An Open- Label, Phase 2, Multicenter Feasibility Study if Manualized MDMA-Assisted Psychotherapy with an fMRI sub-study Assessing Changes in Brain Activity in Subjects with Post-Traumatic Stress Disorder

Published: 15-01-2019
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The overall objective of this study is to use standard clinical measures to explore the safety and effects of open-label manualized MDMA-assisted psychotherapy with a flexible dose of MDMA in participants with severe PTSD, and to serve as an...

Ethical review	Approved WMO
Status	Completed
Health condition type	Psychiatric and behavioural symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON56347

Source
ToetsingOnline

Brief title
MDMA-Assisted Psychotherapy for the Treatment of PTSD

Condition

- Psychiatric and behavioural symptoms NEC

Synonym
Trauma; Posttraumatic Stress Disorder

Research involving

Human

Sponsors and support

Primary sponsor: MAPS Europe B.V.
Source(s) of monetary or material Support: Multidisciplinary Association for Psychedelic Studies (MAPS);a 501(c)3 non-profit and tax exempt charity

Intervention

Keyword: MDMA, Psychotherapy, PTSD, Trauma

Outcome measures

Primary outcome

The primary objective of this study is to evaluate the effect of MDMA-assisted psychotherapy on PTSD, as measured by the estimand of change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).
The primary and key secondary endpoint analyses will be based on the mITT analysis set. Change from Visit 3 (Baseline) in CAPS-5 Total Severity Scores to Visit 14 (Primary Endpoint) will be analyzed with least squares means from a Mixed-Effect Repeated Measures model (MMRM). The mITT analysis set will include all participants who receive IP in at least one Experimental Session and have at least one follow-up CAPS-5 assessment.

The Primary Outcome measure, the change in CAPS-5 from Baseline (V3), is assessed by a centralized Independent Rater (IR) pool at 13 weeks post Baseline (V14). The CAPS-5 is also administered as an exploratory measure after Treatment 1 (V8). The IR pool will be blinded to visit number and number of treatments received and will not have access to data collected by the sites

during the active treatment period.

Secondary outcome

The secondary objective is to evaluate the effectiveness of MDMA-assisted psychotherapy for PTSD in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline).

Safety Objective

The overall safety objective is to assess severity, incidence and frequency of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, and vital signs to support the package insert for MDMA-assisted psychotherapy. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy:

1. Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Product (IP), such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements.
2. Assess incidence of AEs by severity.
3. Assess incidence of Treatment Emergent AEs (TEAEs) by severity.
4. Assess incidence of TEAEs by severity taken during an Experimental Session and through 2 days after IP administration.
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function and abuse liability.
6. Assess incidence of AEs by severity categorized as leading to

discontinuation of IP, resulting in death or hospitalization, and continuing at Study Termination.

7. Assess incidence of SAEs.

8. Assess incidence of psychiatric concomitant medications taken during an Experimental Session and through 2 days after IP administration.

9. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.

10. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).

11. Assess mean changes in blood pressure, heart rate, and body temperature from pre-IP administration to end of each Experimental Session.

Exploratory Objectives: These objectives may be explored to characterize participants receiving MDMA-assisted psychotherapy to support the primary objective:

1. Explore the effect of presence of secondary traumatic stressors (LEC-5) on the CAPS-5 Total Severity analyses

2. Explore changes within-participants in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal, as measured by changes in CAPS-5 subscale scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline)

3. Explore the effect of adverse childhood experiences (ACE) on the CAPS-5 Total Severity analyses

4. Explore changes in:

• Dissociative symptoms associated with PTSD (DSP-I)

• Depression (BDI-II)

• Chronic pain (CPGS)

• Quality of life (EQ-5D-5L)

• Self-compassion (SCS)

• Addictive behaviors including: alcohol use (AUDIT), drug use (DUDIT), and nicotine use (SRNU)

• Eating habits (EAT-26)

• Healthcare utilization (UFEC)

• Subjective effect (SE)

fMRI Sub-Study Objectives and Evaluation:

To explore possible biological correlates of treatment outcomes obtained from MDMA-assisted psychotherapy among participants with PTSD.

- To investigate pre-post effects of MDMA-assisted psychotherapy on brain function and connectivity as measured by functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS), including response to trauma-unrelated emotional stimuli (emotional faces), response to trauma symptom provocation (personal trauma narrative). The outcome variables will be compared between timepoints (Baseline scan V 4.1 and post-treatment scan V 14.1).

