 24.2% (15 of 62 participants) reported positive ideation since the last assessment at treatment exit, 1.6% (1 participant) reported serious ideation, and no participants reported any suicidal behavior.

Long-term follow-up questionnaire: harms and benefits

At 12-month follow-up, 97.6% of participants across studies reported experiencing benefits, and among the participants who reported benefits, 92.2% reported that some to all benefits lasted with 53.2% indicating large benefits that lasted or continued to grow (see Table 3). Participants' responses to an open-ended question on benefits from treatment varied and included changes in other symptoms and improvement in other facets of life (see eTable 4 for details). Seven participants across all studies reported experiencing harms (8.4%), and two participants reported those harms were present at 12-month follow-up (3.1%). Six of seven participants rated the degree of harm experienced during the study as 3 or lower on a five-point scale, and one provided a rating of 4. No participants reported any harms as severe, and all participants who reported harm also reported at least one benefit. The most common harm reported was worsened mood ($n = 3$, 3.6%) and other harms ($n = 3$, 3.6%) (Table 3). On the LTFUQ, nine

Table 2 CAPS-IV total severity scores and PTSD diagnostic criteria

	Total	p value
CAPS-IV total score, LS mean (SE)		
Baseline (n = 107)	85.1 (1.91)	
Treatment exit (n = 100)	40.2 (2.73)	
Change baseline to treatment exit	− 44.8 (2.82)	< .0001
LTFU (n = 91)	35.0 (2.66)	
Change baseline to LTFU	− 50.6 (2.68)	< .0001
Change treatment exit to LTFU	− 5.2 (2.29)	.0245
CAPS-IV diagnostic criteria met, no. (%)		
Treatment exit, n (%)		
No	56 (56.0)	
Yes	44 (44.0)	
LTFU, n (%)		
No	61 (67.0)	
Yes	30 (33.0)	
CAPS-IV 15-point drop		
Baseline to treatment exit, n (%)		
No	18 (18.0)	
Yes	82 (82.0)	
Treatment exit to LTFU, n (%)		
No	67 (73.6)	
Yes	24 (26.4)	
Relapse at LTFU[a], n (%)		
No	80 (87.9)	
Yes	11 (12.1)	

[a] Relapse defined as participants who had a CAPS score drop of 15 points or more at treatment exit and a ≥ 15-point increase in CAPS scores from treatment exit to long-term follow-up

participants reported a relapse of PTSD symptoms since completing the active treatment phase. Of these, all nine indicated they had experienced one or more significantly stressful events. Among those who reported any study harms, six of seven participants at treatment exit (86%), and five of seven participants at LTFU (71%), had clinically significant (≥ 15 points) reductions in PTSD symptoms since baseline.

Factors associated with having benefits vs. harms were assessed using available data, with statistical comparisons limited by the imbalance in the total number of participants who reported any benefits (n = 81) vs. any harms (n = 7). Preliminary data indicated higher baseline mean CAPS-IV scores among participants who reported any harms (mean (SD) = 94.4 (19.56) vs. reporting benefits 87.5 (17.57)). Additionally, those who reported any harms had smaller reductions in CAPS-IV scores at treatment exit (mean (SD) = − 36.7 (27.21) vs. reporting any benefits − 48.9 (27.11)). CAPS-IV change scores, however, were comparable from baseline to long-term follow-up between those who reported any harms vs. any benefits (mean (SD) = − 52.3 (39.51) vs. − 53.7 (25.57)), respectively (data not shown).

Current treatments and substance use at long-term follow-up

At baseline, 26 of 55 participants (47.3%) reported therapy for PTSD vs. 22 participants (40.0%) at LTFU. Approximately one-third of participants (31 of 41) who reported therapy for any reason at baseline also reported therapy at LTFU. Responses on the LTFU questionnaire indicated that 38 of 83 participants (45.8%) reported taking any medications, 22 of 64 participants (34.4%) reported taking medications specifically for psychiatric or psychological conditions, and 3 of 64 participants (4.7%) reported taking medications specifically for PTSD (Table 4). Nearly one-third of participants (18 of 64) reported starting new medications since the study. About 94% of participants reported additional MDMA sessions would have been helpful (from available data) (Table 4), although more data are needed to assess a positive correlation between wanting more treatment and increases in benefits, including reduction in PTSD symptoms.

