

SUBJECT INFORMATION AND CONSENT FORM



Study Title: A Randomized, Double-Blind, Controlled Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

PROTOCOL NO.: **MP-4**
Study Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
1215 Mission Street, Santa Cruz, CA USA 95060
Phone: 831-429-6362 Fax: 831-429-6370

Investigator: [REDACTED]

Sub-Investigator: [REDACTED]

Address: [REDACTED]

24-hour contact number(s): [REDACTED]

Cellular number(s): [REDACTED]

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM

This consent form describes a research study and your role as a participant. Please read this form carefully. Feel free to ask anything about the information provided; it is expected that you will have questions about it.

You are being asked to participate in this research study because you have been diagnosed with posttraumatic stress disorder (PTSD) and because your symptoms have not gone away after psychotherapy or medications for PTSD. You may also be in this study if you had trouble with treatments for your symptoms and had to stop using them.



Please ask the study personnel to explain any words or information in this consent form you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE AND BACKGROUND

This small study is designed to provide information on whether MDMA-assisted psychotherapy is safe and helpful for subjects with PTSD. The study therapists plan to use the results of this study to design future studies of MDMA-assisted psychotherapy.

The study is sponsored by a US-based non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org). MAPS' first small study of MDMA-assisted psychotherapy in 21 people with PTSD is finished in the U.S. MAPS has completed another MDMA/PTSD pilot study in 12 people in Switzerland. Three studies are currently enrolling, two in the U.S. and one in Israel.

MDMA is experimental, which means it has not been approved by Health Canada for medical use, except within research studies like this one. MDMA is illegal to use outside of research and is sometimes known as "Ecstasy" (which is supposed to contain MDMA but can often contain other drugs instead of or in addition to MDMA).

Before it became illegal, some psychotherapists combined MDMA with psychotherapy ("talk therapy") to help people with psychological problems, sometimes including PTSD. Though we do not know if it helps people with PTSD, we know that MDMA increases positive mood and also changes the way we see and think about the world around us, making it easier to think about and recall upsetting experiences, and people say they feel caring and forgiving toward themselves and others after MDMA. Most types of therapy that treat PTSD involve facing the trauma and PTSD symptoms and going over trauma-related emotions. Doing this reduces fear, defensiveness, avoiding things, places or feelings that trigger unwanted feelings or thoughts, and feeling emotionally numb or distant from relationships. If MDMA can temporarily decrease fear and avoidance and increase trust and connection between the person with PTSD and their therapist, then MDMA may make the therapy stronger and more likely to work. It is possible that these effects, when combined with psychotherapy, help people confront and go through the thoughts, memories and emotions related to PTSD.

During the study you will interact with a therapy team consisting of one doctor and one therapist. You will see the same study therapy team for the whole study. You will have your symptoms measured by an independent researcher. Study personnel will contact you to schedule your visits. Some of the visits may be conducted by phone or telemedicine. Telemedicine involves the use of electronic communications.

This study will compare full dose MDMA with a comparator dose, meaning a dose that may or may not contain MDMA in it. During experimental sessions participants will receive full dose of MDMA or a comparator, possibly followed one and a half to two and a half hours later by a second dose equal to half the size of the first dose.



Length of Study

The length of the study depends on your group assignment to the active dose group or the comparator dose group. Participation in the study will require a significant time commitment on your part. Neither you nor the study team will know what group you are being assigned to.

- **Active Dose Group:** This study can take up to 15 months or 18 visits if you are assigned to one of the active doses of MDMA in “Stage 1.” This time period includes active participation for up to 3.5 months and a long-term follow-up visit 12 months after the last experimental session.
- **Comparator Dose Group:** If you receive the comparator dose in Stage 1 the study can take up to 23 months or 28 visits to complete both stage 1 and 2 plus the long term follow up visit. If you are in the comparator group you will have 12 visits in stage 1 and you can choose to have an additional 12 visits in Stage 2 where you receive the active dose of MDMA over an additional 3.5 months. This time period includes 6 months of active participation plus a long-term follow-up visit 12 months after the last experimental session.

The timeline for starting treatment can move fast or slow depending on availability of open appointments. You may start therapy at enrollment or it may take as long as two months if time is needed for medication to leave your body. Depending on your group you will meet with the therapist approximately once a week during the active period of the study. Experimental sessions last all day and require an overnight stay. After these overnight stays, you will also have a brief daily phone call with one of the therapists for 7 days and you will have 3 psychotherapy sessions in person or on the phone or by telemedicine. You will have testing visits 4-5 times during the study. After active participation is complete, you will have a follow up visit one year later.