- To examine the relationship between fMRI outcome variables and the primary outcome variable, namely change in CAPS-5 Total Severity Score from Baseline

(Visit 3) to 13 weeks post Baseline (Visit 14).

Study description

Background summary

PTSD is a serious, debilitating disorder that negatively impacts a person*s daily life. MDMA has been shown to reduce defenses and fear of emotional injury, enhance communication, and increase empathy. MDMA may enhance fear extinction learning in humans. These subjective effects of MDMA create a productive psychological state that enhances the therapeutic process for the treatment of PTSD and other anxiety disorders. This novel treatment package consists of up to three Experimental Sessions spaced a month apart of psychotherapy combined with a flexible dose of MDMA, along with non-drug preparatory and integrative psychotherapy. This study design is supported by data from an international series of Phase 2 pilot studies of MDMA-assisted psychotherapy conducted by the sponsor that provide preliminary evidence that chronic PTSD, independent of cause, is treatable with two to three sessions of MDMA-assisted psychotherapy and associated non-drug preparatory and integrative psychotherapy sessions. The results from multiple independent studies in Phase 2 efficacy analyses demonstrate superiority of MDMA-assisted psychotherapy over psychotherapy with placebo or low dose MDMA. The acceptable risk-benefit safety ratio in early trials justifies further study.

This open-label, lead-in Phase 2 study is intended to gather supportive data on the safety and effectiveness of manualized MDMA-assisted psychotherapy as a treatment for PTSD. The Primary Outcome measure, the change in Clinician Administered PTSD Scale for DSM-5 (CAPS-5) from Baseline to V14, evaluates changes in PTSD symptom severity and is assessed by a centralized Independent Rater (IR) pool in this study and in planned Phase 3 clinical trials. This will be the first study of MDMA-assisted psychotherapy in Europe using the CAPS-5 as a primary outcome measure to confirm assumptions made for statistical power calculations using the Clinician-Administered PTSD Scale for DSM-4 (CAPS-4) which support planned Phase 3 clinical trials. This study will gather supportive data on the safety and effectiveness of manualized MDMA-assisted psychotherapy as a treatment for PTSD and provide clinical supervision to planned Phase 3 therapy teams. This study will also be the first multi-site study of MDMA-assisted psychotherapy for PTSD in Europe and will explore reproducibility of findings from FDA-regulated trials in a multi-site format to further confirm the Phase 3 study design.

In addition, the fMRI Sub-Study will explore possible biological correlates of treatment outcomes obtained from MDMA-assisted psychotherapy among participants with PTSD. The sub-study will investigate pre-post effects of MDMA-assisted

psychotherapy on brain function and connectivity as measured by functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS), including response to trauma-unrelated emotional stimuli (emotional faces), response to trauma symptom provocation (personal trauma narrative).

Study objective

The overall objective of this study is to use standard clinical measures to explore the safety and effects of open-label manualized MDMA-assisted psychotherapy with a flexible dose of MDMA in participants with severe PTSD, and to serve as an opportunity for supervision of therapy teams selected to conduct Phase 3 MDMA-assisted psychotherapy research.

The primary objective of this study is to evaluate the effect of MDMA-assisted psychotherapy on PTSD, as measured by the estimand of change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

The secondary objective is to evaluate the effect of MDMA-assisted psychotherapy for PTSD in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 (Baseline) to 13 weeks post Baseline (Visit 14).

The overall safety objective is to assess severity, incidence and frequency of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, and vital signs to support the package insert for MDMA-assisted psychotherapy. The safety objectives will evaluate the safety of MDMA-assisted psychotherapy.

In addition, the fMRI Sub-Study will explore possible biological correlates of treatment outcomes obtained from MDMA-assisted psychotherapy among participants with PTSD:
- To investigate pre-post effects of MDMA-assisted psychotherapy on brain function and connectivity as measured by functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS), including response to trauma-unrelated emotional stimuli (emotional faces), response to trauma symptom provocation (personal trauma narrative). The outcome variables will be compared between timepoints (Baseline scan V 4.1 and post-treatment scan V 14.1).
- To examine the relationship between fMRI outcome variables and the primary outcome variable, namely change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

Study design

An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an optional fMRI sub-study Assessing Changes

in Brain Activity in Subjects with Post-Traumatic Stress Disorder

Intervention

The treatment consists of a flexible dose of MDMA, followed by a supplemental half-dose unless contraindicated, administered with manualized psychotherapy in two open-label Experimental Sessions spaced a month apart. This ~8-week Treatment Period is preceded by three Preparatory Sessions. During the Treatment Period, each Experimental Session is followed by three Integrative Sessions of non-drug psychotherapy. Experimental Sessions are followed by an overnight stay.