Self-reported use of alcohol and other substances was assessed at LTFU. At baseline, 32 of 107 participants (29.9%) reported at least one prior use of Ecstasy. At LTFU, 8 of 83 participants (9.6%) reported having used Ecstasy or MDMA between treatment exit and long-term follow-up. The eight participants who reported MDMA or Ecstasy use after treatment exit indicated that they used it for therapeutic or recreational purposes. Six of those eight participants had reported Ecstasy use prior to the study. Two participants who did not report previous use sought Ecstasy after exposure to MDMA in a clinical trial. Alcohol consumption since study enrollment decreased among 22 participants (40.0%), stayed the same for 17 participants (30.9%), and increased for 2 participants (3.6%). Some participants reported greater marijuana use at LTFU while others reported less use (Table 4).

Discussion

Across six phase 2 studies, participants with moderate to severe PTSD responded well to MDMA-assisted psychotherapy at treatment exit with decreases in CAPS-IV scores that were sustained at long-term follow-up. At treatment exit, 82% of participants exhibited a clinically significant symptom improvement (15 points or more reduction in CAPS-IV total severity scores) with CAPS-IV total severity scores dropping on average − 44.8 points such that 56% of participants no longer met the criteria for PTSD. PTSD symptoms continued to decrease from treatment exit to long-term follow-up where CAPS-IV total severity scores dropped further on average by − 5.2 points, 67% of participants no longer met the PTSD criteria, and 26% of participants had a clinically significant improvement since study exit. Additionally, proportions of participants who reported positive suicidal ideation decreased

Table 3 Self-reported benefits and harms on the LTFU questionnaire at 12-month follow-up

	Benefits (n = 83)	Harms (n = 83)
Any benefits/harms (yes)[a]	81 (97.6%)	7 (8.4%)
Degree of benefit/harm (1–5)		
1 = slight	0[b]	3 (4.7%)[b]
2	2 (3.1%)[b]	1 (1.6%)[b]
3	5 (7.8%)[b]	2 (3.1%)[b]
4	10 (15.6%)[b]	1 (1.6%)[b]
5 = large benefit/severe harm	45 (70.3%)[b]	0[b]
Has some or all of the benefit/harm lasted until the present? (yes)	59 (92.2%)[b]	2 (3.1%)[b]
How much of the benefit/harm has lasted?		
A = lasted and continued to grow	33 (53.2%)[b]	n/a
B = virtually all the benefit/harm has lasted	6 (9.6%)[b]	n/a
C = most but not all of the benefit/harm has lasted	15 (24.2%)[b]	n/a
D = some but not most of the benefit/harm has lasted	5 (8.1%)[b]	n/a
E = only a small amount of the benefit/harm has lasted	0[b]	n/a
Types of benefits/harms (yes)		
Increased/lessened general well-being	70 (84.3%)	1 (1.2%)
Fewer/increased nightmares, flashbacks, or intrusive memories	59 (71.1%)	2 (2.4%)
Increased ability to feel/difficulty feeling emotions	61 (73.5%)	2 (2.4%)
Less avoidance of/avoiding people or places	57 (68.7%)	2 (2.4%)
Reduced/increased anxiety	57 (68.7%)	2 (2.4%)
Less excessive/excessive vigilance	60 (72.3%)	2 (2.4%)
Improved sleep/sleep disturbance	55 (66.3%)	1 (1.2%)
Other psychological symptoms	16 (25.5%)[b]	1 (1.6%)[b]
Improved/worsened relationships with spouse, partner, or other family	51 (61.5%)	1 (1.2%)
Improved/worsened relationships in general	55 (66.3%)	1 (1.2%)
Improved/diminished work performance	32 (38.6%)	2 (2.4%)
Enhanced/diminished spiritual life	51 (61.5%)	0
Increased/decreased self-awareness and understanding	74 (89.2%)	0
Increased/decreased creativity	39 (47.0%)	2 (2.4%)
Increased/decreased empathy for others	51 (61.5%)	0
More/less involved in the community/world around me	44 (53.0%)	2 (2.4%)
Improved/worsened mood	51 (61.5%)	3 (3.6%)
Other benefits/harms	31 (37.4%)	3 (4.8%)[b]