Types of visits and duration:

Psychotherapy sessions (90 minutes each): 3 introductory sessions at the start of participation and 3 sessions after each experimental session.

Experimental sessions (8 hours long plus an overnight stay): 3 sessions for each person in the active dose group and 2 sessions plus 3 optional sessions for each person in the comparator dose group.

Evaluation Testing Visits (Up to 2 and a half hours): Testing and completing questionnaires 4-5 times, starting with the beginning of the study.

With very few exceptions you will need to take the appointments we schedule because there is a limited time frame for each type of event.



Subject Responsibilities

If you and the study doctor agree that you can and want to be in the study, you will come to all study visits. You will have to avoid taking any psychiatric medications from the beginning of the study up until your last study visit unless the study doctor make a specific exception, such as giving you medication for sleep or anxiety if needed temporarily between experimental sessions. If you are taking psychiatric medication, you will need to give the study doctor permission to talk with your doctor about how best to stop taking your medication. If you are taking certain medications to manage pain, you will need to decrease the dose of medication you are taking right before experimental sessions.

If you are currently seeing a psychotherapist, you may not begin any new psychotherapy or change the frequency or length of visits with your psychotherapist until after the final evaluation session.

For your safety, it is very important to tell the study doctor about all medications you are taking, including herbal or “natural” remedies, and to check with the study doctor before you begin taking a new medication while in this study.

Any study visit you have may be audio and/or video recorded for research and training purposes to help the researchers understand and learn about this type of therapy. The study personnel can give you access to these recordings to watch.

PROCEDURES/WHAT WILL HAPPEN TO YOU

SCREENING/EVALUATION AND BEGINNING OF STUDY

If you agree to take part in this study, you will first sign this form before any study-related procedures are performed. Before you can be in the research study, the study doctor must first make sure that you qualify for the study and that you are generally physically healthy. The screening process will take about 6 hours and may be done over multiple visits in person and on the phone.

The tests will include the following:

- An interview about your PTSD symptoms and how you deal with them in your everyday life. Your score on this interview will be used to decide if you can be in the study. This interview may be video recorded for research purposes.
- A questionnaire about your personality.
- A questionnaire about the quality of your sleep.
- A questionnaire about any detachment symptoms.
- A questionnaire about feelings of depression or other symptoms or feelings you might experience.
- A questionnaire about your mental health.
- Questions about your medical history, including questions about your emotional and psychiatric history. This may include any previous medical or psychiatric problems or treatment and may include questions about difficult experiences you may have had during childhood or at other times of your life.



- Questions about thoughts and feelings you might have about hurting or yourself.
- Two different tests of attention, memory and different types of problem solving. These are not tests of intelligence.
- A visual scale of pain and/or tinnitus (ringing in your ears) levels if you have these symptoms.
- A physical examination that will include measures of your blood pressure, pulse, temperature, and body weight.
- An ECG (electrocardiogram) will also be taken, which is a recording of the electrical activity of your heart.
- A sample of your blood (about 2 tablespoons, or about 30 mL) and a urine sample for routine laboratory testing, including tests of metabolism and liver function. An HIV test will also be run.
- A urine test for drugs of abuse. Your urine drug screen must be negative before experimental sessions.
- A urine pregnancy test if you are a woman and are able to get pregnant. Your urine pregnancy test must be negative for you to take part in the study.

BEGINNING OF STUDY

If you have decided that you want to be in the study and if the study therapists find that you are eligible, you will schedule your first introductory psychotherapy session with one of the study therapist teams. If you were taking psychiatric medicines when the study therapists first checked to see if you could be in the study, you may have your PTSD and other symptoms measured again after you have stopped taking your medication. Your first experimental session will be between 4 and 8 weeks after your baseline PTSD symptoms are measured. The time will depend on scheduling and on the time it takes for any medication to clear from your body.

You must let the study therapists know about any medical conditions or procedures that you had or are having, like surgery, within 48 hours of their occurrence.

You will need to give the study therapists the name and contact information (telephone number, cell phone number or email) of a relative, spouse or close friend to contact in case of medical emergency, as when you might be at risk of hurting yourself, or someone else, so they can reach that person to let them know what is going on.