Initial doses per Experimental Session include 80 mg or 120 mg MDMA, followed 1.5 to 2 hours later by a supplemental half-dose (40 mg or 60 mg). Total amounts of MDMA to be administered per Experimental Session range from 80 mg to 180 mg. MDMA dose ranges proposed in this study have been safely used in previous Phase 2 studies sponsored by MAPS (Protocol section 5.5). Procedures for MDMA-assisted psychotherapy will remain the same across all sessions and all procedures regardless of dose received. Experimental Sessions must be at least 8 hours long, measured from 30 minutes prior to IP administration.

For each participant, the study will consist of:
- Screening Period: phone screen, informed consent, eligibility assessment, and enrollment of eligible participants
- Preparatory Period with Enrollment Confirmation: medication tapering, Preparatory Sessions and Baseline assessments leading to Enrollment Confirmation
- Treatment Period: two Experimental Sessions spaced a month apart and associated Integrative Sessions over ~8 weeks plus one CAPS-5 assessment
- Follow-up Period and Study Termination: ~4 weeks with no study visits, followed by Primary Outcome CAPS-5 and Study Termination visit
- MRI: 2 visits for baseline scan Visit 4.1 and post-treatment scan Visit 14.1

Study burden and risks

During Screening, throughout MDMA-assisted psychotherapy, and during assessment of study measures, participants will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses or suicidal ideation as a result of recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress and exacerbate suicidal ideation during and immediately after psychotherapy sessions. Psychotherapy is conducted as part of this study, and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

Therapy teams will provide emotional support to participants during any psychological distress.
The therapy team will minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants with a history of suicide attempts will not be excluded unless significant risk of suicidal behavior is present at the time of screening.

Blood draws and a full medical examination, including a physical examination, ECG, 1-minute rhythm strip, and laboratory tests, are required to establish eligibility for the study. Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress.
fMRI: taking brain scans is associated with a loud thumping noise, participants will be given hearing protection. Besides possible discomfort, there are no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Are at least 18 years old
2. Are fluent in speaking and reading the predominantly used or recognized language of the study site
3. Are able to swallow pills
4. Agree to have study visits video-recorded, including Experimental Sessions, Independent Rater assessments, and non-drug psychotherapy sessions
5. Must provide a contact (relative, spouse, close friend or other support person) who is willing and able to be reached by the investigators in the event of a participant becoming suicidal or unreachable
6. Must agree to inform the investigators within 48 hours of any medical treatments and procedures
7. If of childbearing potential, must have a negative pregnancy test at study entry and prior to each Experimental Session, and must agree to use adequate birth control through 10 days after the last Experimental Session. Adequate birth control methods include intrauterine device (IUD), injected or implanted hormonal methods, abstinence, oral hormones plus a barrier contraception, vasectomized sole partner or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (i.e. condom plus diaphragm, condom or diaphragm plus spermicide, oral hormonal contraceptives plus spermicide or condom). Not of childbearing potential is defined as permanent sterilization, postmenopausal, or assigned male at birth.
8. Agree to the following lifestyle modifications (described in more detail in Section 4.3 Lifestyle Modifications): comply with requirements for fasting and refraining from certain medications prior to Experimental Sessions, not participate in any other interventional clinical trials during the duration of the study, remain overnight at the study site after each Experimental Session and be driven home after, and commit to medication dosing, therapy, and study procedures
9. At Screening, meet DSM-5 criteria for current PTSD with a symptom duration of 6 months or longer
10. At Screening, have at least severe PTSD symptoms in the last month based on PCL-5 total score of 50 or greater
11. At Screening, may have well-controlled hypertension that has been successfully treated with anti-hypertensive medicines, if they pass additional screening to rule out underlying cardiovascular disease
12. At Screening, may have asymptomatic Hepatitis C virus (HCV) that has previously undergone evaluation and treatment as needed
13. At Baseline, have a confirmed diagnosis of PTSD per CAPS-5 and at least severe symptoms in the last month constituting a CAPS-5 Total Severity Score of 35 or greater.

