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

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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 psychiatric 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. Participants in the 30 mg and 75 mg groups subsequently underwent three 100–125 mg MDMA-assisted psychotherapy sessions in an open-label crossover, and all participants were assessed 12 months after the last MDMA session. Safety was monitored through adverse events, 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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Introduction

Post-traumatic 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 life,[3] overall decreased life satisfaction and happiness, and increased risk of suicide.[4]

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 effectiveness,[5] especially in veterans. Off-label prescription of drugs, including antidepressants,

Research in context

Evidence before this study

Before development of this study's protocol, we searched PubMed, ClinicalTrials.gov, 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 Dec 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 of 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 the Clinician-Administered PTSD Scale (CAPS-IV) scores 2 months after treatment (p=0·066); however, it did show significant symptom reduction compared with baseline 1 year after treatment with active-dose MDMA.

Added value of this study

In this 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 the 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 might also have implications for future exploration of other pharmacological agents that could act as adjuncts or catalysts to psychotherapy.

antipsychotics, mood stabilisers, and benzodiazepines, is common, although risks and benefits for PTSD have not been established in randomised controlled trials. Trauma-focused psychotherapies are more effective than pharmacotherapy.[6] A meta-analysis of trials for military-related PTSD found that both cognitive processing therapy and prolonged exposure therapy 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 diagnosis.[7] High dropout (27–40%) occurs with trauma-focused psychotherapies, partially due to adverse outcomes, such as worsening symptoms, admission to hospital, or disengagement from treatments.[8,9] 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.[5,10] 3,4-methylenedioxymethamphetamine (MDMA) has shown promise as a psychotherapeutic adjunct.[11] 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%)[12,13] and durable improvements (average 45 months in 74% of one cohort).[14] 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.

For the **study protocol** see https://s3-us-west-1.amazonaws.com/mapscontent/pdfs/MP-8_FINAL_Protocol_Amendment+5_16Aug13_REDACTED.pdf

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.

See Online for appendix

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 Neuroticism-Extroversion-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 single-item Global Assessment of Functioning (GAF).[23]

Safety was monitored through adverse events, spontaneously reported expected reactions, vital signs, and