SCHEDULE OF EVENTS

The types of visits in the study consist of screening, preparatory visits, experimental sessions, integrative visits, and follow up visits. Time is counted from the first study visit after you are selected to be in the study. The tables below show the type of visits you will have in Stage 1 and Stage 2 (if you are in the comparator group)





Table 1. Schedule of Events – Stage 1

Stage 1	Screening	Intro and Preparation			Therapy 1				Therapy 2				Evaluation	Therapy 3				Evaluation	Evaluation
Both Groups												Full Dose MDMA Group Only							
Study Visit		1 Enroll	2*	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Screening	X																		
Measure Symptoms	X							X				X	X				X	X	X
Memory/Attention tests	X												X					X	
Psychotherapy		X	X	X		X	X	X		X	X	X			X	X	X		
Psychotherapy with Drug					X				X						X				
Medical Exam	X																		
Learn What You Received													X						
May be by Phone or Telemedicine	X						X	X			X	X	X			X	X	X	X

Table 2. Schedule of Events – Stage 2

Stage 2	Preparation	Therapy 1				Therapy 2				Evaluation	Therapy 3				Evaluation	Long Term Evaluation
Comparator Group Only																
Study Visit #	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	
Measure Symptoms	X*				X				X	X				X	X	X
Memory tests															X	
Psychotherapy	X		X	X	X		X	X	X			X	X	X		
Psychotherapy with MDMA		X				X					X					
May be by Phone or Telemedicine				X	X			X	X	X			X	X	X	X

* Symptoms may be measured again if more than 8 weeks passes between Visit 12 and 18.

 Experimental Sessions
 Study Measures



INTRODUCTORY PSYCHOTHERAPY SESSIONS:

Once screening is complete and you are enrolled in the study you will meet with study therapists three separate times before the first experimental session. These visits will last about 90 minutes. During each introductory session, you will talk about the traumatic incidents that led to your PTSD, the ways PTSD symptoms are affecting your life and what you would like to achieve during these sessions. You will be asked questions about thoughts or feelings you might have about hurting or killing yourself during one of these preparatory sessions. You will also learn more about what to expect during experimental sessions. The introductory session may be recorded to audio and video, so that the study therapists will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. You can ask the study therapists to let you hear or see these recordings if you wish.

SELECTION OF DRUG – FULL DOSE OR COMPARATOR DOSE?

This study is double blind, meaning that neither you nor the study researchers will know what you will get. However, in the event of an emergency the researchers can find out. The drug you get will be decided at random, as if by tossing a coin. Seven people will receive the full dose and five people will receive the comparator. You will have a 58% chance of receiving full dose MDMA and a 42% chance of receiving the comparator. You will find out what you received about 1 month after your second experimental session is complete. There will be 12 participants in this study.

Neither you, the person measuring your PTSD symptoms, nor the study therapists will know who is getting the high dose of MDMA and who is getting the low dose (known as “double blinded”) until after the study is completed. However, this information is available if needed in an emergency.

EXPERIMENTAL SESSIONS:

After you have completed three introductory therapy sessions, you will have two day-long experimental sessions with psychotherapy. During both sessions, you will have full dose MDMA or comparator dose. The sessions will happen three to five weeks apart. Each experimental session will last about eight hours, though one or both study therapists will remain with you for a longer time if needed.

One week before each of the experimental sessions, you will need to avoid taking:

- Any herbal supplement (except with prior permission);
- Any non-prescription medications, unless you have permission (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen [Tylenol]);
- Any prescription medications, unless you have permission (with the exception of birth control pills, thyroid hormones or other medications). You will need to talk to the study therapists about which medications are okay to keep taking.

You must not eat after midnight on the night before each session, but you can drink non-alcoholic liquids during this time, such as water or juice. You cannot use nicotine or



caffeine for 2 hours before and 6 hours after receiving the capsule. The study therapists will give you a paper with these instructions before your first experimental session.

First, you and the study therapists will discuss your goals for the experimental session, and the study therapists will answer any questions you still have about your experimental session.

Before an experimental session:

- Your urine will be tested for drugs of abuse.
- If you are a woman who can become pregnant, a urine pregnancy test will be done.

Throughout an experimental session:

- Your blood pressure and pulse will be measured every 30 minutes.
- Your temperature will be measured every 60 to 90 minutes.
- You will also complete a very short, simple test of how comfortable or upset you feel by marking a number on a sheet of paper that shows the way you feel at that moment. You will complete it every 60 to 90 minutes during each experimental session.
- About an hour before taking the capsule and about 6 hours afterward, you will answer questions about thoughts you might have about hurting or killing yourself.
- The study therapists will check in on you every hour or so to see how you are doing.

The experimental session may be audiotaped and videotaped, so that the study therapists will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. The study therapists can give you access to these recordings for you to watch or hear if you want them.