Note: MP-2 did not administer a LTFU questionnaire

[a] N = 1 participant from MP-8 responded "unsure" to both benefits and harms

[b] % calculation using a sample size (denominator) of N = 64 from MP-4, MP-8, MP-9, and MP-12 (excludes MP-1)

from approximately 60% at baseline to 24% at LTFU, and one participant reported serious ideation at LTFU. Overall, these findings suggest MDMA-assisted psychotherapy consisting of two to three MDMA-assisted psychotherapy sessions with appropriate preparation and follow-up might have the potential to sustain clinically significant improvement in PTSD symptoms at least 1 year post-treatment. Importantly, the conclusions of these data were limited by the lack of a long-term control group, as all participants had received an active dose MDMA by LTFU assessment, which limited our ability to draw conclusions concerning causality. These findings add to previously published LTFU results from one phase 2 study (Mithoefer et al. 2013) and provide insights to inform long-term assessment of future trials.

LTFU response rates were high among participants who received two to three active doses of MDMA: 91 participants completed CAPS-IV assessments, and 83 participants completed the LTFUQ (which excludes MP2, N = 12). Although most PTSD symptom improvement occurred by 1 to 2 months post-treatment, there were further reductions in CAPS-IV total

Table 4 Self-reported responses on the LTFU questionnaire

	N	n (%)
Medications (yes)	83	38 (45.8%)
Indication = psychological	64	22 (34.4%)[a]
Indication = PTSD	64	3 (4.7%)[a]
New since study	64	18 (28.1%)[a]
Therapy at start of study (yes)	83	53 (63.9%)
PTSD	55	26 (47.3%)[b]
Rank 1	55	21 (38.3%)[b]
Rank 2	55	3 (5.5%)[b]
Rank 3	55	2 (3.6%)[b]
Other psychiatric diagnosis	55	2 (3.6%)[b]
Rank 2	55	2 (3.6%)[b]
Personal growth/greater self-understanding	55	21 (38.2%)[b]
Rank 1	55	3 (5.5%)[b]
Rank 2	55	5 (9.1%)[b]
Rank 3	55	9 (16.4%)[b]
Rank 4	55	4 (7.3%)[b]
Other (specify)	55	7 (12.7%)[b,c]
Rank 1	55	2 (3.6%)[b,c]
Rank 3	55	1 (1.8%)[b,c]
Rank 5	55	4 (7.3%)[b,c]
Therapy now (yes)	83	41 (49.4%)
PTSD	55	22 (40.0%)[b]
Rank 1	55	17 (30.9%)[b]
Rank 2	55	3 (5.5%)[b]
Rank 3	55	1 (1.8%)[b]
Rank 4	55	1 (1.8%)[b]
Other psychiatric diagnosis	55	1 (1.8%)[b]
Rank 4	55	1 (1.8%)[b]
Personal growth/greater self-understanding	55	21 (38.2%)[b]
Rank 1	55	5 (9.1%)[b]
Rank 2	55	6 (10.9%)[b]
Rank 3	55	9 (16.4%)[b]
Rank 4	55	1 (1.8%)[b]
Other (specify)	55	5 (9.1%)[b,d]
Rank 2	55	3 (5.5%)[b,d]
Rank 5	55	2 (3.6%)[b,d]
Substance use		
Ecstasy	83	8 (9.6%)
Street or recreational drugs	83	33 (39.8%)
Alcohol		
Decreased since study	55	22 (40.0%)[b]
Stayed the same	55	17 (30.9%)[b]
Increased since study	55	2 (3.6%)[b]
Marijuana		
Decreased since study	55	10 (18.2%)[b]
Stayed the same	55	6 (10.9%)[b]
Increased since study	55	10 (18.2%)[b]
New stressors	64	43 (67.2%)[a]
Relapse (yes)	55	9 (16.4%)[b]

Note: MP-2 did not administer a LTFU questionnaire

[a] % Calculation using a sample size (denominator) of $N = 64$ from MP-4, MP-8, MP-9, and MP-12 (excludes MP-1)

[b] % calculation using a sample size (denominator) of $N = 55$ from MP-4, MP-8, and MP-12 (excludes MP-1 and MP-9)

[c] Rank 1: challenges in adult life healing childhood wounds, help with marriage, stress of running a business; Rank 3: leaving very physically abusive husband; Rank 5: depression, sleep, marriage, N/A