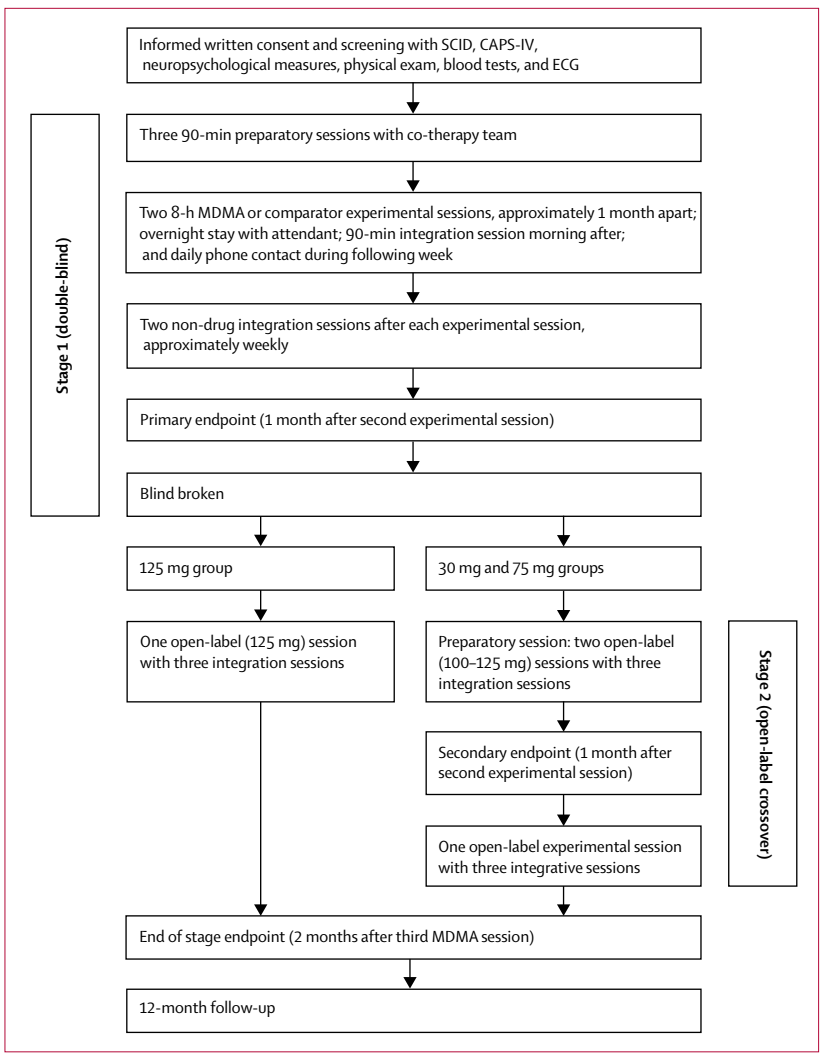

Figure 1: **Study design**
SCID=Structured Clinical Interview for DSM-IV Axis I Disorders. CAPS-IV=Clinician Administered PTSD Scale. PTSD=post-traumatic stress disorder. ECG=electrocardiogram. MDMA=3,4-methylenedioxymethamphetamine.

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 demographics 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

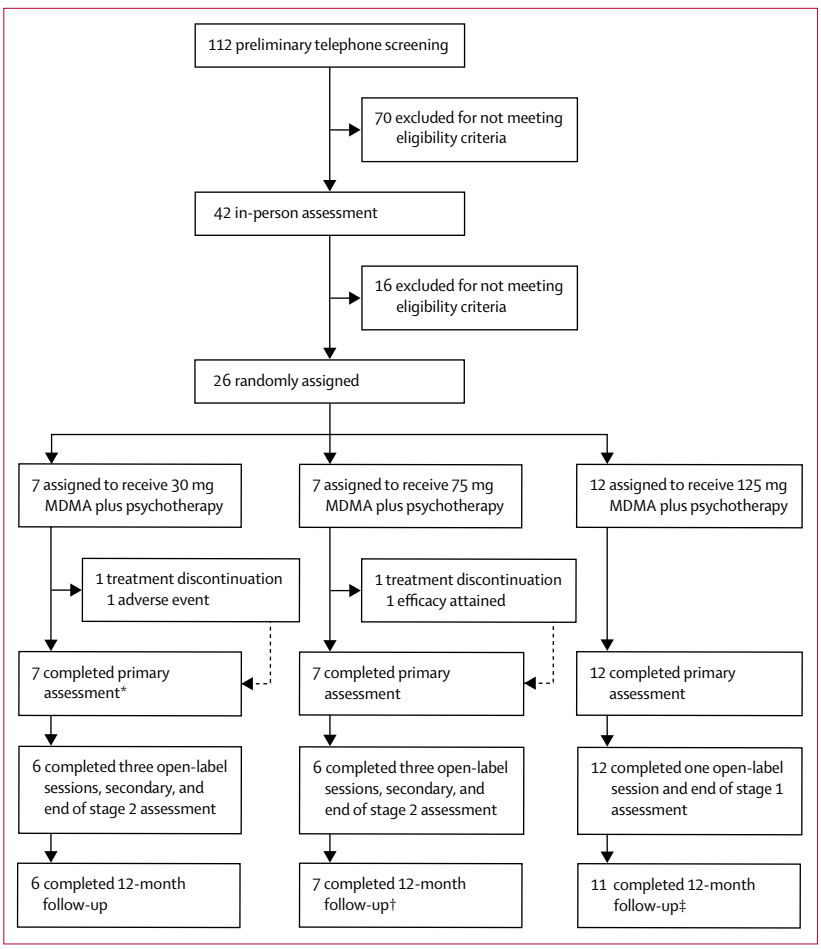

Figure 2: **Trial profile**
MDMA=3,4-methylenedioxymethamphetamine. *One participant completed one experimental session and primary endpoint assessment. †One participant discontinued treatment after one experimental session because of treatment efficacy (felt further MDMA sessions were unnecessary) but completed the primary and 12-month follow-up assessments. ‡One participant lost to follow-up.

