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Title: 3,4-methylenedioxyamphetamine (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

Authors:

Michael C. Mithoefer M.D.

Clinical Assistant Professor

Medical University of South Carolina

Mount Pleasant, SC 29464

Ann T. Mithoefer, B.S.N

Sub-Investigator

Mount Pleasant, SC 29464

Allison A. Feduccia Ph.D.

Clinical Data Scientist

MAPS Public Benefit Corporation

1115 Mission St

Santa Cruz, CA 95060

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Lisa Jerome Ph.D.

Clinical Research and Information Specialist

MAPS Public Benefit Corporation

1115 Mission St

Santa Cruz, CA 95060

Mark Wagner, Ph.D.

Professor of Neurology

Medical University of South Carolina

Charleston, South Carolina 29425

Joy Wymer, Ph.D.

Assistant Professor of Neurology

Medical University of South Carolina

Neuropsychologist

Tidewater Neuropsychology

Mount Pleasant, SC 29464

Julie Holland, M.D.

Psychiatrist

Private Practice Office

New York, NY 10016

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Scott Hamilton, Ph.D.

Associate Professor

Stanford School of Medicine

Palo Alto, CA 94304-5778

Berra Yazar-Klosinski, Ph.D.

Associate Director of Clinical Research

Multidisciplinary Association for Psychedelic Studies

1115 Mission St

Santa Cruz, CA 95060

Amy Emerson, B.A.

Executive Director and Director of Clinical Research

MAPS Public Benefit Corp.

1115 Mission St

Santa Cruz, CA 95060

Rick Doblin, Ph.D.

Executive Director

Multidisciplinary Association for Psychedelic Studies

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1115 Mission St
Santa Cruz, CA 95060

Corresponding Author:

Allison Feduccia, Ph.D.
Clinical Data Scientist
MAPS Public Benefit Corporation
1115 Mission St
Santa Cruz, CA 95060
Office: 831-429-6362 x110
alli@mapsbcorp.com

Author Contributions:

Dr. Scott Hamilton is responsible for integrity of the data and accuracy of data analyses.
Study concept and design: M. Mithoefer, A. Mithoefer, L. Jerome, A. Emerson, B. Yazar-Klosinski, R. Doblin
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: M. Mithoefer, A. Feduccia, L. Jerome
Critical revision of the manuscript for important intellectual content: All authors.
Obtained funding: R. Doblin
Study supervision: M. Mithoefer, A. Mithoefer

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Summary

Background Post-traumatic stress disorder (PTSD) is prevalent in military personnel and first responders, many of whom do not respond to currently available treatments. This study aimed to assess the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treating chronic PTSD in this population.

Methods We did a randomised, double-blind, dose-response, phase 2 trial at an outpatient clinic in the USA. We included service personnel who were 18 years or older, with chronic PTSD duration of 6 months or more, and who had a Clinician-Administered PTSD Scale (CAPS-IV) total score of 50 or greater. Using a web-based randomisation system, we randomly assigned participants (1:1:2) to three different dose groups of MDMA plus psychotherapy: 30 mg (active control), 75 mg, or 125 mg. We masked investigators, independent outcome raters, and participants until after the primary endpoint. MDMA was administered orally in two 8-h sessions with concomitant manualised psychotherapy. The primary outcome was mean change in CAPS-IV total score from baseline to 1 month after the second experimental session. Safety was monitored through adverse, spontaneously reported expected reactions, vital signs, and suicidal ideation and behaviour. This study is registered with ClinicalTrials.gov, number NCT01211405.

Findings Between Nov 10, 2010, and Jan 29, 2015, 26 veterans and first responders met eligibility criteria and were randomly assigned to receive 30 mg (n=7), 75 mg (n=7), or 125 mg (n=12) of MDMA plus psychotherapy. At the primary endpoint, the 75 mg and 125 mg groups had significantly greater decreases in PTSD symptom severity (mean change CAPS-IV total scores of -58.3 [SD 9.8] and -44.3 [28.7]; $p=0.001$) than the 30 mg group (-11.4 [12.7]).

Compared with the 30 mg group, Cohen's *d* effect sizes were large: 2.8 (95% CI 1.19–4.39) for the 75 mg group and 1.1 (0.04–2.08) for the 125 mg group. In the open-label crossover with full-dose MDMA (100–125 mg), PTSD symptom severity significantly decreased in the group that had previously received 30 mg ($p=0.01$), whereas no further significant decreases were observed in the group that previously achieved a large response after 75 mg doses in the blinded segment ($p=0.81$). PTSD symptoms were significantly reduced at the 12-month follow-up compared with baseline after all groups had full-dose MDMA (mean CAPS-IV total score of 38.8 [SD 28.1] vs 87.1 [16.1]; $p<0.0001$). 85 adverse events were reported by 20 participants. Of these adverse events, four (5%) were serious: three were deemed unrelated and one possibly related to study drug treatment.

Interpretation Active doses (75 mg and 125 mg) of MDMA with adjunctive psychotherapy in a controlled setting were effective and well tolerated in reducing PTSD symptoms in veterans and first responders.

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Research in Context

Evidence before this study

Before development of this study's protocol, we searched PubMed, the clinicaltrials.gov registry, and books containing extensive bibliographies of 3,4-methylenedioxymethamphetamine (MDMA) research for all articles and listings containing the terms "MDMA" or "ecstasy",

including non-clinical studies, clinical trials and case reports of varying quality published from Jan 1, 1978, to December 17, 2009. We considered all these articles published in English only, except for case reports. In 2001, the first comprehensive review was presented in our MDMA Investigator's Brochure; 1044 MDMA-related papers were included. Early reports published in the mid-1980s described the use of MDMA as a psychotherapeutic adjunct, including use in psychotherapy for post-traumatic stress disorder (PTSD). These accounts, an early uncontrolled study, and an incomplete dose-response study that provided safety data led to the design and implementation of two randomised, double-blind studies of MDMA-assisted psychotherapy in people with chronic PTSD, one using inactive placebo and the other comparing an active low dose MDMA. The studies followed a manualised form of psychotherapy similar but not identical to psychotherapy using classic psychedelics. The current study design was informed by confirmation that no other research of MDMA-assisted psychotherapy had been published, and by the design and preliminary results of two pilot studies that were ongoing at the time of development of this study. When completed, one pilot study reported a significant reduction in PTSD symptoms in MDMA versus inactive placebo that lasted beyond 12 months after study completion. The second pilot study had a similar effect size as the first study, but did not detect a significant difference in Clinician-Administered PTSD Scale (CAPS-IV) scores two months after treatment ($p=.066$); however, it did show significant symptom reduction compared to baseline 1 year after treatment with active-dose MDMA.

Added value of this study

This is the first dose-response study of MDMA-assisted psychotherapy to compare three doses of MDMA, in a population of first responders and veterans with PTSD, we showed that active

doses of MDMA had a significant improvement compared with the control dose in the primary measure of PTSD symptom severity, as well as in some of the secondary measures of depression symptoms and sleep quality, confirming and extending findings of the first studies.

Implications of all the available evidence

This study is among the six Phase 2 trials that led to the US Food and Drug Administration designation of MDMA-assisted psychotherapy for PTSD as a breakthrough therapy. Together these Phase 2 trials support drug development programme of the Multidisciplinary Association for Psychedelic Studies aimed at making MDMA-assisted psychotherapy a prescription treatment delivered in specialised clinics. Pending the results of multicentre phase 3 clinical trials, this well tolerated and efficacious treatment might prove to be an important addition to the available treatments for PTSD, and may also have implications for future exploration of other pharmacological agents that could act as adjuncts or catalysts to psychotherapy.

Introduction

Posttraumatic stress disorder (PTSD) is a major public health problem, particularly among military veterans. Prevalence of PTSD in military personnel and veterans (17.1%)¹ and first responders (10-32%)² is much higher than the lifetime occurrence in the general population (8%). In addition to the severe psychological burden, chronic PTSD is associated with increased medical morbidity, occupational and relationship problems, decreased quality of life³, overall decreased life satisfaction and happiness, and increased risk of suicide⁴.

Treatment options for PTSD include pharmacotherapy and psychotherapies. The two medications approved by the US Food and Drug Administration (FDA) for PTSD, sertraline and

paroxetine, reduce symptom severity with limited effectiveness⁵, especially in veterans. Off-label prescription of drugs, including antidepressants, antipsychotics, mood stabilizers, and benzodiazepines, is common, though risks and benefits for PTSD have not been established in randomised controlled trials⁶. Trauma-focused psychotherapies are more effective than pharmacotherapy⁷. A meta-analysis of trials for military-related PTSD found that both Cognitive Processing Therapy and Prolonged Exposure had large effect sizes with 49-70% of participants attaining clinically meaningful symptom improvement; however, 60-72% of veterans receiving either of these therapies retained their PTSD diagnosis⁹. High dropout rates (27-40%) occur with trauma-focused psychotherapies, partially due to adverse outcomes, such as worsening symptoms, admission to hospital, or disengagement from treatments^{10,11}. Relatively few randomised clinical trials of military-related PTSD have been done.

Development of new treatments should address the common reasons for treatment avoidance, failure and dropout. One approach to developing more effective psychotherapy is to administer a drug during psychotherapy sessions intended to catalyse the psychotherapeutic process^{6,8}. 3,4-methylenedioxymethamphetamine (MDMA) has shown promise as a psychotherapeutic adjunct¹². Two published clinical trials of MDMA-assisted psychotherapy showed large effect sizes (1.24 and 1.05) with low dropout (8.7% and 14.3%)^{13,14} and durable improvements (average 45 months in 74% of one cohort)¹⁵. Most participants had crime-related PTSD, such as sexual abuse, assault and rape. Therefore, we aimed to assess the efficacy and safety of MDMA-assisted psychotherapy in military veterans, firefighters, and police officers with PTSD resulting from their service.

Methods

Study design and participants

We did a randomised, double-blind, dose-response, phase 2 trial at an outpatient psychiatric clinic in Charleston, SC, USA. The protocol for this study was approved by Western-Copernicus Group institutional review board. The protocol provides full details of the study design. We recruited participants through referrals by mental health professionals and internet advertisements or word of mouth. We included participants of either sex who were veterans, firefighters, or police officers with chronic PTSD resulting from traumatic experience during their service. Additionally, we included only participants who were 18 years or older, with PTSD duration of 6 months or more, and who had a Clinician-Administered PTSD Scale (CAPS-IV)¹⁵ total score of 50 or more. Inclusion criteria required failure to respond to or inability to tolerate previous pharmacotherapy or psychotherapy. Participants were required to taper and abstain from psychotropic medications during study participation except for sedative hypnotics or anxiolytics used as needed between MDMA sessions. Exclusion criteria included major medical conditions except controlled hypertension or adequately treated hypothyroidism, and pregnant or lactating women or women not using effective contraception. Permitted comorbid disorders were anxiety disorders, affective disorders except bipolar disorder type 1, substance abuse or dependence in remission for 60 days or more, and eating disorders without active purging. We also had an additional exclusion criterion that cannot be revealed publicly until a future phase 3 trial is complete. Participants who gave written informed consent were assessed by an independent rater for psychiatric screening using the CAPS-IV and Structured Clinical Interview for DSM-IV Axis I Disorders,¹⁶ and by a physician for assessment of non-psychiatric medical criteria.