[d] Rank 2: bodywork, heal and move forward, improve life with family; Rank 5: N/A

severity scores at LTFU (average of 1.5 years across six studies). Sustained effects of MDMA-assisted psychotherapy post-treatment were comparable to other PTSD treatments examined in longitudinal studies, including intensive inpatient psychotherapy (Johnson et al. 1996), eye movement desensitization (Edmond and Rubin 2004; Hogberg et al. 2008; van der Kolk et al. 2007; Zimmermann et al. 2007), and cognitive-behavioral and psycho-educational treatments (Dorrepaal et al. 2010; Solomon et al. 2005). Overall, among enrolled participants, all of whom previously failed to tolerate or respond to other medications and/or therapies, there was a 7.6% dropout rate in the treatment period across the six MDMA phase 2 studies. This falls close to the lower range cited in the literature for other pharmacotherapies and trauma-focused psychotherapies (0–79%) (Imel et al. 2013; Lee et al. 2016; Merz et al. 2019) and below an average reported dropout rate of 29% (Lee et al. 2016). Additionally, 94% of participants reported the opinion that more MDMA sessions would be helpful. The low dropout rate, high follow-up rates, and high proportion of "yes" responses to additional sessions suggest treatment tolerability of MDMA-assisted psychotherapy.

In the present analysis, participants received a total of two or three full active doses of MDMA alongside non-drug therapy sessions over the course of 3 to 4 months. The compound MDMA changes brain activity to produce subjective effects, often including an acute sense of well-being, reduction in anxiety, and less distress when facing unpleasant memories (Bedi et al. 2009; Carhart-Harris et al. 2014, 2015; Gamma et al. 2000). In therapeutic settings, MDMA has been described as enhancing emotional memory processing of traumatic memories with greater tolerability (Carhart-Harris et al. 2014; Mithoefer et al. 2013). The pharmacological effects of MDMA can also produce feelings of trust that can lead to a strong therapeutic alliance (Dolder et al. 2018), which has consistently shown to be a greater predictor of outcome than the type of intervention among available psychotherapy treatments (Ardito and Rabellino 2011). Common reasons for dropout in other psychiatric treatments include feeling overwhelmed by intense emotions and having undesired side effects of medications (Goetter et al. 2015; Mott et al. 2014). The pharmacologic effects of MDMA administered within a course of psychotherapy engender a unique therapeutic process that seems to enhance treatment engagement, reduce treatment discontinuation, and extend treatment effects.

Patient preferences have been shown to influence treatment refusal, discontinuation, and outcomes (Swift and Callahan 2011; Swift et al. 2017). Given the high prevalence of resistance to available PTSD treatments, MDMA-assisted psychotherapy could offer a novel treatment option that is tolerable, safe, and efficacious and would provide an additional choice to those who do not tolerate or respond to other treatments. There were no indications of abuse potential for MDMA or other substances including alcohol or marijuana post-

treatment, although further investigation is needed with adequate study design and sample size (MP-1 and MP-9 data were not available). Urinary drug screens performed in MP-2 were all negative for MDMA at LTFU (Oehen et al. 2013).

In addition to clinically and statistically significant improvements in PTSD symptoms, study participants reported benefits beyond decreased CAPS scores. Continued improvement several months after completion of MDMA-assisted psychotherapy might be explained, at least in part, by these additional benefits and any persistent psychological and interpersonal changes that may have resulted. Some of these benefits were related to underlying symptoms of or reduction of PTSD, but others such as having an "enhanced spiritual life," "increased self-awareness and understanding," "increased empathy," and "greater involvement in the community" might be unique and enduring effects of MDMA-assisted psychotherapy. The majority of participants reported lasting benefits at LTFU, and over half reported benefits continued to grow, suggesting participants were able to successfully integrate therapeutic experiences into their daily lives to cultivate continued healing and growth. Studies drawn from specific phase 2 trials found participants who received active doses of MDMA were more likely to change facets of personality (i.e., "openness to experiences"), as assessed by the Neuroticism Extroversion Openness Inventory (Mithoefer et al. 2018; Wagner et al. 2017), which might be considered a deep-rooted transformation. An interview-based qualitative study of MP-8 participants found enduring benefits including experiencing greater engagement in new activities, improved quality of life, and increased openness to further psychotherapy at LTFU (Barone et al. 2019). There is also evidence suggesting that MDMA-assisted psychotherapy may bolster posttraumatic growth (Gorman et al. 2020), a person's sense of improved intrapersonal, social, and/or spiritual quality of life as a result of undergoing a traumatic experience (Tedeschi and Calhoun 1996), with posttraumatic growth still apparent at LTFU. More studies are needed to support these descriptive and preliminary findings and elucidate relationships between MDMA-assisted psychotherapy with long-term improvements on PTSD and other enduring benefits.