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)	Total (n=26)
Mean age, years	39·2 (9·7)	29·1 (4·0)	40·7 (11·1)	37·2 (10·3)
Sex				
Men	5 (71%)	6 (86%)	8 (67%)	19 (73%)
Women	2 (29%)	1 (14%)	4 (33%)	7 (27%)
Ethnicity				
White	6 (86%)	4 (57%)	12 (100%)	22 (85%)
Latino or Hispanic	1 (14%)	1 (14%)	0	2 (8%)
Native American	0	1 (14%)	0	1 (4%)
Native American and white	0	1 (14%)	0	1 (4%)
Mean BMI	32·5 (4·7)	27·9 (5·4)	27·5 (3·6)	29·0 (4·8)
Occupation associated with trauma				
Military	6 (86%)	7 (100%)	9 (75%)	22 (85%)
Firefighter	1 (14%)	0	2 (17%)	3 (12%)
Police officer	0	0	1 (8%)	1 (4%)
Mean duration of PTSD, months	68·9 (15·0)	58·3 (32·3)	110·9 (85·1)	85·4 (63·9)
Pre-study therapy				
Eye movement desensitisation reprocessing	2 (29%)	0	1 (8%)	3 (12%)
Group psychotherapy	2 (29%)	2 (29%)	3 (25%)	7 (27%)
Prolonged exposure therapy	3 (43%)	1 (14%)	1 (8%)	5 (19%)
Cognitive processing therapy	0	1 (14%)	0	1 (4%)
Cognitive behavioural therapy, not otherwise specified	7 (100%)	6 (86%)	11 (92%)	24 (92%)
Psychodynamic therapy	2 (29%)	0	3 (25%)	5 (19%)
Interpersonal therapy	0	1 (14%)	0	1 (4%)
Other	5 (71%)	3 (43%)	8 (67%)	16 (62%)
None	0	0	1 (8%)	1 (4%)
Pre-study psychiatric medications				
Antidepressants	6 (86%)	7 (100%)	12 (100%)	25 (96%)
Anxiolytics	6 (86%)	5 (71%)	12 (100%)	23 (88%)
Antipsychotics	5 (71%)	2 (29%)	3 (25%)	10 (38%)
Mood stabiliser	0	0	2 (17%)	2 (8%)
Sleep aids	4 (57%)	2 (29%)	7 (58%)	13 (50%)
Stimulants	2 (29%)	4 (57%)	2 (17%)	8 (31%)
Other	2 (29%)	1 (14%)	5 (42%)	8 (31%)
Psychiatric comorbid disorders				
Major depression	5 (71%)	5 (71%)	10 (83%)	20 (77%)
Panic disorder	4 (57%)	2 (29%)	3 (25%)	9 (35%)
Generalised anxiety disorder	0	1 (14%)	1 (8%)	2 (8%)
Lifetime C-SSRS*				
Positive ideation	5 (71%)	6 (86%)	11 (92%)	22 (85%)
Serious ideation	1 (14%)	2 (29%)	5 (42%)	8 (31%)
Positive behaviour	4 (57%)	2 (29%)	5 (42%)	11 (42%)

Data are mean (SD) or n (%). Participants could have or report more than one pre-study therapy, pre-study psychiatric medication, and psychiatric comorbid disorder. MDMA=3,4-methylenedioxymethamphetamine. BMI=body-mass index. PTSD=post-traumatic stress disorder. C-SSRS=Columbia-Suicide Severity Rating Scale. *Lifetime accounts for all suicidal ideation and behaviour before this study, according to participant recall and medical records. According to the C-SSRS scoring guide, scores of 4 or 5 on the suicidal ideation category are considered serious ideation, and scores of 1 or greater are considered positive behaviour or ideation. Participants could have met criteria for more than one CSSRS category.