Randomisation and masking

We randomly assigned participants using a web-based randomisation system that used unique container numbers instituted by individuals monitoring the randomisation process who did not communicate with site staff, those monitoring the study, or data and statistical analysts.

Approximately 24 h before the first experimental MDMA session, participants were randomly assigned (1:1:2) to three different dose groups of MDMA plus psychotherapy. We masked investigators, independent outcome raters, and participants until after the primary endpoint. After the primary endpoint, the blind was broken and the study entered the crossover design, which was open-label. MDMA was manufactured by David Nichols (Purdue University, West Lafayette, IN, USA). A pharmacist compounded the drug into gelatin capsules with lactose to ensure all blinded capsules had similar appearance and weight.

Procedures

Depending on the dose groups, MDMA was administered orally at 30 mg (active control), 75 mg, or 125 mg in two blinded experimental sessions spaced 3–5 weeks apart (initial dose followed 1.5–2 h later by an optional supplemental dose of half the initial dose). Figure 1 depicts the flow of participants through the study. The first MDMA session was preceded by three 90-min psychotherapy sessions to establish a therapeutic alliance and prepare participants for the MDMA experience. MDMA was administered at monthly intervals during 8-h experimental sessions of manualised psychotherapy with a male or female co-therapy team. The relatively non-directive or client-directed psychotherapy used during MDMA-assisted sessions, and the approaches to preparation and follow-up sessions, are described in the treatment manual.¹⁷ Experimental sessions were followed by an overnight stay onsite, 7 days of telephone contact,

and three 90-min psychotherapy sessions aimed at integrating the experience. Overall, a course of treatment included 18 h of non-drug psychotherapy and 16–24 h (2–3 sessions) of MDMA-assisted psychotherapy. Outcome measures were administered by masked independent raters at baseline and 1 month after the second experimental session (primary endpoint), just before the blind was broken. Subsequently, participants randomly assigned to receive 125 mg of MDMA had one open-label session (within 3–5 weeks of the previous blinded MDMA session) with associated integrative visits and a 2-month follow-up with outcomes assessed (end of stage 1). Participants randomly assigned to receive 30 mg or 75 mg of MDMA crossed over to have one 90-min preparatory session (within 5 months of the primary endpoint), then three open-label sessions spaced a month apart with flexible dosing of MDMA (100–125 mg) followed by the integrative visits and outcome assessments (secondary endpoint, end of stage 2) at corresponding intervals to the blinded segment. Data were collected during the active treatment period from baseline to 2 months after the final MDMA session, and participants in all three groups were assessed 12 months after the last full dose. A choice between 100 mg and 125 mg (according to the participant's preference and investigators' judgment) was added in the open-label crossover as part of a protocol amendment (appendix) to gain pilot data about this dose without affecting the blinded stage of the study.

Outcomes

The primary outcome was mean change in the CAPS-IV total score from baseline to 1 month after the second experimental session. CAPS-IV is a semi-structured interview done by an independent rater that identifies and assesses PTSD through diagnostic and symptom severity scores. Secondary outcomes included the following measures: depression symptoms, measured

with the self-reported Beck Depression Inventory-II (BDI-II);¹⁸ self-reported sleep quality, assessed by the Pittsburgh Sleep Quality Index (PSQI);¹⁹ perceived growth following trauma, assessed with the Post-Traumatic Growth Inventory (PTGI);²⁰ personality factors, assessed via the NeuroticismExtroversion-Openness-Personality Inventory-Revised (NEO-PI-R);²¹ symptoms of dissociation, assessed in a subset of participants with the self-reported Dissociative Experiences Scale II (DES-II);²² and general psychological function, scored by independent raters using the singleitem Global Assessment of Functioning (GAF).²³ Safety was monitored through adverse events, spontaneously reported expected reactions, vital signs, and suicidal ideation and behaviour. Adverse events requiring medical intervention were recorded until 2 months following the last experimental session. Events requiring changes in psychiatric medication were recorded throughout the study. Expected reactions were recorded during experimental sessions and 7 days after the sessions. Blood pressure and heart rate were measured via an automated sphygmomanometer (5200 series, Welch Allyn, Skaneateles Falls, NY, USA) every 15 min for the first 4 h, then every 30 min until the session ended. Body temperature was measured at 60–90 min intervals via a tympanic thermometer (Thermo Scan, Braun, Kronberg, Germany). The clinician-administered Columbia-Suicide Severity Rating Scale (C-SSRS),²⁴ a structured interview addressing presence and intensity of suicidal ideation and behaviour, was used at all visits and twice during the 7 days of telephone contact.

Statistical analysis

This trial was a pilot dose-response study; therefore, it was not powered to detect statistical significance. The study design and sample size were informed by two previous phase 2 pilot studies.^{12–14} Efficacy analyses were done on the intention-to-treat population, which included

all participants who were randomly allocated to the dose groups of MDMA with at least one dose exposure. The primary outcome measure was analysed by ANOVA at an α level of 0.05. Preplanned t tests were used to compare each MDMA dose group. Changes in the secondary measure scores were analysed in the same manner. Effect sizes were computed with Cohen's d independent-groups pretest–post-test design. Open-label crossover data were analysed by within-subjects t tests, comparing scores at primary endpoint to stage two secondary endpoint. Scores at 12-month follow-up were compared with baseline by within-subjects t tests. Exploratory analyses of effects after two versus three sessions were also done with within-subjects t tests. Peak vital signs from MDMA sessions were analysed with ANOVA, then t tests for pairwise comparisons. We did the analyses using SPSS (version 20). This trial is registered with ClinicalTrials.gov, number NCT01211405.

Role of the funding source

MAPS Public Benefit Corporation (MPBC), a wholly owned subsidiary of the Multidisciplinary Association for Psychedelic Studies (MAPS), was the trial organiser. Both the funder and MPBC assisted with study design; monitoring of study data; analysis, management, and interpretation of data; preparation, review, and approval of manuscript; and decision to submit the manuscript for publication. The funder had no role in data collection or study conduct. The first author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 10, 2010, and Jan 29, 2015, 26 service personnel met eligibility criteria and were enrolled into this study: four participants enrolled through referrals by mental health professionals and 22 through internet advertisements or word of mouth. These 26 participants were randomly assigned to receive 30 mg (n=7), 75 mg (n=7), or 125 mg (n=12) of MDMA plus psychotherapy (figure 2). Table 1 shows the baseline characteristics and demographic of these veterans (n=22), firefighters (n=3), and police officer (n=1). Participants had moderate-to-severe PTSD, with a mean baseline CAPS-IV total score of 87.1 (SD 16.13). Six (23%) of 26 participants had previously taken ecstasy 2–5 times before study enrolment. 24 (92%) participants completed treatments through the 1-month follow-up, and two (8%) completed the baseline assessment (one experimental session, and at least one follow-up assessment). Six (86%) of seven participants who were assigned to the 30 mg group and six (86%) of seven assigned to the 75 mg group completed the crossover open-label sessions and assessments. 24 participants completed the 12-month follow-up assessments. The mean change in the CAPS-IV total score from baseline to 1 month after the second blinded experimental session of MDMA plus psychotherapy was -11.4 (SD 12.7) for the 30 mg group, -58.3 (9.8) for the 75 mg group, and -44.3 (28.7) for the 125 mg group (table 2; figure 3). The 75 mg ($p=0.0005$) and 125 mg ($p=0.004$) MDMA groups had significantly greater improvements in PTSD symptom severity than the 30 mg MDMA group (ANOVA for mean change in CAPS-IV total score $p=0.001$); no significant differences were found between the 75 mg and 125 mg groups ($p=0.185$). Compared with the 30 mg group, Cohen's d effect sizes were large: 2.8 (95% CI 1.19–4.39) for the 75 mg group and 1.1 (0.04–2.08) for the 125 mg group. At the primary endpoint (ie, after the 1-month second blinded experimental session), a larger percentage of participants in the active dose groups did not meet PTSD diagnostic criteria on CAPS-IV compared with the comparator group

(six [86%] of seven participants in the 75 mg group and seven [58%] of 12 in the 125 mg group vs two [29%] of seven in the 30 mg group). Additionally, more participants reached a clinically significant decrease of more than 30% in CAPS-IV total score after two active doses of MDMA (all seven [100%] in the 75 mg group, eight [67%] in the 125 mg group, and two [29%] in the 30 mg group). A sensitivity analysis adjusting for baseline scores produced similar results (data not shown). 1 month after the second blinded experimental session, depression symptoms for the 125 mg group were significantly reduced compared with the 30 mg group (mean change in BDI-II score of -24.6 vs -4.6 ; $p=0.0003$), while comparison of the 75 mg group with the 30 mg group was not significant (-15.4 vs -4.6 ; $p=0.052$; table 2), with the 75 mg group showing a larger average drop from baseline (ANOVA for mean change in BDI-II scores $p=0.001$; figure 3). For mean change in PSQI scores (figure 3), the 75 mg group showed the greatest improvement in sleep quality followed by the 125 mg and 30 mg groups (ANOVA for mean change in PSQI scores $p=0.029$). *t* tests indicated superiority in the 75 mg ($p=0.014$) and 125 mg ($p=0.022$) groups compared with the 30 mg group. Post-traumatic growth followed a similar trajectory in mean PTGI scores (ANOVA for mean change in PTGI scores $p<0.0001$), with the active dose groups reporting significant post-traumatic growth compared with the 30 mg group ($p<0.0001$). Global psychological function improved (ANOVA for mean change in GAF scores $p=0.004$), with significantly higher functioning in the 75 mg ($p=0.004$) and 125 mg ($p=0.002$) groups than the 30 mg group. Similarly, the active dose groups had significant improvement in dissociative symptoms compared with the 30 mg group ($p=0.02$ for the 75 mg group vs 30 mg group; $p=0.01$ for the 125 mg group vs 30 mg group; ANOVA for mean change in DES-II scores $p=0.026$). For the NEO-PI-R, only changes in openness produced significant differences between groups (ANOVA for mean