There were several limitations to this study including the use of pooled, open-label, long-term follow-up data that lacked a control group. The sample consisted of participants across several studies that varied in number of MDMA-assisted psychotherapy sessions, length of time between end of study and LTFU assessment, location of clinic sites, and in some cases, study design and methods. For example, the MP-8 study consisted of veterans and first responders, and MP-9 was conducted in Israel, where the study and assessments were administered in Hebrew. The final MMRM model adjusted for potential covariates including "study" to account for these differences. However, caution is necessary in generalizing results from these samples to a wider population. Open-label data were

pooled to examine (i) changes in the primary outcome measure (CAPS-IV) at comparable time points that included baseline, treatment exit, and LTFU and (ii) self-reported questionnaire items at LTFU (LTFUQ). Outcome measures were compared over time, while questionnaire responses were presented as descriptive data only. Importantly, the lack of a control group limited causal inferences between MDMA-assisted psychotherapy and any long-term effects. Specifically, long-term improvements in PTSD symptoms and benefits/harms could be attributed to other factors beyond the study treatment. At LTFU, approximately 49% of participants reported being in therapy for any reason (40% specifically for PTSD), and 46% were taking any medications (5% for PTSD). Therefore, it is possible that other treatment effects contributed to long-term effects in post-study treatment.

Approximately 94% of participants reported wanting additional experimental sessions at LTFU. Further study will be needed to determine whether this might suggest the need for additional treatment for PTSD or is indicative of a desire to address other psychological issues or an interest in further psychological growth and enriched relationships. It might, however, support the tolerability of, and perhaps even preference for, MDMA-assisted psychotherapy. Another possibility is that some people may be motivated more by the desire to experience the pleasurable effects of MDMA than by the above factors. This possibility cannot be excluded; however, it is contrary to what study participants have reported and does not align with the clinical impressions of the therapists who supported them in this intensive, challenging, and often painful therapeutic work.

There were large differences between the number of those who reported having any benefits (97.6%) vs. the number reporting harms (8.4%). Sample bias was not likely given the relatively high response rates to the LTFUQ. A total of seven participants indicated experiencing any harms, zero reported any harms as severe, and two indicated that the harms lasted until the present (at LTFU). Statistical comparisons were not performed owing to the small number of participants who reported any harms. However, a preliminary subset analysis indicated all seven participants reported at least one benefit from study participation; six of the seven participants showed a clinically meaningful reduction of PTSD symptoms at treatment exit (86%), and five of the seven participants at LTFU (71%).

Conclusion

Overall findings from the present analyses support MDMA-assisted psychotherapy as an efficacious treatment for PTSD with symptom improvements that were sustained at 1 to 3.8 years pos-treatment. These findings corroborate and expand preliminary results from the first phase 2 trial of this treatment (Mithoefer et al. 2013). Self-reported benefits

outweighed the frequency of harms, and there were no indications of abuse potential of MDMA/Ecstasy or other substances among participants following treatment. Results suggest possible long-term benefits beyond PTSD symptom reduction and therefore warrant further investigation.

Compliance with ethical standards

Role of the funder/sponsor MAPS and MPBC assisted with the study design; monitoring of study data; analysis, management, and interpretation of data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication. The funder had no role in the collection of data or conduct of the study.

Conflicts of interest Lisa Jerome, Allison Feduccia, and Julie Wang received salary support for full-time employment with MPBC. Scott Hamilton, Mt Tam Data Analysis, received salary support from MPBC as an independent biostatistician. Berra Yazar-Klosinski received salary support for full-time employment with MAPS. Amy Emerson received salary support for full-time employment with MPBC. Michael Mithoefer received salary support from MPBC as a clinical investigator and clinical trial medical monitor as well as for training and supervision of research psychotherapists. Rick Doblin received salary support for full-time employment with MAPS.