Table 1: **Demographics and baseline characteristics**

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 open-label 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

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)
Primary efficacy measure			
Mean CAPS-IV total score			
Baseline	87·4 (14·1)	82·4 (17·3)	89·7 (17·3)
After two experimental sessions of MDMA	76·0 (23·4)	24·1 (17·2)	45·3 (33·8)
Change†	−11·4 (12·7)	−58·3 (9·8)	−44·3 (28·7)
p value‡	NA	0·0005	0·004
Secondary efficacy measures			
Number of participants who met CAPS-IV PTSD diagnostic criteria (primary endpoint)			
Yes	5 (71%)	1 (14%)	5 (42%)
No	2 (29%)	6 (86%)	7 (58%)
Number of participants who had more than 30% decrease in CAPS-IV total score (primary endpoint)			
Yes	2 (29%)	7 (100%)	8 (67%)
No	5 (71%)	0	4 (33%)
Mean BDI-II score			
Baseline	30·4 (13·7)	24·7 (12·6)	36·6 (10·5)
After two experimental sessions of MDMA	25·9 (11·2)	9·3 (6·8)	12·0 (9·0)
Change†	−4·6 (8·8)	−15·4 (9·5)	−24·6 (10·6)
p value‡	NA	0·052	0·0003
Mean PSQI§			
Baseline	10·8 (5·7)	13·6 (4·2)	14·6 (3·6)
After two experimental sessions of MDMA	12·6 (5·2)	7·2 (4·1)	9·4 (5·1)
Change†	1·8 (2·8)	−6·4 (7·1)	−4·8 (4·1)
p value‡	NA	0·01	0·02
Mean PTGI score			
Baseline	23·9 (8·6)	29·9 (9·4)	31·5 (17·3)
After two experimental sessions of MDMA	12·3 (15·1)	66·0 (14·1)	65·2 (22·8)
Change†	−11·6 (12·2)	36·1 (12·0)	33·7 (24·0)
p value‡	NA	<0·0001	<0·0001
Mean GAF score			
Baseline	41·9 (11·8)	48·1 (9·1)	40·2 (7·2)
After two experimental sessions of MDMA	43·0 (12·8)	67·6 (6·2)	58·6 (12·1)
Change†	1·1 (4·6)	19·4 (6·1)	18·4 (14·4)
p value‡	NA	0·004	0·002
Mean DES-II score§			
Baseline	13·5 (17·7)	17·7 (9·1)	17·6 (10·7)
After two experimental sessions of MDMA	15·2 (17·4)	9·2 (10·9)	8·8 (8·0)
Change†	1·8 (0·9)	−8·6 (1·9)	−8·8 (6·2)
p value‡	NA	0·02	0·01
Mean NEO-PI-R score¶			
Neuroticism			
Baseline	62·0 (14·8)	65·3 (11·4)	75·1 (6·4)
After two experimental sessions of MDMA	60·2 (14·9)	53·6 (12·4)	58·6 (12·8)
Change†	−4·6 (5·5)	−12·0 (3·6)	−16·5 (11·8)
p value‡	NA	0·23	0·03
Extroversion			
Baseline	33·1 (9·4)	37·4 (8·9)	34·2 (8·5)

(Table 2 continues on next page)

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)
(Continued from previous page)			
After two experimental sessions of MDMA	36·0 (11·2)	46·4 (8·6)	42·2 (13·3)
Change†	2·2 (4·3)	10·0 (9·4)	8·0 (9·4)
p value‡	NA	0·17	0·22
Openness			
Baseline	48·9 (9·6)	55·6 (12·1)	57·4 (16·7)
After two experimental sessions of MDMA	49·2 (10·2)	66·0 (7·8)	59·4 (9·9)
Change†	−0·6 (9·9)	15·6 (5·3)	2·0 (10·5)
p value‡	NA	0·02	0·62
Agreeableness			
Baseline	44·7 (8·0)	33·1 (15·2)	39·8 (13·7)
After two experimental sessions of MDMA	40·6 (13·6)	33·4 (9·6)	45·7 (11·4)
Change†	−1·2 (8·4)	5·4 (8·0)	5·9 (4·9)
p value‡	NA	0·13	0·05
Conscientiousness			
Baseline	41·3 (9·9)	53·6 (18·3)	41·3 (13·5)
After two experimental sessions of MDMA	39·8 (6·8)	56·4 (10·1)	47·8 (10·0)
Change†	−3·2 (7·9)	2·4 (15·0)	6·5 (13·4)
p value‡	NA	0·50	0·17