change in NEO-PI-R personality scores $p=0.025$), with the 75 mg group showing qualities of being more open than the 30 mg group ($p=0.02$). 1 month after completing two open-label sessions of 100–125 mg of MDMA in the crossover, the group that received 30 mg during blinded sessions showed reductions in symptom severity, mean change from the primary endpoint was CAPS-IV total score -27.0 (SD 17.5), and two (33%) of six participants did not meet CAPS-IV PTSD diagnostic criteria (appendix). Within-subject t tests comparing scores at primary and secondary endpoints showed significant improvements in mean CAPS-IV total score ($p=0.01$) and four (67%) of six participants attained a decrease of more than 30% in CAPS-IV total score (appendix). The 75 mg group did not have further significant decreases in mean CAPS-IV total score after the two open-label sessions ($p=0.81$), but all of the participants no longer met CAPS-IV PTSD criteria. Although CAPS-IV total scores continued to trend towards further improvement, within-subject comparison of two versus three sessions of MDMA did not yield significant differences for any measures or groups (appendix). PTSD symptoms were significantly reduced at the 12-month follow-up compared with the baseline for all MDMA groups combined (mean CAPS-IV total score of 38.8 [SD 28.1] vs 87.1 [16.1]; $p<0.0001$; table 3). Of the 24 participants who completed the 12-month follow-up, 16 (67 %) did not meet CAPS-IV PTSD criteria. On the one hand, two participants who did not meet PTSD criteria at treatment exit (after three active doses of the MDMA sessions) met PTSD diagnostic criteria at 12-month follow-up. On the other hand, three participants who met criteria at exit did not meet criteria at the 12-month follow-up. Scores on all secondary measures at 12-month follow-up showed improvement compared with baseline (table 3). Depression symptom severity as measured on BDI-II was severe at baseline and changed to minimal by 12-month follow-up ($p<0.0001$). Similarly, sleep quality was vastly improved at the last endpoint as

measured by PSQI ($p=0.0002$). Findings for post-traumatic growth ($p<0.0001$) and global functioning ($p<0.0001$) showed marked gains, and severity of dissociative symptoms was reduced ($p=0.046$). Compared with baseline, all NEO personality traits had significantly improved except conscientiousness ($p=0.36$; table 3). Two (8%) of 24 participants reported taking ecstasy once during the 12 months following the active treatment phase. At study enrolment, both of these participants had used ecstasy two times previously (6 months to 2 years before enrolment). The treatment was well tolerated. 85 adverse events were reported by 20 participants during the study (appendix), of which four (5%) occurred before drug administration. Four (5%) of 85 were serious adverse events: three were deemed unrelated and one possibly related to study drug treatment. Serious adverse events deemed unrelated were suicidal ideation in response to life events, major depression (same participant), and appendicitis. One participant who had exhibited a premature ventricular contraction at baseline developed an acute increase in premature ventricular contractions during the third openlabel session, detected on-site through routine heart rate readings. This participant had an overnight hospital stay for observation and cardiac assessment, and recovered fully without evidence for vascular or structural cardiac disease. The number of participants reporting at least one treatment-emergent adverse event was similar across groups: six (86%) of seven in the 30 mg and 75 mg groups, and eight (67%) of 12 in the 125 mg group. The most frequently reported treatment-emergent adverse events were psychiatric symptoms (table 4). The most frequently reported expected adverse reactions during experimental sessions included anxiety, headache, fatigue, and muscle tension (table 4). Adverse reactions during 7 contact days included fatigue, anxiety, and insomnia (table 4). Most adverse reactions were mild to moderate in severity, with occurrence decreasing across the 7 days following experimental sessions. Self-limited elevations in pulse,

blood pressure, and body temperature were observed during MDMA sessions and did not require medical intervention (appendix). ANOVA of peak vital signs during blinded sessions showed a significant dose effect for systolic blood pressure (SBP; $p < 0.0001$), diastolic blood pressure (DBP; $p = 0.003$), and heart rate (HR; $p < 0.0001$) but not for body temperature ($p = 0.095$). The 125 mg group was significantly higher than the 30 mg for SBP ($p < 0.0001$), DBP ($p = 0.0007$), and HR ($p < 0.0001$), and the 75 mg group was significantly higher than the 30 mg for SBP ($p = 0.007$) and HR ($p = 0.018$). At all post-treatment endpoints, the percentage of participants reporting suicidal ideation and behaviour was reduced compared with baseline life-time and pre-treatment reports (table 1; appendix). During the treatment period, transient increases in suicidal ideation were observed in the 30 mg, 125 mg, and open-label groups. One participant, who had a history of suicide attempts before enrolment, was admitted to hospital for 6 days by their psychiatrist because of suicidal thoughts 13 days after their second 30 mg session. This patient subsequently completed the study. There were no treatment-emergent reports of positive suicidal behaviour.

Discussion

MDMA-assisted psychotherapy with 75 mg or 125 mg resulted in marked improvement of PTSD symptoms in veterans and first responders with chronic PTSD who had failed previous treatment. This study extends findings of significant results combining MDMA with the same manualised psychotherapy for treating crime-related PTSD,¹² and supports the durability of symptomatic improvement seen in a previous report.¹⁴ Participants in the comparator group of 30 mg receiving the same psychotherapy had significantly less symptom remission than the active dose groups of 75 mg and 125 mg, indicating that adequate doses of MDMA potentiate the effects of psychotherapy. An unexpected finding was that the 75 mg dose led to larger decreases in CAPS-

IV total score than the 125 mg dose. This difference might have been due to chance in this small sample size or might be due to other reasons. For example, participants of the 125 mg group had a higher mean baseline depression score than the other groups, and therefore could have been harder to treat. Another possible explanation is that the 75 mg dose might have allowed for more focused processing of traumatic experiences than the 125 mg dose, and might be the optimal dose for at least some patients. Phase 3 trials will use a flexible dose range of 80–120 mg MDMA, and will provide further information about variables that contribute to response. Results from measures of depression and sleep quality parallel findings from CAPS-IV, providing further evidence of benefits of this treatment. Severity of depression symptoms was significantly reduced for the 125 mg group compared with the 30 mg group; however, this reduction was not significant for the 75 mg group compared with the 30 mg group. Sleep quality and dissociative symptoms also significantly improved for both active dose groups compared with the control dose group. Additionally, there were gains in psychological, occupational, and social functioning for participants treated with active doses of MDMA, and similar to the improvements in PTSD symptoms, these gains continued to grow in the year following treatment. Increased scores on the PTGI indicate that perceptions of self, others, and life events were reframed during the therapeutic processing, suggesting that treatment effects went beyond reductions in PTSD and mood symptoms to include psychological growth. Compared with the 30 mg group, change in personality traits showed statistically significant reductions in neuroticism in the 125 mg group and increases in openness in the 75 mg group. Although many personality theorists would argue that personality traits are relatively stable constructs throughout much of adulthood and are not subject to change, evidence suggests that certain personality features are associated with traumatic experience.²⁵ MacLean and colleagues²⁶ found an effect of psilocybin on changes in

one of the five broad domains of personality (openness) measured by the NEO-PI-R, and speculated about the potential clinical application and therapeutic benefit of change in personality variables as a result of pharmacologically induced “mystical experiences”. We have previously found persistent personality changes in openness and neuroticism following MDMA treatment, providing support for the notion that the effect of MDMA-assisted psychotherapy extends beyond effects on specific PTSD symptomatology,²⁷ and fundamentally alters personality structure. In the current study, the fact that participants exhibited long-term changes in personality traits at 12-month follow-up that included a reduction in neuroticism and an increase in agreeableness, openness, and extroversion further suggests that combining MDMA with psychotherapy can shift aspects of personality that were assumed to be stable across time. These pervasive therapeutic effects raise interesting questions for future research into other possible indications for MDMA-assisted psychotherapy, and about whether MDMA effects might be better understood as equipping people to face a range of psychological challenges effectively than as narrowly targeting specific diagnoses. After participants in the 30 mg group crossed over to receive two open-label sessions of 100–125 mg MDMA, mean CAPS-IV total score showed an additional 27-point average decline, suggesting that the same psychotherapy alone was not nearly as effective without a sufficient dose of MDMA. After the third open-label session, the mean change in CAPS-IV total score (–27 points) and the percentage of participants no longer meeting criteria for PTSD (50%) in this group was less than the other groups; however, the proportion of participants with more than a 30% decrease in CAPS-IV total score was more than the 125 mg group (67% vs 50%). The fact that the total decrease in mean CAPS-IV score at the primary endpoint was less for the 30 mg group could mean this group was more difficult to treat than the 75 mg and 125 groups; however, it is also of note that low-dose MDMA

appears to have a counter-therapeutic effect as reported by Oehen and colleagues,¹³ and as reflected in the fact that a previous study using inactive placebo with the same psychotherapy showed a greater decrease in mean CAPS-IV total score than the 30 mg group showed in the current study (-33 vs -11.4).¹² Other factors might also have influenced response in the control groups across these studies with small samples. The study was not designed to determine whether response is greater after two versus three sessions but results suggest that a high degree of improvement can be reached after two sessions. Future studies should evaluate the degree of added long-term benefit that might occur from three versus two sessions. The long-term follow-up results showing significant CAPS-IV total score reductions 12 months after the last MDMA-assisted treatment make it unlikely that the more immediate results were simply due to placebo effect or lingering expectancy effects of having received MDMA. MDMA was well tolerated with low treatment discontinuation (7.7%) that did not correlate with dose. Vital signs transiently increased in a dose-dependent manner during experimental sessions, and returned to approximate baseline values at the session end. Incidence of expected reactions and adverse events differed little across groups, although known acute side-effects of MDMA, such as jaw clenching and perspiration, did occur at higher frequency with active doses. Most events were mild to moderate, with many of the psychiatric symptoms possibly attributable to PTSD. Suicidal ideation was similar across groups. No suicidal behaviour occurred during treatment, suggesting that MDMA-assisted psychotherapy did not potentiate the risk of suicide. Indications of suicidal ideation were lower after completing the treatment. When MDMA is administered in a controlled clinical setting, the liability for subsequent abuse or compulsive seeking of ecstasy is presumed low, as shown in the current trial. Participants who were naive to ecstasy before study participation did not report taking ecstasy after receiving MDMA in the trial. Two participants

reported taking ecstasy once during the 12-month follow-up, but both had taken the drug before study enrolment. Overall safety data support a favourable risk-to-benefit ratio for limited doses of MDMA for treating a population with PTSD.^{12–14} This model of treatment is different to most pharmacological interventions, in that its effectiveness appears to be mediated through pharmacological effects augmenting meaningful psychotherapeutic experiences. MDMA might attenuate response to anxiety-provoking thoughts or feelings during recall of trauma memories by reducing activity in the amygdala^{28,29} and insular cortex,³⁰ and simultaneously improve top-down modulation of thoughts and emotions by increasing activity in the prefrontal cortex.²⁹ Increased functional connectivity between the amygdala and hippocampus during MDMA administration²⁸ suggests that reconsolidation of traumatic memories might occur, rendering them less activating during ordinary states.³¹ Conversely, veterans with symptomatic PTSD have shown decreased resting state functional connectivity between the amygdala and hippocampus.³² MDMA modulates emotional memory circuits dysfunctional in PTSD,³³ and engages neural networks illustrated to be important for other trauma processing therapies.³⁴ By increasing prosocial and empathetic feelings, MDMA might improve therapeutic alliance and engagement with difficult psychological material. Because this study was not designed to explore mechanisms of action, the importance of these

pharmacological effects and neural correlates remains speculative but is consistent with investigators' observations during research sessions. Possible mechanisms should also take into account the interactions between drug effects and participants' psychological experiences. The manualised approach to psychotherapy used¹⁷ includes elements that contribute to the safety and efficacy of MDMA as an adjunct to psychotherapy: careful medical and psychological screening, preparing participants for the MDMA experience and the treatment, a largely non-directive