References

Ardito RB, Rabellino D (2011) Therapeutic alliance and outcome of psychotherapy: historical excursus, measurements, and prospects for research. Front Psychol 2:270

Baggott MJ, Kirkpatrick MG, Bedi G, de Wit H (2015) Intimate insight: MDMA changes how people talk about significant others. J Psychopharmacol 29:669–677

Baggott MJ, Coyle JR, Siegrist JD, Garrison KJ, Galloway GP, Mendelson JE (2016) Effects of 3,4-methylenedioxymethamphetamine on socioemotional feelings, authenticity, and autobiographical disclosure in healthy volunteers in a controlled setting. J Psychopharmacol 30:378–387

Barone W, Beck J, Mitsunaga-Whitten M, Perl P (2019) Perceived benefits of MDMA-assisted psychotherapy beyond symptom reduction: qualitative follow-up study of a clinical trial for individuals with treatment-resistant PTSD. J Psychoactive Drugs 51:199–208

Batelaan NM, Bosman RC, Muntingh A, Scholten WD, Huijbregts KM, van Balkom A (2017) Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials. BMJ (Clinical research ed) 358:j3927

Bedi G, Phan KL, Angstadt M, de Wit H (2009) Effects of MDMA on sociability and neural response to social threat and social reward. Psychopharmacology 207:73–83

Bedi G, Hyman D, de Wit H (2010) Is ecstasy an "empathogen"? Effects of +/−3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. Biol Psychiatry 68:1134–1140

Bedi G, Cecchi GA, Slezak DF, Carrillo F, Sigman M, de Wit H (2014) A window into the intoxicated mind? Speech as an index of psychoactive drug effects. Neuropsychopharmacology 39:2340–2348

Bershad AK, Miller MA, Baggott MJ, de Wit H (2016) The effects of MDMA on socio-emotional processing: does MDMA differ from other stimulants? J Psychopharmacol 30:1248–1258

Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM (1995) The development of a clinician-administered PTSD scale. J Trauma Stress 8:75–90

Carhart-Harris RL, Wall MB, Erritzoe D, Kaelen M, Ferguson B, De Meer I, Tanner M, Bloomfield M, Williams TM, Bolstridge M, Stewart L, Morgan CJ, Newbould RD, Feilding A, Curran HV, Nutt DJ (2014) The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. Int J Neuropsychopharmacol 17:527–540

Carhart-Harris RL, Murphy K, Leech R, Erritzoe D, Wall MB, Ferguson B, Williams LT, Roseman L, Brugger S, De Meer I, Tanner M, Tyacke R, Wolff K, Sethi A, Bloomfield MA, Williams TM, Bolstridge M, Stewart L, Morgan C, Newbould RD, Feilding A, Curran HV, Nutt DJ (2015) The effects of acutely administered 3,

4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. Biol Psychiatry 78:554–562

Cipriani A, Williams T, Nikolakopoulou A, Salanti G, Chaimani A, Ipser J, Cowen PJ, Geddes JR, Stein DJ (2018) Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis. Psychol Med 48:1975–1984

Dolder PC, Muller F, Schmid Y, Borgwardt SJ, Liechti ME (2018) Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects. Psychopharmacology 235:467–479

Dorrepaal E, Thomaes K, Smit JH, van Balkom AJ, van Dyck R, Veltman DJ, Draijer N (2010) Stabilizing group treatment for complex posttraumatic stress disorder related to childhood abuse based on psycho-education and cognitive behavioral therapy: a pilot study. Child Abuse Negl 34:284–288

Edmond T, Rubin A (2004) Assessing the long-term effects of EMDR: results from an 18-month follow-up study with adult female survivors of CSA. J Child Sex Abus 13:69–86

Eftekhari A, Ruzek JI, Crowley JJ, Rosen CS, Greenbaum MA, Karlin BE (2013) Effectiveness of national implementation of prolonged exposure therapy in Veterans Affairs care. JAMA Psychiatry 70:949–955

Feduccia AA, Mithoefer MC (2018) MDMA-assisted psychotherapy for PTSD: are memory reconsolidation and fear extinction underlying mechanisms? Prog Neuro-Psychopharmacol Biol Psychiatry 84:221–228