Data are mean (SD) or n (%). MDMA=3,4-methylenedioxymethamphetamine. CAPS-IV=Clinician-Administered PTSD Scale. PTSD=post-traumatic stress disorder. NA=not applicable. 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=Neuroticism-Extroversion-Openness Personality Inventory-Revised. *All outcomes are based on the intention-to-treat population. †Change from baseline. ‡Compared with 30 mg MDMA. §Reduced sample size because of protocol amendment (PSQI: n=5 for 30 mg group, n=5 for 75 mg group, and n=10 for 125 mg group. DES-II: n=3 for 30 mg group, n=3 for 75 mg group, and n=6 for 125 mg group). ¶n=5 for the NEO-PI-R sample size of the 75 mg group at the primary endpoint.

Table 2: **Outcome measures* at the primary endpoint of 1 month after the second experimental MDMA session**

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 colleagues[26] 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

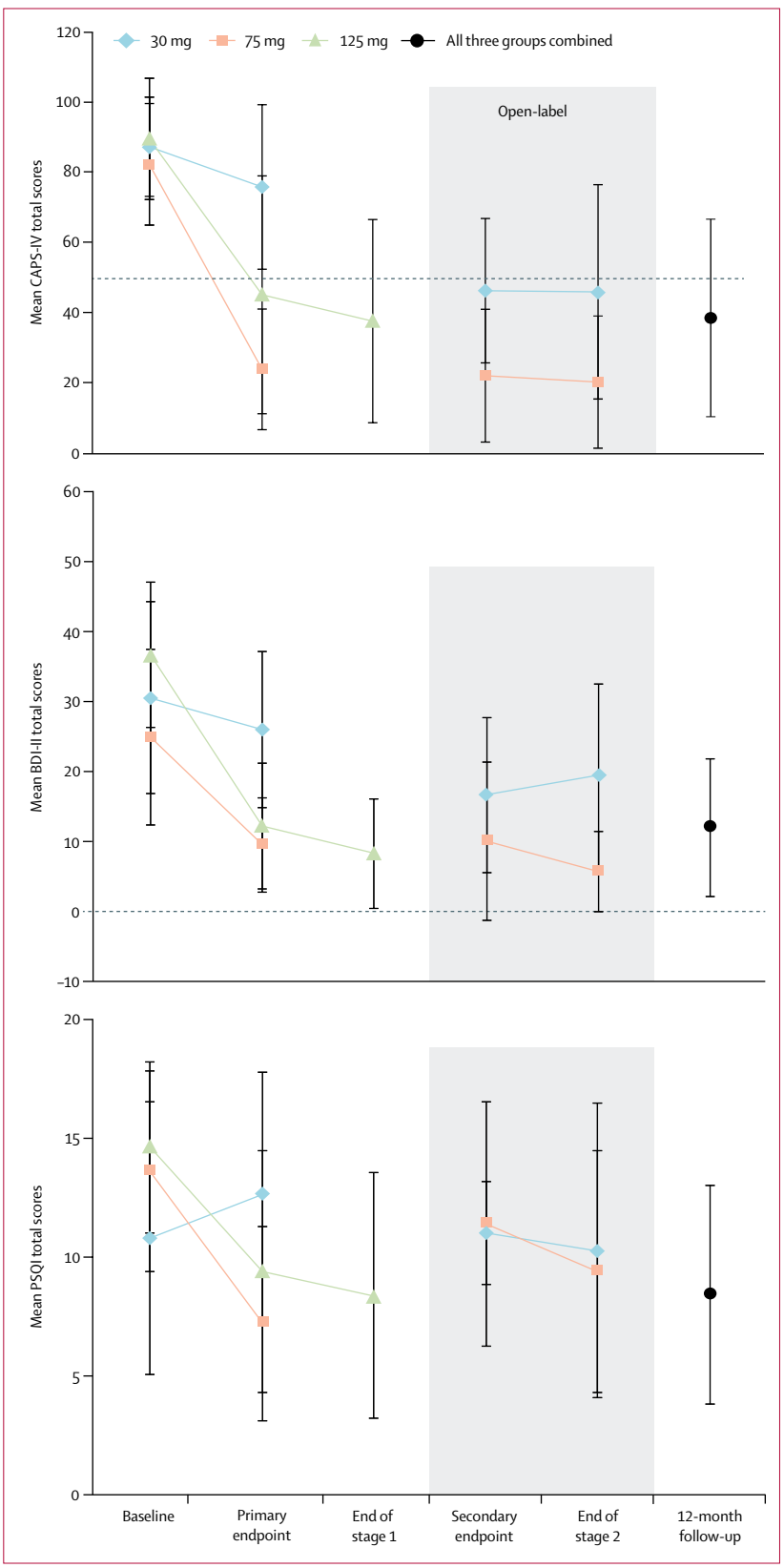

***Figure 3*: Mean CAPS-IV, BDI-II, and PSQI scores over time from baseline to endpoints (intention-to-treat population)**

Error bars are SDs. The dotted line at CAPS-IV total score 50 was one of the inclusion criteria for study enrolment. Assessments for graphs selected on the basis of representation of PTSD severity and most common associated symptoms—ie, depression and sleep disturbance. CAPS-IV=Clinician Administered PTSD Scale. PTSD=post-traumatic stress disorder. BDI-II=Beck Depression Inventory-II. PSQI=Pittsburgh Sleep Quality Index.

	30 mg MDMA plus psycho-therapy (n=7)	75 mg MDMA plus psycho-therapy (n=7)	125 mg MDMA plus psycho-therapy (n=12)	Total (n=26)	p value†
Primary efficacy measure					