approach that includes periods of inner focus alternating with periods of interaction with male and female co-therapists, and close follow-up to support integration of the MDMA experience. Previous reports comparing MDMA with inactive placebo,¹² and the current study using low-dose MDMA as a comparator, show that this model of psychotherapy without an active dose of MDMA does lead to improvement in CAPS-IV total score, but the combined effect of the psychotherapy in conjunction with active doses of MDMA is significantly larger. This study has limitations regarding the design and small sample size. Most participants were white men. Maintaining the study blind was only partially accomplished by using low-dose MDMA instead of inactive placebo. The co-therapists guessed dose assignment incorrectly for 40.7–42.6% of blinded sessions and participants guessed incorrectly for 53.7%, suggesting some success in blinding, although most incorrect guesses were between active doses, not between an active dose and low dose, so we cannot rule out some bias from this limitation. There appears to be a threshold effect beyond which MDMA catalyses an effective therapeutic process, and participants and therapists can distinguish the active drug effects from subthreshold effects of low-dose MDMA or inactive placebo. To prevent observer expectancy effects and minimise bias, an observer blind was used by having masked independent outcome raters who were not present during therapy sessions. Widely accepted evidence for the effectiveness of trauma-based psychotherapy for PTSD exists, yet it is impossible to effectively blind psychotherapy trials.⁶ Similar limitations to blinding exist for MDMA and other drugs with prominent psychoactive effects. A limitation of the 12-month follow-up results is that after the primary endpoint, the 30 mg dose and 75 mg dose groups crossed over to receive a full dose of MDMA; therefore, no control group for comparison at 12 months existed. Additionally, 12 participants were taking psychiatric medications, although none specifically for an indication of PTSD, at the long-term follow-up visit.

This trial provides further evidence that MDMA-assisted psychotherapy can be used safely and effectively for treating patients with chronic PTSD. This novel approach to pharmacotherapy offers a means to accelerate substantially the therapeutic process with a short-acting psychoactive compound administered only a few times at monthly intervals in conjunction with a course of psychotherapy designed to maximise the safety and efficacy of drug administration. Promising phase 2 efficacy and safety results have now been shown in six studies.¹¹ If findings are validated in MAPS' phase 3 clinical trials, set to start in 2018,¹¹ MDMA-assisted psychotherapy might become a viable, FDA-approved treatment option for PTSD by 2021.

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Declaration of Interests

Michael Mithoefer received research funds from MAPS Public Benefit Corporation as a clinical investigator and clinical trial medical monitor as well as for training and supervision of research psychotherapists.

Anne Mithoefer received research funds from MAPS Public Benefit Corporation as a clinical investigator and for training and supervision of research psychotherapists.

Allison Feduccia received salary support for full time employment with MAPS Public Benefit Corporation.

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Mark Wagner received research funds to conduct study assessments.

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Julie Holland, M.D. has nothing to disclose.

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Author Contributions

Dr. Scott Hamilton is responsible for integrity of the data and accuracy of data analyses.

Study concept and design: M. Mithoefer, A. Mithoefer, L. Jerome, A. Emerson, B. Yazar-Klosinski, R. Doblin

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: M. Mithoefer, A. Feduccia, L. Jerome

Critical revision of the manuscript for important intellectual content: All authors.

Obtained funding: R. Doblin

Study supervision: M. Mithoefer, A. Mithoefer

Figure 1. (A) Study Design & (B) Trial Profile

^a Participant completed one experimental session and primary endpoint assessment

^b Participant discontinued treatment after one experimental session due to treatment efficacy (felt further MDMA sessions were unnecessary), completed all assessments through 12-month follow-up.

Figure 2. Scores over time on CAPS-IV^a, BDI-II^b, and PSQI^c from Baseline to Endpoints (Intent-to-treat set). Assessments for graphs selected based on representation of PTSD severity and most common associated symptoms, i.e. depression and sleep disturbance.

^aCAPS-IV=Clinician Administered PTSD Scale. Error bars represent standard deviations.

^bBDI-II=Beck Depression Inventory-II. Error bars represent standard deviations.

^cPSQI=Pittsburgh Sleep Quality Index. Error bars represent standard deviations.

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Table 1. Demographics and Baseline Characteristics

Characteristic	30 mg MDMA (n = 7)	75 mg MDMA (n = 7)	125 mg MDMA (n = 12)	Total (n = 26)
Age, mean (SD), y	39.2 (9.7)	29.1 (4.0)	40.7 (11.1)	37.2 (10.3)
Sex, No. (%)				
Male	5 (71.4)	6 (85.7)	8 (66.7)	19 (73.1)
Female	2 (28.6)	1 (14.3)	4 (33.3)	7 (26.9)
Ethnicity, No. (%)				
White/Caucasian	6 (85.7)	4 (57.1)	12 (100.0)	22 (84.6)
Latino/Hispanic	1 (14.3)	1 (14.3)	0	2 (7.7)
Native American	0	1 (14.3)	0	1 (3.8)
Native American & Caucasian	0	1 (14.3)	0	1 (3.8)
BMI, mean (SD)	32.5 (4.7)	27.9 (5.4)	27.5 (3.6)	29.0 (4.8)
Occupation assoc. with trauma				
Military	6 (85.7)	7 (100.0)	9 (75.0)	22 (84.6)
Fire Fighter	1 (14.3)	0	2 (16.7)	3 (11.5)
Police Officer	0	0	1 (8.3)	1 (3.8)
Duration of PTSD, mean (SD), months	68.9 (15.0)	58.3 (32.3)	110.9 (85.1)	85.4 (63.9)
Pre-study therapy, No. (%)				
EMDR	2 (28.6)	0	1 (8.3)	3 (11.5)
Group Psychotherapy	2 (28.6)	2 (28.6)	3 (25.0)	7 (26.9)
PE	3 (42.9)	1 (14.3)	1 (8.3)	5 (19.2)
CPT	0	1 (14.3)	0	1 (3.8)
CBT, not otherwise specified	7 (100.0)	6 (85.7)	11 (91.7)	24 (92.3)
Psychodynamic	2 (28.6)	0	3 (25.0)	5 (19.2)
IPT	0	1 (14.3)	0	1 (3.8)
Other	5 (71.4)	3 (42.9)	8 (66.7)	16 (61.5)
None	0	0	1 (8.3)	1 (3.8)
Pre-study Psychiatric Medications, No. (%)				
Antidepressants	6 (85.7)	7 (100.0)	12 (100.0)	25 (96.2)
Anxiolytics	6 (85.7)	5 (71.4)	12 (100.0)	23 (88.5)
Antipsychotics	5 (71.4)	2 (28.6)	3 (25.0)	10 (38.5)
Mood Stabilizer	0	0	2 (16.7)	2 (7.7)
Sleep Aids	4 (57.1)	2 (28.6)	7 (58.3)	13 (50.0)
Stimulants	2 (28.6)	4 (57.1)	2 (16.7)	8 (30.8)
Other	2 (28.6)	1 (14.3)	5 (41.7)	8 (30.8)
Psychiatric Comorbid Disorders, No. (%)				
Major Depression	5 (71.4)	5 (71.4)	10 (83.3)	20 (76.9)
Panic Disorder	4 (57.1)	2 (28.6)	3 (25.0)	9 (34.6)
Generalized Anxiety	0	1 (14.3)	1 (8.3)	2 (7.7)

Disorder				
Lifetime C-SSRS ^a , No. (%)				
Positive Ideation	5 (71·4)	6 (85·7)	11 (91·7)	22 (84·6)
Serious Ideation	1 (14·3)	2 (28·6)	5 (41·7)	8 (30·8)
Positive Behavior	4 (57·1)	2 (28·6)	5 (41·7)	11 (42·3)

EMDR=Eye Movement Desensitization Reprocessing; CBT=Cognitive Behavioral Therapy; PE=Prolonged Exposure; CPT=Cognitive Processing Therapy; IPT=Interpersonal Therapy

^a Lifetime accounts for all suicidal ideation and behavior prior to study, according to participant recall and medical records. According to the C-SSRS scoring guide, scores of four or five on the suicidal ideation category are considered serious ideation, and scores of one or greater are considered positive behavior or ideation.

Table 2. Outcome Measures^a at the Primary Endpoint

Variable	30 mg MDMA (n = 7)	75 mg MDMA (n = 7)	125 mg MDMA (n = 12)
Primary Efficacy Variable			
CAPS-IV Total Score, mean (SD)			
Baseline	87.4 (14.1)	82.4 (17.3)	89.7 (17.3)
Post 2 experimental sessions	76.0 (23.4)	24.1 (17.2)	45.3 (33.8)
Change ^b	-11.4 (12.7)	-58.3 (9.8)	-44.3 (28.7)
<i>P</i> value ^c	NA	0.0005	0.004
Secondary Efficacy Variable			
CAPS-IV PTSD Diagnostic Criteria Met (primary endpoint), No. (%)			
Yes	5 (71.4)	1 (14.3)	5 (41.7)
No	2 (28.6)	6 (85.7)	7 (58.3)
>30% CAPS-IV Total Score Decrease (primary endpoint), No. (%)			
Yes	2 (28.6)	7 (100.0)	8 (66.7)
No	5 (71.4)	0	4 (33.3)
BDI-II, mean (SD)			
Baseline	30.4 (13.7)	24.7 (12.6)	36.6 (10.5)
Post 2 experimental sessions	25.9 (11.2)	9.3 (6.8)	12.0 (9.0)
Change ^b	-4.6 (8.8)	-15.4 (9.5)	-24.6 (10.6)
<i>P</i> value ^c	NA	0.052	0.0003
PSQI, mean (SD) ^d			
Baseline	10.8 (5.7)	13.6 (4.2)	14.6 (3.6)
Post 2 experimental sessions	12.6 (5.2)	7.2 (4.1)	9.4 (5.1)
Change ^b	1.8 (2.8)	-6.4 (7.1)	-4.8 (4.1)
<i>P</i> value ^c	NA	0.01	0.02
PTGI, mean (SD)			
Baseline	23.9 (8.6)	29.9 (9.4)	31.5 (17.3)
Post 2 experimental sessions	12.3 (15.1)	66.0 (14.1)	65.2 (22.8)
Change ^b	-11.6 (12.2)	36.1 (12.0)	33.7 (24.0)
<i>P</i> value ^c	NA	< 0.0001	< 0.0001
GAF, mean (SD)			
Baseline	41.9 (11.8)	48.1 (9.1)	40.2 (7.2)
Post 2 experimental sessions	43.0 (12.8)	67.6 (6.2)	58.6 (12.1)
Change ^b	1.1 (4.6)	19.4 (6.1)	18.4 (14.4)
<i>P</i> value ^c	NA	0.004	0.002
DES-II, mean (SD) ^d			
Baseline	13.5 (17.7)	17.7 (9.1)	17.6 (10.7)
Post 2 experimental sessions	15.2 (17.4)	9.2 (10.9)	8.8 (8.0)
Change ^b	1.8 (0.9)	-8.6 (1.9)	-8.8 (6.2)
<i>P</i> value ^c	NA	0.02	0.01
NEO-PI-R, mean (SD) ^f			