Feduccia AA, Holland J, Mithoefer MC (2018) Progress and promise for the MDMA drug development program. Psychopharmacology 235:561–571

Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer M, Doblin R (2019) Breakthrough for trauma treatment: safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. Front Psychiatry 10:1–7

Gamma A, Buck A, Berthold T, Liechti ME, Vollenweider FX (2000) 3, 4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by $[H_2^{15}O]$-PET in healthy humans. Neuropsychopharmacology 23:388–395

Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, Brenneisen R (2014) Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis 202:513–520

Goetter EM, Bui E, Ojserkis RA, Zakarian RJ, Brendel RW, Simon NM (2015) A systematic review of dropout from psychotherapy for posttraumatic stress disorder among Iraq and Afghanistan combat veterans. J Trauma Stress 28:401–409

Gorman I, Belser AB, Jerome L, Hennigan C, Shechet B, Hamilton S, Yazar-Klosinski B, Emerson A, Feduccia AA (2020) Posttraumatic growth after MDMA-assisted psychotherapy for posttraumatic stress disorder. J Trauma Stress 33:161–170

Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol 30:1181–1197

Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer GR (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 68:71–78

Grof S (2008) LSD psychotherapy: 4th edition. Multidisciplinary Association for Psychedelic Studies, Santa Cruz

Hogberg G, Pagani M, Sundin O, Soares J, Aberg-Wistedt A, Tarnell B, Hallstrom T (2008) Treatment of post-traumatic stress disorder with eye movement desensitization and reprocessing: outcome is stable in 35-month follow-up. Psychiatry Res 159:101–108

Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL (2004) Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med 351:13–22

Imel ZE, Laska K, Jakupcak M, Simpson TL (2013) Meta-analysis of dropout in treatments for posttraumatic stress disorder. J Consult Clin Psychol 81:394–404

Javidi H, Yadollahie M (2012) Post-traumatic stress disorder. Int J Occup Environ Med 3:2–9

Johnson DR, Rosenheck R, Fontana A, Lubin H, Charney D, Southwick S (1996) Outcome of intensive inpatient treatment for combat-related posttraumatic stress disorder. Am J Psychiatry 153:771–777

Kadel R, Kip K (2012) A SAS macro to compute effect size (Cohen's d) and its confidence interval from raw survey data. Proceedings of the annual southeast SAS users group conference

Kamilar-Britt P, Bedi G (2015) The prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA): controlled studies in humans and laboratory animals. Neurosci Biobehav Rev 57:433–446

Kessler RC, Ames M, Hymel PA, Loeppke R, McKenas DK, Richling DE, Stang PE, Ustun TB (2004) Using the World Health Organization health and work performance questionnaire (HPQ) to evaluate the indirect workplace costs of illness. J Occup Environ Med 46:S23–S37

Kirkpatrick MG, Baggott MJ, Mendelson JE, Galloway GP, Liechti ME, Hysek CM, de Wit H (2014) MDMA effects consistent across laboratories. Psychopharmacology 231:3899–3905

Kline AC, Cooper AA, Rytwinksi NK, Feeny NC (2018) Long-term efficacy of psychotherapy for posttraumatic stress disorder: a meta-analysis of randomized controlled trials. Clin Psychol Rev 59:30–40

Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, Karam EG, Meron Ruscio A, Benjet C, Scott K, Atwoli L, Petukhova M, Lim CCW, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, Bunting B, Ciutan M, de Girolamo G, Degenhardt L, Gureje O, Haro JM, Huang Y, Kawakami N, Lee S, Navarro-Mateu F, Pennell BE, Piazza M, Sampson N, Ten Have M, Torres Y, Viana MC, Williams D, Xavier M, Kessler RC (2017) Posttraumatic stress disorder in the World Mental Health Surveys. Psychol Med 47:2260–2274

Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW (2016) Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. Depress Anxiety 33:792–806

Merz J, Schwarzer G, Gerger H (2019) Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: a network meta-analysis. JAMA Psychiatry

Mithoefer M (2017) A manual for MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder; Version 8.1, http://www.maps.org/research/mdma/mdma-research-timeline/4887-a-manual-for-mdma-assisted-psychotherapy-in-the-treatment-of-ptsd