14. Absence of Traumatic Brain Injury
15. Absence of metal implants or metal fragments in the body
16. PTSD must be of non-dissociative sub-type
17. Absence of claustrophobia
18. Absence of tattoos in the head/neck or permanent eye makeup

Exclusion criteria

1. Are not able to give adequate informed consent
2. Are currently engaged in compensation litigation whereby financial gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorders
3. Are likely, in the investigator*s opinion and via observation during the Preparatory Period, to be re-exposed to their index trauma or other significant trauma, lack social support, or lack a stable living situation
4. Have used Ecstasy (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the first Experimental Session; or have previously participated in a MAPS-sponsored MDMA clinical trial
5. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation, Psychiatric History, 1. Have received Electroconvulsive Therapy (ECT) within 12 weeks of enrollment
2. Have a history of, or a current primary psychotic disorder, bipolar affective disorder type 1 assessed via MINI or dissociative identity disorder assessed via DDIS
3. Have Dissociative Subtype of PTSD assessed via CAPS-5
4. Have a current eating disorder with active purging assessed via MINI
5. Have current major depressive disorder with psychotic features assessed via MINI
6. Meet DSM-5 criteria for current substance use disorder for alcohol or substance use disorder other than caffeine or nicotine assessed via MINI, AUDIT, DUDIT, drug test, and blood %carbohydrate-deficient transferrin (%CDT)
7.Have current Personality Disorders (paranoid, schizoid, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, obsessive-compulsive) assessed via CIPD. Diagnoses will be confirmed via clinical interview
8. Any participant presenting current serious suicide risk, as determined through psychiatric interview, responses to C-SSRS, and clinical judgment of the investigator will be excluded; however, history of suicide attempts is not an exclusion. Any participant who is likely to require hospitalization related to suicidal ideation and behavior, in the judgment of the investigator, will not be enrolled
9. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist
10. Require ongoing concomitant therapy with a psychiatric medication with

exceptions described in Section 12.0: Concomitant Medications., Medical History, 1. Have evidence on clinical examination or history of significant (controlled or uncontrolled) hematological, endocrine, cerebrovascular, traumatic brain injury (TBI) with residual neurological signs or symptoms on the physical exam, cardiovascular, coronary artery disease (using the New York Heart Association criteria) cerebral or peripheral vascular disease, pulmonary, renal, hepatic disease with abnormal liver enzymes (outside of the normal clinical range), gastrointestinal, immunocompromising, or neurological disease, including seizure disorder, or any other medical disorder judged by the investigator to significantly increase the risk of MDMA administration (participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded). Note: if participants present with a history of glaucoma, enrollment would be allowed only with the approval of their ophthalmologist
2. Have uncontrolled hypertension using the standard criteria of the American Heart Association (values of 140/90 milligrams of Mercury [mmHg] or higher assessed on three separate occasions)
3. Have a marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds [ms] corrected by Bazett*s formula). Abnormal ECG (including sinus bradycardia of less than 50 beats per minute, sinus tachycardia of more than 100 beats per minute or prolonged QTc of more than 450 ms in males and 460 ms in females).
4. Have a history of additional risk factors for Torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)
5. Require use of concomitant medications that prolong the QT/QTc interval during Experimental Sessions. Refer to Section 12.0 Concomitant Medications.
6. Have symptomatic liver disease
7. Have history of hyponatremia (defined as outside of the normal range of 135 to 145 mmol/L) or hyperthermia
8. Weigh less than 48 kilograms (kg)
9. Are pregnant or nursing or are of childbearing potential and are not practicing an effective means of birth control.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	04-12-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	magnetic resonance imaging (MRI)
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	MDMA
Generic name:	3,4-methylenedioxymethamphetamine hydrochloride

Ethics review

Approved WMO

Date:	15-01-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	18-10-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	21-02-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	08-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	10-08-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	12-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	03-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	13-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	21-12-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	13-01-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	02-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	07-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	24-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	02-11-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-001718-13-NL
CCMO	NL67928.058.18

Study results

Date completed: 21-09-2023

Results posted: 12-12-2024

Actual enrolment: 8

First publication
06-12-2024