Neuroticism			
Baseline	62.0 (14.8)	65.3 (11.4)	75.1 (6.4)
Post 2 experimental sessions	60.2 (14.9)	53.6 (12.4)	58.6 (12.8)
Change ^b	-4.6 (5.5)	-12.0 (3.6)	-16.5 (11.8)
<i>P</i> value ^a	NA	0.23	0.03

Extroversion			
Baseline	33.1 (9.4)	37.4 (8.9)	34.2 (8.5)
Post 2 experimental sessions	36.0 (11.2)	46.4 (8.6)	42.2 (13.3)
Change ^b	2.2 (4.3)	10.0 (9.4)	8.0 (9.4)
<i>P</i> value ^a	NA	0.17	0.22

Openness			
Baseline	48.9 (9.6)	55.6 (12.1)	57.4 (16.7)
Post 2 experimental sessions	49.2 (10.2)	66.0 (7.8)	59.4 (9.9)
Change ^b	-0.6 (9.9)	15.6 (5.3)	2.0 (10.5)
<i>P</i> value ^a	NA	0.02	0.62

Agreeableness			
Baseline	44.7 (8.0)	33.1 (15.2)	39.8 (13.7)
Post 2 experimental sessions	40.6 (13.6)	33.4 (9.6)	45.7 (11.4)
Change ^b	-1.2 (8.4)	5.4 (8.0)	5.9 (4.9)
<i>P</i> value ^a	NA	0.13	0.05

Conscientiousness			
Baseline	41.3 (9.9)	53.6 (18.3)	41.3 (13.5)
Post 2 experimental sessions	39.8 (6.8)	56.4 (10.1)	47.8 (10.0)
Change ^b	-3.2 (7.9)	2.4 (15.0)	6.5 (13.4)
<i>P</i> value ^a	NA	0.50	0.17

CAPS-IV=Clinician Administered PTSD Scale; BDI-II=Beck Depression Inventory-II; PSQI=Pittsburgh Sleep Quality Index; PTGI=Post Traumatic Growth Inventory; GAF=Global Assessment of Functioning; DES-II=Dissociative Experiences Scale II; NEO-PI-R=NEO Personality Inventory – Revised

^aAll outcomes are based on intent-to-treat set

^bChange from Baseline

^cCompared to 30 mg MDMA

^dReduced sample size due to Amendment (PSQI: 30 mg, n=5; 75 mg, n=5; 125 mg n=10; DES-II: 30 mg, n=3; 75 mg, n=3; 125 mg n=6)

^fNEO-PI-R sample size (75 mg, n=5 at primary endpoint)

Table 3. Outcome Measures at 12-month follow-up^a

Variable	30 mg MDMA (n = 7)	75 mg MDMA (n = 7)	125 mg MDMA (n = 12)	Total^b (n = 26)	P value^c
Primary Efficacy Variable					
CAPS-IV Total Score, mean (SD)					
Baseline	87.4 (14.1)	82.4 (17.3)	89.7 (17.3)	87.1 (16.1)	
12-month follow-up	52.7 (41.2)	28.3 (23.0)	37.8 (21.4)	38.8 (28.1)	< 0.0001
Secondary Efficacy Variable					
CAPS-IV PTSD Diagnostic Criteria Met (12-month), No. (%)					
Yes	3 (50.0)	2 (28.6)	3 (27.3)	8 (33.3)	
No	3 (50.0)	5 (71.4)	8 (72.7)	16 (66.7)	NA
BDI-II, mean (SD)					
Baseline	30.4 (13.7)	24.7 (12.6)	36.6 (10.5)	31.7 (12.5)	
12-month follow-up	15.2 (13.4)	11.0 (9.3)	10.5 (8.6)	11.8 (9.9)	< 0.0001
PSQI, mean (SD)					
Baseline	10.8 (5.7)	13.6 (4.2)	14.6 (3.6)	13.4 (4.4)	
12-month follow-up	9.8 (4.3)	7.4 (4.6)	8.4 (5.0)	8.4 (4.6)	0.0002
PTGI, mean (SD)					
Baseline	23.9 (8.6)	29.9 (9.4)	31.5 (17.3)	29.0 (13.5)	
12-month follow-up	49.0 (32.2)	74.1 (15.0)	78.2 (15.1)	69.7 (23.1)	< 0.0001
GAF, mean (SD)					
Baseline	41.9 (11.8)	48.1 (9.1)	40.2 (7.2)	42.8 (9.4)	
12-month follow-up	54.0 (20.2)	66.7 (14.8)	64.8 (12.8)	62.7 (15.6)	< 0.0001
DES-II, mean (SD)					
Baseline	13.5 (17.7)	17.7 (9.1)	17.6 (10.7)	16.6 (11.3)	
12-month follow-up	10.5 (1.8)	9.6 (6.3)	12.5 (12.8)	11.2 (8.7)	0.046
NEO-PI-R, mean (SD)					
Neuroticism					
Baseline	62.0 (14.8)	65.3 (11.4)	75.1 (6.4)	68.9 (11.7)	
12-month follow-up	57.0 (12.2)	61.1 (8.4)	57.2 (9.3)	58.3 (9.6)	< 0.0001
Extroversion					
Baseline	33.1 (9.4)	37.4 (8.9)	34.2 (8.5)	34.8 (8.7)	
12-month follow-up	37.3 (6.8)	46.4 (6.9)	45.4 (11.0)	43.7 (9.4)	0.0002
Openness					
Baseline	48.9 (9.6)	55.6 (12.1)	57.4 (16.7)	54.6 (13.9)	
12-month follow-up	51.0 (11.5)	65.0 (7.5)	60.5 (15.6)	59.5 (13.3)	0.02
Agreeableness					
Baseline	44.7 (8.0)	33.1 (15.2)	39.7 (13.7)	39.3 (13.1)	
12-month follow-up	43.8 (9.8)	38.6 (11.6)	47.4 (13.0)	43.9 (12.0)	0.007
Conscientiousness					
Baseline	41.3 (9.9)	53.6 (18.3)	41.2 (13.5)	44.6 (14.7)	

12-month follow-up 43.5 (5.7) 53.1 (11.5) 46.9 (10.8) 47.9 (10.3) 0.36

CAPS-IV=Clinician Administered PTSD Scale; BDI-II=Beck Depression Inventory-II;
PSQI=Pittsburgh Sleep Quality Index; PTGI=Post Traumatic Growth Inventory; GAF=Global
Assessment of Functioning; DES-II=Dissociative Experiences Scale II; NEO-PI-R=NEO
Personality Inventory – Revised

^aAll outcomes are based on intent-to-treat set

^bAt 12-month follow-up (n=24)

^cWithin-subject t-tests with groups combined

^dReduced sample size due to Amendment (PSQI: 30 mg, n=4; 75 mg, n=5; 125 mg n=10; DES-II: 30 mg, n=3; 75 mg, n=3; 125 mg n=5)

^eNEO-PI-R sample size (125 mg, n=11 at 12-month follow-up)

Table 4. Treatment-Emergent Adverse Events and Expected Reactions During Two MDMA Sessions and Seven Days Following

	30 mg MDMA (n = 7)	75 mg MDMA (n = 7)	125 mg MDMA (n = 12)	Total (n = 26)
Top Reactions during Experimental Sessions, No. (%)^a				
Anxiety	4 (57.1)	6 (85.7)	11 (91.7)	21 (80.8)
Fatigue	5 (71.4)	4 (57.1)	7 (58.3)	16 (61.5)
Headache	5 (71.4)	5 (71.4)	8 (66.7)	18 (69.2)
Jaw clenching, tight jaw	0	4 (57.1)	9 (75.0)	13 (50.0)
Lack of appetite	3 (42.9)	4 (57.1)	8 (66.7)	15 (57.7)
Muscle tension	4 (57.1)	3 (42.9)	9 (75.0)	16 (61.5)
Perspiration	2 (28.6)	2 (28.6)	5 (41.7)	9 (34.6)
Restlessness	4 (57.1)	5 (71.4)	3 (25.0)	12 (46.2)
Sensitivity to cold	4 (57.1)	4 (57.1)	6 (50.0)	14 (53.8)
Top Reactions during 7 Days of Contact, No. (%)^a				
Anxiety	4 (57.1)	5 (71.4)	10 (83.3)	19 (73.1)
Fatigue	6 (85.7)	7 (100.0)	10 (83.3)	23 (88.5)
Insomnia	5 (71.4)	3 (42.9)	10 (83.3)	18 (69.2)
Need more sleep	6 (85.7)	6 (85.7)	9 (75.0)	21 (80.8)
Headache	2 (28.6)	3 (42.9)	7 (58.3)	12 (46.2)
Muscle tension	2 (28.6)	3 (42.9)	7 (58.3)	12 (46.2)
Increased irritability	4 (57.1)	2 (28.6)	6 (50.0)	12 (46.2)
Lack of appetite	2 (28.6)	1 (14.3)	6 (50.0)	9 (34.6)
Difficulty concentrating	2 (28.6)	0	5 (41.7)	7 (26.9)
Low mood	3 (42.9)	0	3 (25.0)	6 (23.1)
Psychiatric TEAEs, No. (%)^b				
Anxiety	1 (14.3)	0	1 (8.3)	2 (7.7)
Flashbacks	0	0	1 (8.3)	1 (3.8)
Low mood	2 (28.6)	0	0	2 (7.7)
Negative thoughts	1 (14.3)	0	0	1 (3.8)
Suicidal ideation	1 (14.3)	0	0	1 (3.8)
Tic	0	0	1 (8.3)	1 (3.8)
Trichotillomania	1 (14.3)	0	0	1 (3.8)

TEAEs=Treatment Emergent Adverse Events

^aFrequency of subjects who reported an expected, spontaneously reported reaction collected during and seven days following blinded experimental sessions 1 and 2.