Mean CAPS-IV total score					
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 measures					
Number of participants who met CAPS-IV PTSD diagnostic criteria (12-month)					
Yes	3 (50%)	2 (29%)	3 (27%)	8 (33%)	..
No	3 (50%)	5 (71%)	8 (72%)	16 (67%)	NA
Mean BDI-II score					
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
Mean PSQI‡					
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
Mean PTGI score					
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
Mean GAF score					
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
Mean DES-II score‡					
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
Mean NEO-PI-R score§					
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)	0·015
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

Data are mean (SD) or n (%). MDMA=3,4-methylenedioxymethamphetamine. CAPS-IV=Clinician Administered PTSD Scale. PTSD=post-traumatic stress disorder. NA=not applicable. 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=Neuroticism-Extroversion-Openness Personality Inventory-Revised. *All outcomes are based on the intention-to-treat population. †Within-subject *t* tests with groups combined. ‡Reduced sample size because of protocol amendment (PSQI: n=4 for 30 mg group, n=5 for 75 mg group, and n=10 for 125 mg group. DES-II: n=3 for 30 mg group, n=3 for 75 mg group, and n=5 for 125 mg group). §n=11 for NEO-PI-R sample size of the 125 mg group at 12-month follow-up.

Table 3*: Outcome measures at 12-month follow-up

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 administration[28] 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 used[17] 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.