Mithoefer MC, Wagner MT, Mithoefer AT, 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. J Psychopharmacol 25:439–452

Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, Michel Y, Brewerton TD, 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. J Psychopharmacol 27:28–39

Mithoefer MC, Grob CS, Brewerton TD (2016) Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. Lancet Psychiatry 3:481–488

Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, Holland J, Hamilton S, Yazar-Klosinski B, Emerson A, Doblin R (2018) 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. Lancet Psychiatry 5: 486–497

Mithoefer MC, Feduccia AA, 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: 2735–2745

Mott JM, Mondragon S, Hundt NE, Beason-Smith M, Grady RH, Teng EJ (2014) Characteristics of U.S. veterans who begin and complete prolonged exposure and cognitive processing therapy for PTSD. J Trauma Stress 27:265–273

Nagy LM, Morgan CA 3rd, Southwick SM, Charney DS (1993) Open prospective trial of fluoxetine for posttraumatic stress disorder. J Clin Psychopharmacol 13:107–113

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). J Psychopharmacol 27:40–52

Ot'alora GM, Grigsby J, Poulter B, Van Derveer JW 3rd, Giron SG, Jerome L, Feduccia AA, Hamilton S, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R (2018) 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: a randomized phase 2 controlled trial. J Psychopharmacol 32:1295–1307

Posner K, Oquendo MA, 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. Am J Psychiatry 164:1035–1043

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ (2011) The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 168:1266–1277

Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA (2002) A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. J Consult Clin Psychol 70: 867–879

Schmid Y, Hysek CM, Simmler LD, Crockett MJ, Quednow BB, Liechti ME (2014) Differential effects of MDMA and methylphenidate on social cognition. J Psychopharmacol 28:847–856

Schnurr PP (2007) The rocks and hard places in psychotherapy outcome research. J Trauma Stress 20:779–792

Solomon Z, Shklar R, Mikulincer M (2005) Frontline treatment of combat stress reaction: a 20-year longitudinal evaluation study. Am J Psychiatry 162:2309–2314

Steenkamp MM, Litz BT, Hoge CW, Marmar CR (2015) Psychotherapy for military-related PTSD: a review of randomized clinical trials. JAMA 314:489–500

Swift JK, Callahan JL (2011) Decreasing treatment dropout by addressing expectations for treatment length. Psychother Res 21:193–200

Swift JK, Greenberg RP, Tompkins KA, Parkin SR (2017) Treatment refusal and premature termination in psychotherapy, pharmacotherapy, and their combination: a meta-analysis of head-to-head comparisons. Psychotherapy (Chic) 54:47–57

Tedeschi RG, Calhoun LG (1996) The Posttraumatic Growth Inventory: measuring the positive legacy of trauma. J Trauma Stress 9:455–471

van der Kolk BA, Spinazzola J, Blaustein ME, Hopper JW, Hopper EK, Korn DL, Simpson WB (2007) A randomized clinical trial of eye movement desensitization and reprocessing (EMDR), fluoxetine, and pill placebo in the treatment of posttraumatic stress disorder: treatment effects and long-term maintenance. J Clin psychiatry 68: 37–46

Wagner MT, Mithoefer MC, Mithoefer AT, MacAulay RK, Jerome L, Yazar-Klosinski B, Doblin R (2017) Therapeutic effect of increased openness: investigating mechanism of action in MDMA-assisted psychotherapy. J Psychopharmacol 31:967–974

Young MB, Andero R, Ressler KJ, Howell LL (2015) 3,4-Methylenedioxymethamphetamine facilitates fear extinction learning. Transl Psychiatry 5:e634

Young MB, Norrholm SD, Khoury LM, Jovanovic T, Rauch SAM, Reiff CM, Dunlop BW, Rothbaum BO, Howell LL (2017) Inhibition of serotonin transporters disrupts the enhancement of fear memory extinction by 3,4-methylenedioxymethamphetamine (MDMA). Psychopharmacology 234:2883–2895

Zimmermann P, Biesold KH, Barre K, Lanczik M (2007) Long-term course of post-traumatic stress disorder (PTSD) in German soldiers: effects of inpatient eye movement desensitization and reprocessing therapy and specific trauma characteristics in patients with non-combat-related PTSD. Mil Med 172:456–460