^bFrequency of subjects who self-reported Psychiatric Adverse Events after first drug administration until the day before experimental session 3

Comment

3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in service personnel

“...In thy faint slumbers I by thee have watch'd, And heard thee murmur tales of iron wars...”
William Shakespeare, Henry IV Part One, Act 2, Scene 3

As described by his wife, Kate, Hotspur's behaviour convincingly meets criteria for post-traumatic stress disorder (PTSD),¹ not unexpectedly in someone whose life is characterised by relentless martial activity. Indeed the diagnosis of PTSD was first formalised in DSM-III in 1980, in the context of persistent trauma-related symptomatology in veterans of the Vietnam War. Of course, traumatic events are widespread in civilian life, but the prevalence of PTSD is higher in military veterans and members of the emergency services (the so-called first responders) than in the general population.^{2,3} Also, in military veterans, evidence-based treatments (pharmacotherapy and trauma-focused psychotherapies) seem less effective, with approximately two-thirds of patients retaining the diagnosis of PTSD after treatment and many of them not completing the courses of therapy.^{2,3} The psychosocial consequences of persistent symptoms are serious and include substance misuse, aggressive behaviour, unemployment, family disruption, and suicide.^{2–5} Might it be possible to enhance the effectiveness of psychotherapy for PTSD through pharmacological augmentation of psychological treatment sessions? Perhaps the most studied approach has involved the partial N-methyl-D-aspartate receptor agonist, D-cycloserine, which in animal experimental work facilitates extinction of conditioned behaviour through glutamatergic mechanisms; however, its benefits in patients with PTSD are equivocal.⁶ In *The Lancet Psychiatry*, Michael Mithoefer and colleagues⁷ report the effect of a different pharmacological intervention in which two extended 8-h sessions of non-directive psychotherapy are coupled with administration of the serotonin and dopamine releasing agent, 3,4-methylenedioxymethamphetamine (MDMA). MDMA is a stimulant that elevates mood and activity; however, it also engenders powerful feelings of insight, relatedness, and empathy, leading it to be sometimes termed an entactogen or empathogen. The sympathetic and empathetic properties have encouraged proposals that MDMA-assisted psychotherapy might facilitate recovery in PTSD by allowing compassionate reappraisal of the trauma as well as promoting long-term positive psychological development—in particular, increased openness and selfawareness.⁸ Finding the appropriate control condition for psychoactive drugs with obvious and profound subjective effects is challenging. Mithoefer and colleagues⁷ used a low-dose strategy (30 mg of MDMA as the control group), and acknowledged that differences in the subjective effect of this dose and the two active doses (75 mg and 125 mg) might have compromised blinding for the participants. Nevertheless, in 26 participants (the majority were military veterans [n=22], with the remainder being firefighters [n=3] and a police officer [n=1]), both active doses of MDMA were substantially more effective than the 30 mg dose in lowering mean total scores on the Clinician Administered PTSD Scale (CAPS-IV) at the primary endpoint, 1 month after the second MDMA session. The decrease in mean CAPS-IV total scores with the 75 mg and 125 mg doses were significantly greater than those seen with the 30 mg dose (−58.3 [SD 9.8] and −44.3 [28.7] vs −11.4 [12.7]; p=0.001) and considerably more than the changes reported in studies using trauma-related psychotherapies in veteran groups.² However, the absence of a dose-response of the two active treatments and the wide CIs for the 125 mg dose

(Cohen's $d = 1.1$ [95% CI 0.04–2.08]) raise some doubts about the robustness of the MDMA effect. Nevertheless, at the primary endpoint, more participants in the active treatment groups no longer met diagnostic criteria for PTSD compared with the low-dose group (six [86%] of seven participants in the 70 mg group and seven [58%] of 12 in the 125 mg group vs two [29%] of seven in the 30 mg group). At 12-month follow-up, after further open-label treatment sessions with full-dose MDMA (100–125 mg), most participants continued to do well, suggesting that the beneficial effect of treatment was not simply a temporary response to an intense psychological experience or the high level of psychotherapeutic care received by participants. However, it is worth noting that 22 of the 26 participants were recruited via internet advertisement or word of mouth, which is likely to have enriched the sample with those keen to try the effect of MDMA, perhaps with resultant expectancy effects; this potential bias might limit the external validity of the findings. MDMA is legally proscribed and there have been numerous safety concerns attached to its recreational use in the form of ecstasy, which might not contain pure MDMA, including acute fatal toxicity as well as the possibility of long-term cognitive impairment and damage to serotonin neurons.⁹ Recreational users can also experience a rebound—ie, lowering of mood a few days after MDMA ingestion¹⁰—which is a particular concern in individuals vulnerable to depression and suicidal feelings. However, Mithoefer and colleagues show that with rigorous sourcing of MDMA and close medical and psychological supervision, its short-term use in carefully selected patients with PTSD seems safe. Moreover, it does not appear that those naive to MDMA before the study became ecstasy users over the following year. This current study⁷ describes the therapeutic use of MDMA by committed experts in a specialised setting in a small group of participants, most of whom self-referred for the trial. The unmet need for better PTSD treatment, particularly in veterans and first responders, is undoubted.^{2,3,11} However, the generalisability of the benefit of MDMA-assisted psychotherapy to more mainstream psychiatry remains to be established,¹² recalling perhaps the famous American watchword, “Will it play in Peoria?”

Andrea Cipriani, *Philip J Cowen Department of Psychiatry, University of Oxford, Oxford, UK; and Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford OX3 7JX, UK phil.cowen@psych.ox.ac.uk We declare no competing interests. 1 Bennet G. Shakespeare and post-traumatic stress disorder. *Brit J Psychiatry* 2011; 198: 255. 2 Steenkamp MM, Litz BT, Hoge CW, et al. Psychotherapy for military-related PTSD: a review of randomized clinical trials. *JAMA* 2015; 314: 489–500. 3 Krystal JH, Davis LL, Neylan TC, et al. It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: a consensus statement of the PTSD Psychopharmacology Working Group. *Biol Psychiatry* 2017; 82: e51–59. 4 Thomas JL, Wilk JE, Riviere LA, et al. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. *JAMA Psychiatry* 2010; 67: 614–23. 5 Afzali MH, Sunderland M, Batterham PJ, et al. Trauma characteristics, posttraumatic symptoms, psychiatric disorders and suicidal behaviours: Results from the 2007 Australian National Survey of Mental Health and Wellbeing. *Aust NZ J Psychiatry* 2017; 51: 1142–51. 6 Marin MF, Lonak SF, Milad MR. Augmentation of evidence-based psychotherapy for PTSD with cognitive enhancers. *Curr Psychiatry Rep* 2015; 17: 39. 7 Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 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* 2018; published online May 1. <http://dx.doi.org/10.1016/S2215->

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Supplemental Content

Participant’s Perspective

Here we describe a participant’s perspective from this trial. Mr. B enrolled in the study five years after his second tour in Iraq as a Marine turret gunner on a Humvee. Despite prior treatment at the VA, he continued to have severe PTSD symptoms from multiple war experiences. The symptom that troubled him most was uncontrollable rage during which he would yell at his wife and punch holes in the wall. At baseline, his CAPS IV total score was 75.

During his first MDMA psychotherapy session, like many participants, he had anxiety as the MDMA effects came on, “...I had this really intense feeling come over my body, and my heart started beating real fast... I started feeling afraid; it kind of felt like when a panic attack comes on... but then once I started breathing I really felt my heart beat start to slow down, and just relax... I’ve never felt that before.... amazing how in control I felt of making it go away.” After 30 minutes focused inward with eyeshades and headphones he then described his next experience, “...this voice, this part of me so wise and so intelligent brought this peace over me... and then I tried thinking of that aspect of me that’s so rageful, ...I realized I have that part of me locked up in jail... I went and opened the door and hugged him and his evil eyes faded away, I

visualized taking its knife out of my side and taking my hands off its neck. I think I was so afraid of him - I mean I know it's me but I describe him that way - because I saw what he was capable of in Iraq." He went on to forgive himself and make peace with "the warrior I thought was a monster... When I think about Iraq now, I feel really peaceful that that's part of my journey. ...I know this is part of the drug, but when I think, 'am I going to be able to hold onto this understanding... I have now. I think it's so profound that I don't think I could really forget it.'" Later in that session, and in subsequent sessions, he revisited various experiences in Iraq with enhanced recall, "When I think about when I got blown up myself... I can really go back and visualize it, I've never been able to visualize it so hard before, and really feel what it was like." Following this first session his wife confirmed that his rage attacks ceased. Other symptoms decreased markedly over the ensuing weeks. "While I found the healing I needed in my very first session, every other session seemed to add more and more to it. It went beyond Iraq and down into my childhood, ...I would have profound visions and insights.... The drug really facilitates these forgiving experiences. ...It feels almost like the inner healer or the MDMA is like a maid doing spring cleaning. It's as if you thought you were cleaning before but when you got to things you didn't really want to deal with you'd just stick them in the attic. If you're going to clean the house you can't skip the stuff in the attic." His CAPS-IV score at the Primary Endpoint was 6; at 12-month follow-up it was 19.

Results of Secondary Outcomes in the Open-label Crossover

One month after completing two open-label (MDMA 100-125 mg) sessions in the crossover, the group that had previously received 30 mg during blinded sessions showed positive gains assessed by secondary measures (eTable 3). Within-subject t-tests comparing scores at primary

and secondary endpoints showed significant improvements in sleep quality [PSQI, $t(3) = 4.0$, $P = 0.027$], the personality trait Openness [NEO, $t(4) = 3.2$, $P = .033$], and global functioning [GAF, $t(5) = -2.6$, $P = 0.050$] nearly reached. BDI-II, PTGI, DES-II, and other NEO-PI-R personality traits analysis failed to reach significance. The 75 mg group only attained further significant improvement on the NEO-PI-R personality trait Agreeableness [$t(3) = -7.9$, $P = 0.004$] after three open-label sessions.

eTable 1. Summary of Protocol Amendments Relevant for this Publication

eTable 2. Assessments Used in Study

eTable 3. Results of Open-label Crossover Analysis

eTable 4. Results of Exploratory Analysis of Two vs. Three MDMA Sessions

eTable 5. Columbia Suicide Severity Rating Scale (C-SSRS) across Experimental Sessions and at Endpoints

eTable 6. Vital signs during Experimental Sessions

eTable 7. Frequency of Participants Reporting Treatment Emergent Adverse Events

eTable 8. Frequency of Participants with Psychiatric Medication Use during the 12-month Follow-up

eTable 1. Summary of Protocol Amendments Relevant for this Publication

Protocol Amendment^a	Study Design Change (n)^b
Amendment 1	No changes in study design. No subjects were enrolled during Amendment 1 (n= 0)
Amendment 2	Restricted population to “chronic” [treatment resistant] PTSD from original (n = 5)
Amendment 3	PSQI added (n = 0).
Amendment 3	Permitted scheduling first preparatory session either before or after enrollment. Increased maximum time interval from enrollment to first experimental session from 3 to 5 weeks to up to six weeks (n = 0).
Amendment 4	Blind broken after 2 sessions instead of 3; crossover for 30 mg and 75 mg after 2 sessions instead of 3 (data not shown in tables for n=3 at End of Stage 1), and third session open label for 125 mg participants (n = 17); NEO-PI-R administered one month after two experimental sessions in accordance with change in breaking of blind, without being administered again at the two-month time point. (n= 9)
Amendment 4	Clarified restriction in relation to past ecstasy use, from “five times” without a specified time interval to “five times within the last 10 years” (n = 9).
Amendment 4	Change in viewing of blood pressure during experimental study, so that for participants without a diagnosis of controlled hypertension, after viewing baseline values, will only view the blood pressure or pulse values in the case of a medical indication, intended to improve the effectiveness of condition blinding (n = 9).
Amendment 4	Sample size increased from 16 to 24 participants (6 in 30 mg, 6 in 75 mg and 12 in 125 mg conditions; sample population expanded to include firefighters and police officers) (n = 9).
Amendment 5	Option for 100 mg dose in open-label crossover (n = 12).