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)	Total (n=26)
Most reported reactions during experimental sessions*				
Anxiety	4 (57%)	6 (86%)	11 (92%)	21 (81%)
Fatigue	5 (71%)	4 (57%)	7 (58%)	16 (62%)
Headache	5 (71%)	5 (71%)	8 (67%)	18 (69%)
Jaw clenching or tight jaw	0	4 (57%)	9 (75%)	13 (50%)
Reduced appetite	3 (43%)	4 (57%)	8 (67%)	15 (58%)
Muscle tension	4 (57%)	3 (43%)	9 (75%)	16 (62%)
Perspiration	2 (29%)	2 (29%)	5 (42%)	9 (35%)
Restlessness	4 (57%)	5 (71%)	3 (25%)	12 (46%)
Sensitivity to cold	4 (57%)	4 (57%)	6 (50%)	14 (54%)
Most reported reactions during 7 days of contact*				
Anxiety	4 (57%)	5 (71%)	10 (83%)	19 (73%)
Fatigue	6 (86%)	7 (100%)	10 (83%)	23 (88%)
Insomnia	5 (71%)	3 (43%)	10 (83%)	18 (69%)
Need more sleep	6 (86%)	6 (86%)	9 (75%)	21 (81%)
Headache	2 (29%)	3 (43%)	7 (58%)	12 (46%)
Muscle tension	2 (29%)	3 (43%)	7 (58%)	12 (46%)
Increased irritability	4 (57%)	2 (29%)	6 (50%)	12 (46%)
Lack of appetite	2 (29%)	1 (14%)	6 (50%)	9 (35%)
Difficulty concentrating	2 (29%)	0	5 (42%)	7 (27%)
Low mood	3 (43%)	0	3 (25%)	6 (23%)
Psychiatric treatment-emergent adverse events†				
Anxiety	1 (14%)	0	1 (8%)	2 (8%)
Flashbacks	0	0	1 (8%)	1 (4%)
Low mood	2 (29%)	0	0	2 (8%)
Negative thoughts	1 (14%)	0	0	1 (4%)
Suicidal ideation	1 (14%)	0	0	1 (4%)
Tic	0	0	1 (8%)	1 (4%)
Trichotillomania	1 (14%)	0	0	1 (4%)

Data are n (%). MDMA=3,4-methylenedioxymethamphetamine. *Frequency of participants who reported an expected, spontaneously reported reaction collected during and 7 days following blinded experimental sessions one and two. †Frequency of participants who self-reported psychiatric adverse events after first drug administration until the day before experimental session three.

Table 4: **Treatment-emergent adverse events and expected reactions during two MDMA sessions and 7 days following these sessions**

Contributors

SH is responsible for the integrity of the data and accuracy of data analyses. MCM, ATM, LJ, BY-K, AE, and RD conceived and designed the study. All authors acquired, analysed, and interpreted all data. MCM, AAF, and LJ drafted the manuscript. All authors critically revised the manuscript. RD obtained funding. MCM and ATM supervised the study.

Declaration of interests

MCM has received research funds from the Multidisciplinary Association for Psychedelic Studies (MAPS) Public Benefit Corporation

as a clinical investigator and clinical trial medical monitor, as well as for training and supervision of research psychotherapists. ATM has received research funds from MAPS Public Benefit Corporation as a clinical investigator and for training and supervision of research psychotherapists. AAF, LJ, and AE are full-time employees of MAPS Public Benefit Corporation. MW and JW have received research funds to do study assessments. JH declares no competing interests. SH has received research funds from MAPS Public Benefit Corporation for his role as a biostatistician. BY-K and RD are full-time employees of MAPS.

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References

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

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

3 Shea MT, Vujanovic AA, Mansfield AK, Sevin E, Liu F. Posttraumatic stress disorder symptoms and functional impairment among OEF and OIF national guard and reserve veterans. *J Trauma Stress* 2010; **23:** 100–07.

4 Sareen J, Cox BJ, Stein MB, Afifi TO, Fleet C, Asmundson GJ. Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. *Psychosom Med* 2007; **69:** 242–48.

5 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.

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

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

8 Goetter EM, Bui E, Ojserkis RA, Zakarian RJ, Brendel RW, Simon NM. A systematic review of dropout from psychotherapy for posttraumatic stress disorder among Iraq and Afghanistan combat veterans. *J Trauma Stress* 2015; **28:** 401–09.

9 Mott JM, Mondragon S, Hundt NE, Beason-Smith M, Grady RH, Teng EJ. Characteristics of US veterans who begin and complete prolonged exposure and cognitive processing therapy for PTSD. *J Trauma Stress* 2014; **27:** 265–73.