^aNo participants were enrolled under the original protocol or protocol amendment 1; the first participants were enrolled under Amendment 2. No participants were enrolled under Amendment 3.

^bNumber of participants enrolled when this criterion and amendment was in place, up through all 26 participants.

eTable 2. Assessments Used in Study

Scale/Measure Name	Administration	Description
Structured Clinical Interview for DSM-IV-1-RV (SCID-IV)	Investigator administered and assessed	Structured diagnostic interview for assessing presence of psychiatric disorders, flexible and including items to assess included and excluded psychiatric disorders.
Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV)	Independent-rater administered & rated	The Clinician Administered PTSD Scale (CAPS-IV), based on the Diagnostic and Statistical Manual of Mental Disorders 4th edition, is a 23-item semi-structured interview assessing PTSD through diagnostic and symptom severity scores; total symptom severity scores range from 0 to 136, the higher value designating greater symptom severity. CAPS-IV assigns diagnosis as being present or absent ^{1,2} .
Beck Depression Inventory II (BDI-II)	Self-report	The Beck Depression Inventory-II (BDI-II) is a 21-item self-report measure of depressive symptoms ³ , with scores ranging from 0 to 63, higher scores indicative of greater (more severe) depression.
Pittsburgh Sleep Quality Index (PSQI)	Self-report	The Pittsburgh Sleep Quality Index (PSQI) is 19-item self-report measure of sleep quality over a one-month period ⁴ , with seven subscales (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction) and a total score ranging from 0-21, higher scores reflective of poorer sleep quality.
Post Traumatic Growth Inventory (PTGI)	Self-report	The Post Traumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event ⁵ . It contains five subscales - relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life. In this study, participants completed the PTGI in reference to the time since the trauma at baseline, but responded in reference to the beginning of their participation in the study on all subsequent occasions.
Global Assessment of Functioning (GAF)	Independent-rater assessed	The Global Assessment of Functioning (GAF) is a measure of global functioning and general function made through observations ⁶ . The GAF consists of a single score (scores ranging from 0 to 100) with 100 reflecting superior function and zero reflecting serious risk of causing harm to the self or others. The GAF was recorded by the independent rater according to the Time and Events table.
Dissociative Experience Scale-II (DES-II)	Self-report	The Dissociative Experiences Scale-II (DES-II) is a 28-item self-report measure of dissociation, defined as a lack of normal integration of an individual's thoughts, feelings ^{7,8} , or experiences into the stream of consciousness or memory. It is an established measure of dissociative symptoms. The scale consists of statements describing facets of dissociation. The scale is scored by treating percentages as single digits to produce a total score. The DES-II can have three factors - amnesia, depersonalization, and derealization.
Neuroticism-Extroversion-Openness-Personality Inventory-Revised	Self-report	The NEO-PI-R served as a measurement of personality ⁹ . The NEO-PI-R is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model.
Columbia Suicide Severity Rating Scale (C-SSRS)	Investigator-administered and rated	The C-SSRS is a clinician-administered measure of suicidal ideation and behavior devised to detect potential ^{10,11} . It consists of a series of graded Yes/No

Scale/Measure Name	Administration	Description
		<p>questions about suicidal ideation, 5 items referring to when participant is feeling the most suicidal, responses on a 0-5 scale, and five Yes/No questions in reference to suicidal behavior. Scores include a 5-point score for suicidal ideation and a score for intensity of suicidal ideation, and a score for suicidal behavior, with higher scores indicating more severe or greater suicidal ideation or behavior. Suicidal ideation and behavior is summarized according to suggestions made in the Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide ¹². A positive response for suicidal ideation is counted when a subject answers “yes” to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS, i.e. a score > 0 for suicidal ideation score. Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when a subject answers “yes” to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS, i.e. a score > 0 for suicidal behavior score.</p>
Physiologic Vitals	Investigator-measured	<p>During experimental sessions, blood pressure and heart rate were measured via automated sphygmometer (Welch Allyn, Skaneateles Falls, NY) every 15 minutes for the first four hours, then every 30 minutes until session end. Body temperature was measured at 60-90 minute intervals via tympanic thermometer (Braun, Kronberg, Germany).</p>
Spontaneously Reported Reactions	Participant-reported, investigator recorded	<p>Set of expected adverse events spontaneously reported by the participant during each experimental session and for seven days afterward. List based on reports in Phase 1 studies up through 2012, with several items added after observing reports from their initial study in people with PTSD. List included anxiety, diarrhea, difficulty concentrating, dizziness, drowsiness, dry mouth, fatigue, headache, heavy legs, impaired gait/balance, impaired judgment, increased irritability, insomnia, jaw clenching, lack of appetite, low mood, muscle tension, nausea, need more sleep, nystagmus, parasthesias, perspiration, restlessness, rumination, sensitivity to cold, thirst, weakness ^{13-20,21}.</p>

eTable 3. Results of Stage 2 Open-label Crossover

Variable	30 mg MDMA/ Open-label (n = 6)	75 mg MDMA/ Open-label (n = 6)
CAPS-IV Total Score, mean (SD)		
Primary endpoint	76.0 (23.4)	24.1 (17.2)
Stage 2 secondary (post 2 open-label sessions)	46.5 (20.5)	22.3 (18.9)
<i>P</i> value ^a	0.01	0.81
CAPS-IV PTSD Diagnostic Criteria Met (Stage 2 secondary), No. %		
Yes	4 (66.7)	0
No	2 (33.3)	6 (100.0)
>30% CAPS-IV Total Score Decrease (Primary to Stage 2 secondary), No. (%)		
Yes	4 (66.7)	3 (50.0)
No	2 (33.3)	3 (50.0)
BDI-II, mean (SD)		
Primary endpoint	25.9 (11.2)	9.3 (6.8)
Stage 2 secondary (post 2 open-label sessions)	16.5 (11.1)	9.8 (11.4)
<i>P</i> value ^a	0.19	0.89
PSQI, mean (SD) ^b		
Primary endpoint	12.6 (5.2)	7.2 (4.1)
Stage 2 secondary (post 2 open-label sessions)	11.0 (2.2)	11.4 (5.1)
<i>P</i> value ^a	0.03	0.76
PTGI, mean (SD)		
Primary endpoint	12.3 (15.1)	66.0 (14.1)
Stage 2 secondary (post 2 open-label sessions)	43.0 (32.7)	77.2 (10.5)
<i>P</i> value ^a	0.13	0.12
GAF, mean (SD)		
Primary endpoint	43.0 (12.8)	67.6 (6.2)
Stage 2 secondary (post 2 open-label sessions)	52.3 (12.3)	66.7 (14.5)
<i>P</i> value ^a	0.05	0.72
DES-II, mean (SD) ^b		
Primary endpoint	15.2 (17.4)	9.2 (10.9)
Stage 2 secondary (post 2 open-label sessions)	10.2 (4.3)	6.4 (6.1)
<i>P</i> value ^a	0.63	0.48
NEO-IP-R, mean (SD) ^c		
Neuroticism		
Primary endpoint	60.2 (14.9)	53.6 (12.4)
End of Stage 2 (post 3 open-label sessions)	58.5 (14.1)	55.7 (11.0)
<i>P</i> value ^a	0.48	0.18
Extroversion		
Primary endpoint	36.0 (11.2)	46.4 (8.6)
End of Stage 2 (post 3 open-label sessions)	40.3 (7.9)	52.3 (4.2)
<i>P</i> value ^a	0.13	0.13
Openness		
Primary endpoint	49.2 (10.2)	66.0 (7.8)
End of Stage 2 (post 3 open-label sessions)	45.2 (9.4)	66.7 (7.9)
<i>P</i> value ^a	0.03	0.25
Agreeableness		
Primary endpoint	40.6 (13.6)	33.4 (9.6)
End of Stage 2 (post 3 open-label sessions)	43.3 (11.7)	46.0 (9.1)
<i>P</i> value ^a	1.0	0.004
Conscientiousness		
Primary endpoint	39.8 (6.8)	56.4 (10.1)

End of Stage 2 (post 3 open-label sessions)	42.3 (5.2)	55.8 (11.9)
<i>P</i> value ^a	0.59	0.70

CAPS-IV=Clinician Administered PTSD Scale; BDI-II=Beck Depression Inventory-II; PSQI=Pittsburgh Sleep Quality Index; PTGI=Post Traumatic Growth Inventory; GAF=Global Assessment of Functioning; DES-II=Dissociative Experiences Scale II; NEO-PI-R=NEO Personality Inventory – Revised

^aWithin-subjects t-tests

^bReduced sample size due to Amendment (PSQI: 30 mg, n = 4; 75 mg, n = 5; 125 mg n = 11; DES: 30 mg, n = 3; 75 mg, n = 3; 125 mg, n = 12)

^cReduced sample size because of change in study administration time (NEO-PI-R: 30 mg, n = 5; 75 mg, n = 5; 125 mg, n = 12)

eTable 4. Results of Exploratory Analysis of Two vs. Three MDMA Sessions

Variable	30 mg MDMA/ Open-label (n = 6)	75 mg MDMA/ Open-label (n = 6)	125 mg MDMA (n = 12)
CAPS-IV Total Score, mean (SD)			
Primary (Post 2 experimental sessions)	76.0 (23.4)	24.1 (17.2)	45.3 (33.8)
End of Stage 1 (Post 3 MDMA sessions)	---	---	37.8 (28.9)
<i>P</i> value ^a	---	---	.40
Stage 2 Secondary (Post 2 open-label sessions)	46.5 (20.5)	22.3 (18.9)	---
End of Stage 2 (Post 3 open-label sessions)	46.2 (30.5)	20.5 (18.8)	---
<i>P</i> value ^{a0}	0.95	0.83	---
CAPS-IV PTSD Diagnostic Criteria Met, No. %			
End of Stage 1			
Yes	---	---	4 (33.3)
No	---	---	8 (66.7)
End of Stage 2			
Yes	3 (50.0)	2 (33.3)	---
No	3 (50.0)	4 (66.7)	---
>30% CAPS-IV Total Score decrease			
End of Stage 1 ^b			
Yes	---	---	6 (50.0)
No	---	---	6 (50.0)
End of Stage 2 ^c			
Yes	2 (33.3)	3 (50.0)	---
No	4	3 (50.0)	---
BDI-II, mean (SD)			
Primary (Post 2 experimental sessions)	25.9 (11.2)	9.3 (6.8)	12.0 (9.0)
End of Stage 1 (Post 3 MDMA sessions)	---	---	8.1 (7.9)
Stage 2 Secondary (Post 2 open-label sessions)	16.5 (11.1)	9.8 (11.4)	---
End of Stage 2 (Post 3 open-label sessions)	19.3 (13.1)	5.5 (5.8)	---
PSQI, mean (SD)^d			
Primary (Post 2 experimental sessions)	12.6 (5.2)	7.2 (4.1)	9.4 (5.1)
End of Stage 1 (Post 3 MDMA sessions)	---	---	8.4 (5.2)
Stage 2 Secondary (Post 2 open-label sessions)	11.0 (2.2)	11.4 (5.1)	---
End of Stage 2 (Post 3 open-label sessions)	10.3 (6.2)	9.4 (5.1)	---
PTGI, mean (SD)			
Primary (Post 2 experimental sessions)	12.3 (15.1)	66.0 (14.1)	65.2 (22.8)
End of Stage 1 (Post 3 MDMA sessions)	---	---	77.1 (14.7)
Stage 2 Secondary (Post 2 open-label sessions)	43.0 (32.7)	77.2 (10.5)	---
End of Stage 2 (Post 3 open-label sessions)	47.2 (32.4)	84.5 (5.5)	---
GAF, mean (SD)			
Primary (Post 2 experimental sessions)	43.0 (12.8)	67.6 (6.2)	58.6 (12.1)
End of Stage 1 (Post 3 MDMA sessions)	---	---	60.2 (10.4)
Stage 2 Secondary (Post 2 open-label sessions)	52.3 (12.3)	66.7 (14.5)	---
End of Stage 2 (Post 3 open-label sessions)	52.0 (19.6)	72.5 (11.3)	---
DES-II, mean (SD)^d			
Primary (Post 2 experimental sessions)	15.2 (17.4)	9.2 (10.9)	8.8 (8.0)
End of Stage 1 (Post 3 MDMA sessions)	---	---	7.9 (7.3)
Stage 2 Secondary (Post 2 open-label sessions)	10.2 (4.3)	6.4 (6.1)	---
End of Stage 2 (Post 3 open-label sessions)	9.5 (2.7)	5.0 (2.9)	---

CAPS-IV=Clinician Administered PTSD Scale; BDI-II=Beck Depression Inventory-II; PSQI=Pittsburgh Sleep Quality Index; PTGI=Post Traumatic Growth Inventory; GAF=Global Assessment of Functioning; DES-II=Dissociative Experiences Scale II; NEO-PI-R=NEO Personality Inventory – Revised

^aWithin-subjects t-tests

^bParticipants attaining a >30% CAPS-IV Total Score decrease from primary to End of Stage 1

^cParticipants attaining a >30% CAPS-IV Total Score decrease from secondary to End of Stage 2

^dReduced sample size due to Amendment (PSQI: 30 mg, n = 4; 75 mg, n = 5; 125 mg, n = 11; DES-II: 30 mg, n = 3; 75 mg, n = 3; 125 mg, n = 6)

eTable 5. Columbia Suicide Severity Rating Scale (C-SSRS)^a across Experimental Sessions and at Endpoints

Experimental Session 1								
No. (%)								
Dose		Pre-Drug ^b	During-Drug ^c	Integration Visit 1	Contact Day 2	Contact Day 7	Integration Visit 2	Integration Visit 3
30 mg	PI	1 (14.3)	1 (14.3)	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	7	7	7	7	7	3	6
75 mg	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	7	7	7	7	7	4	7
125 mg	PI	0 (0)	0 (0)	1 (8.3)	0 (0)	0 (0)	2 (25.0)	3 (25.0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	12	12	12	12	12	8	12
Experimental Session 2								
No. (%)								
30 mg	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.3)	2 (40.0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	6	6	3	5
75 mg	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	6	6	2	6
125 mg	PI	1 (8.3)	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (11.1)	2 (20.0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	12	12	12	12	12	9	10
Experimental Session 3								
No. (%)								
30 mg	PI	1 (50.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	2	2	2	2	2	2	2
75 mg	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	1	1	1	1	1	1	1
125 mg	PI	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (8.3)	2 (20.0)	2 (18.2)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	12	12	12	12	12	10	11
Experimental Session 4								
No. (%)								
30 mg/ Open Label	PI	0 (0)	0 (0)	1 (16.7)	1 (16.7)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	6	6	2	6
75 mg/ Open Label	PI	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	6	6	1	6
Experimental Session 5								
No. (%)								
30 mg/ Open Label	PI	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	6	6	3	6
75 mg/ Open Label	PI	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	6	6	1	6
Experimental Session 6								
No. (%)								

30 mg/	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Open	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Label	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	5	6	3	5
75 mg/	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Open	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Label	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	6	6	2	5

Endpoints No. (%)						
Dose		Baseline ^d	Primary	End of Stage 1	Open-label Dose	End of Stage 2
30 mg	PI	2 (28.6)	0 (0)	0 (0)	100-125 mg	0 (0)
	SI	0 (0)	0 (0)	0 (0)		0 (0)
	PB	0 (0)	0 (0)	0 (0)		0 (0)
	N	7	4	2		6
75 mg	PI	1 (14.3)	0 (0)	0 (0)	100-125 mg	0 (0)
	SI	0 (0)	0 (0)	0 (0)		0 (0)
	PB	0 (0)	0 (0)	0 (0)		0 (0)
	N	7	5	1		6
125 mg	PI	4 (33.3)	0 (0)	2 (16.7)	---	---
	SI	0 (0)	0 (0)	0 (0)		---
	PB	1 (8.3)	0 (0)	0 (0)		---
	N	12	8	12		---

PI=Positive Ideation; SI=Serious Ideation; PB=Positive Behavior; N=Number of Participants

^aAccording to the C-SSRS scoring guide, scores of four or five on the suicidal ideation category are considered serious ideation, and scores of one or greater are considered positive behavior or ideation.

^bPre-drug measurement taken day of experimental session prior to drug administration.

^cDuring-drug observation measured at experimental session endpoint, approximately 6 hours after drug administration.

^dBaseline represents frequency of participants reporting during Preparatory Sessions and before drug administration in Experimental Session 1

eTable 6. Vital signs during Experimental Sessions

Dose	30 mg (n = 7)	75 mg (n = 7)	125 mg (n = 12)	Open Label (n = 24)
Systolic Blood Pressure (mmHg)				
Pre-drug				
Mean (SD)	114.0 (11.9)	125.4 (10.0)	132.9 (14.1)	124.7 (14.1)
Min/Max	94/134	109/145	115/170	103/171
Peak				
Mean (SD)	132.3 (14.0)	147.0 (14.4) ^a	159.8 (13.9) ^{a, c}	156.1 (15.3)
Min/Max	110/155	123/179	136/194	124/193
Final				
Mean (SD)	118.5 (11.6)	127.4 (11.8)	136.5 (9.4)	126.9 (13.3)
Min/Max	98/140	107/147	117/153	77/158
Diastolic Blood Pressure (mmHg)				
Pre-drug				
Mean (SD)	73.5 (8.0)	77.9 (9.7)	84.7 (9.2)	79.1 (8.1)
Min/Max	60/87	56/95	70/102	62/103
Peak				
Mean (SD)	85.5 (7.5)	91.4 (12.1)	94.9 (4.9) ^a	96.3 (10.6)
Min/Max	75/99	78/118	87/105	82/126
Final				
Mean (SD)	76.7 (6.2)	78.4 (11.2)	84.6 (7.9)	79.6 (8.7)
Min/Max	68/91	59/100	72/104	63/99
Body Temperature (°C)				
Pre-drug				
Mean (SD)	36.2 (0.5)	36.6 (0.5)	36.6 (0.5)	36.5 (0.5)
Min/Max	35.3/36.9	35.9/37.8	35.8/37.4	35.6/37.7
Peak				
Mean (SD)	37.0 (0.4)	37.1 (0.5)	37.3 (0.5)	37.4 (0.5)
Min/Max	36.4/37.9	36.3/37.8	36.3/38.2	36.1/38.5
Final				
Mean (SD)	36.6 (0.5)	36.7 (0.4)	36.9 (0.6)	36.9 (0.6)
Min/Max	35.7/37.3	36.1/37.3	35.7/38.1	35.4/38.4
Heart Rate (BPM)				
Pre-drug				
Mean (SD)	67.7 (13.9)	73.7 (8.3)	76.9 (15.9)	73.7 (13.9)
Min/Max	45/91	61/85	52/122	44/111
Peak				
Mean (SD)	81.1 (16.0)	96.2 (16.1) ^b	108.3 (17.2) ^{a, d}	110.3 (22.9)
Min/Max	54/102	75/123	80/145	64/156
Final				
Mean (SD)	72.7 (13.0)	82.9 (13.3)	91.4 (17.9)	82.7 (15.3)
Min/Max	50/89	63/102	70/135	52/118

Min=minimum; Max=maximum; mmHg=millimeters of mercury; °C=Celsius; BPM=beats per minute

^a P < 0.01 vs 30 mg

^b P < 0.05 vs 30 mg

^c P < 0.01 vs 75 mg

^d P < 0.05 vs 75 mg

eTable 7. Frequency of Participants Reporting Treatment Emergent Adverse Events

	30 mg^a (n = 7)	75 mg^a (n = 7)	125 mg^a (n = 12)	Open Label (n = 23)
Cardiac disorders	0	0	0	1 (4.3)
Ear and labyrinth disorders	1 (14.3)	0	1 (8.3)	0
Endocrine disorders	1 (14.3)	0	0	0
Eye disorders	0	3 (42.9)	0	1 (4.3)
Gastrointestinal disorders	1 (14.3)	0	1 (8.3)	4 (17.4)
General disorders and administration site conditions	2 (28.6)	0	0	1 (4.3)
Infections and infestations	3 (42.9)	2 (28.6)	2 (16.7)	3 (13.0)
Injury, poisoning and procedural complications	1 (14.3)	0	2 (16.7)	1 (4.3)
Metabolism and nutrition disorders	1 (14.3)	0	0	1 (4.3)
Musculoskeletal and connective tissue disorders	0	0	1 (8.3)	5 (21.7)
Nervous system disorders	2 (28.6)	0	0	4 (17.4)
Psychiatric disorders	3 (42.9)	0	3 (25.0)	4 (17.4)
Respiratory, thoracic and mediastinal disorders	2 (28.6)	0	0	2 (8.7)
Skin and subcutaneous tissue disorders	1 (14.3)	2 (28.6)	0	2 (8.7)

^aBlinded treatment period

eTable 8. Frequency of Participants with Psychiatric Medication Use during the 12-month Follow-up

	Total (n = 24)
Indications for Current Medications, No. (%)	
Attention deficit/hyperactivity disorder	2 (8.3)
Insomnia	7 (29.2)
Anxiety	4 (16.7)
Social phobia	1 (4.2)
Stress	1 (4.2)
Depression	1 (4.2)
Generalized anxiety disorder	1 (4.2)
Any	12 (50.0)
None	12 (50.0)
Indications for Stopped Medications^a, No. (%)	
Anxiety	1 (4.2)
Insomnia	2 (8.3)
Phobia	1 (4.2)
Any	3 (12.5)
None	21 (87.5)

^a Four participants reported taking a psychiatric medication during the 12-month follow-up period but were not currently taking the medication at the 12-month visit. Two of the four were currently taking a different medication at 12-month follow-up visit and were also included in the subject counts for this variable.

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