10 Feduccia AA, Mithoefer MC, Jerome L, Holland J, Emerson A, Doblin R. Response to the consensus statement of the PTSD Psychopharmacology Working Group. *Biol Psychiatry* 2017; published online Nov 23. DOI:10.1016/j.biopsych.2017.11.023.

11 Feduccia AA, Holland J, Mithoefer MC. Progress and promise for the MDMA drug development program. *Psychopharmacology* 2018; **235:** 561–71.

12 Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. 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* 2011; **25:** 439–52.

13 Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (±3,4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *J Psychopharmacol* 2013; **27:** 40–52.

14 Mithoefer MC, Wagner MT, Mithoefer AT, et al. 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* 2013; **27:** 28–39.

15 Blake DD, Weathers FW, Nagy LM, et al. A clinician rating scale for assessing current and lifetime PTSD: the CAPS-1. *Behav Ther* 1990; **13:** 187–88.

16 First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders—patient edition (SCID-I/P, version 2.0, 4/97 revision). New York: Biometrics Research Department and New York State Psychiatric Institute, 1997.

17 Mithoefer M. A manual for MDMA-assisted psychotherapy in the treatment of PTSD (version 8). 2016. http://www.maps.org/research/mdma/mdma-research-timeline/4887-a-manual-for-mdma-assisted-psychotherapy-in-the-treatment-of-ptsd (access March 16, 2017).

18 Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *J Pers Assess* 1996; **67:** 588–97.

19 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28:** 193–213.

20 Tedeschi RG, Calhoun LG. The Posttraumatic Growth Inventory: measuring the positive legacy of trauma. *J Trauma Stress* 1996; **9:** 455–71.

21 Costa PT, Macrae RR. The NEO personality inventory manual. Odessa, FL: Psychological Assessment Resources, 1985.

22 Carlson EB, Putnam FW. An update on the Dissociative Experiences Scale. *Dissociation* 1993; **6:** 16–27.

23 American Psychiatric Association. Diagnostic and statistical manual of mental disorders: 4th edition. Arlington, VA: American Psychiatric Association, 2000.

24 Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011; **168:** 1266–77.

25 Talbert FS, Braswell LC, Albrecht JW, Hyer LA, Boudewyns PA. NEO-PI profiles in PTSD as a function of trauma level. *J Clin Psychol* 1993; **49:** 663–69.

26 MacLean KA, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *J Psychopharmacol* 2011; **25:** 1453–61.

27 Wagner MT, Mithoefer MC, Mithoefer AT, et al. Therapeutic effect of increased openness: investigating mechanism of action in MDMA-assisted psychotherapy. *J Psychopharmacol* 2017; **31:** 967–74.

28 Carhart-Harris RL, Murphy K, Leech R, et al. 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* 2015; **78:** 554–62.

29 Gamma A, Buck A, Berthold T, Liechti ME, Vollenweider FX. 3,4-methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans. *Neuropsychopharmacology* 2000; **23:** 388–95.

30 Walpola IC, Nest T, Roseman L, et al. Altered insula connectivity under MDMA. *Neuropsychopharmacology* 2017; **42:** 2152–62.

31 Feduccia AA, Mithoefe MC. MDMA-assisted psychotherapy for PTSD: are memory reconsolidation and fear extinction underlying mechanisms? *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **84:** 221–28.

32 Sripada RK, King AP, Garfinkel SN, et al. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *J Psychiatry Neurosci* 2012; **37:** 241–49.

33 Fredman SJ, Monson CM, Adair KC. Implementing cognitive-behavioral conjoint therapy for PTSD with the newest generation of veterans and their partners. *Cogn Behav Pract* 2011; **18:** 120–30.

34 Cisler JM, Steele JS, Lenow JK, et al. Functional reorganization of neural networks during repeated exposure to the traumatic memory in posttraumatic stress disorder: an exploratory fMRI study. *J Psychiatr Res* 2014; **48:** 47–55.