After urine test results come back, you will be given a capsule containing either the comparator dose or full dose MDMA. After taking the capsule, you will sit or lie down in a comfortable position. You can ask for an eye-shade if you wish. You will be able to listen to music through headphones during much of each experimental session. You might be asked to remove the headphones to talk to the study therapists, and you may also remove them yourself if you want to talk to the study therapists or for periods of silence. Lying or sitting in a comfortable position and listening to music are meant to bring out thoughts and feelings, including thoughts and feelings about the trauma. Both study therapists will stay with you, and they will help you if you need them to do so. They will talk to you and ask you to talk to them at least once an hour, but you can talk to them whenever you wish. There may be times when the study therapists will suggest that you stop talking for a while in order to pay attention to your thoughts and feelings. There will be water, juices or drinks containing electrolytes available to drink whenever you like within the limits of what is safe for your body. Later on, food will also be provided.

About one and a half to two and a half hours later, you and the study therapists will talk about taking a second capsule. The second dose will be half the amount of the first



dose. If you and the study therapists agree, then you will take the second dose. If you and the study therapists notice problems after the first capsule, then you will not get the second capsule.

The study therapists will continue to measure blood pressure, pulse and temperature, and they will watch for any side effects (unwanted effects or health problems), which will be treated if they occur. If this happens, the study therapists will let you know what they are doing.

If you are still confused or very upset eight or more hours after the start of the experimental session, the study therapists will stay with you until you have recovered more fully. If the study therapists think you are at risk for hurting yourself or someone else, they will either stay with you all night or have you stay in a nearby hospital until they are certain you are not at risk. If the study therapists decide that the effects of the drug have worn off and you are in an okay frame of mind, they will leave the office with the attendant in charge. The study therapists will ask you about thoughts of killing or harming yourself before and after taking the first capsule.

You will spend the night in a comfortably furnished room in the offices of the Investigator. If you request and the study therapists agree, you may also have a companion stay with you at the office during or after an experimental session. An attendant will stay in another room at the same location from the time after you are done with the experimental session until the non-drug session on the next day. The attendant will offer dinner and breakfast, help you with any physical needs if requested, and contact the study therapists to speak with them or to have them return to the office at your request or if the attendant thinks it is needed.

On the next day, you will have a non-drug therapy session with the study therapists. You will need to arrange ahead of time to have someone take you home from this session, because we don't know how the experimental session will affect you and some people report feeling tired or less alert. If you cannot find anyone to take you home, the study therapists will either call a taxi or make arrangements for someone to drive you home.

After you return home, one of the study therapists will telephone you every day for a week to ask about how you are feeling and decide whether you should see them for your next non-drug (integrative) psychotherapy session. These telephone calls will take approximately 5 to 15 minutes, though they can last as long you need them to. You may schedule additional meetings with the study therapists besides those that are scheduled as part of the study.

You can contact the study therapists at any time. The study therapists will give you a card with telephone numbers for reaching them, the organization sponsoring the study, or the Institutional Review Board – IRB Services (an independent committee that reviewed the ethical parts of this study to help protect the rights and welfare of study



participants). At least one of the study therapists will be on call (reachable by telephone or pager) 24 hours a day throughout the research study.

If there are delays in following the usual study schedule, the study therapists will telephone you at least once a week to talk about how you're doing. These telephone calls will take approximately 15 minutes, and you should call the study therapists if any of the following things happens: you have an increase in symptoms for which you were previously took medication, you need to contact your outside therapist other than for the usual appointments, you start or stop taking prescribed medication, and/or you go to the hospital for any reason.

If you have very high blood pressure, get sick, or have a significant lasting unwanted effect or health problem after the first experimental session, you or the study doctor may decide that you should not participate in the second experimental session. If the study doctor decides to take you out of the study, they will let you know that they are doing this and their reason for doing this. If you are taken out of the study or decide you do not want to be in the study, the study researcher will ask you to complete final questionnaires about your PTSD and other symptoms and tests of memory and problem solving. If you decide you do not want to continue in the study during an experimental session, you will still have to stay in the office until the study doctor thinks that you are well enough to go and that all the effects of the drug have worn off.

The experimental sessions will occur two to five weeks apart. The experimental sessions will all be carried out in an identical manner.

At this time MDMA is not available for use outside of research studies. The study therapist will discuss treatment options with you at your last study visit.

PSYCHOTHERAPY AFTER EXPERIMENTAL SESSIONS :

After the experimental sessions, you will have regular psychotherapy to help you express, understand and integrate (bring together and connect to your life) any thoughts or feelings you may be having about your symptoms and their causes and about your experiences during experimental sessions. You will have psychotherapy with the study therapists the morning of the day after each experimental session and then during two additional sessions after each experimental session. These sessions will last 60 to 90 minutes. You and the study therapists will also discuss ways to use what you learned to help work on treating your PTSD, face and solve difficulties you may have faced during the experimental sessions and gain maximum benefit and understanding from experimental sessions. Some of these visits may be done by telephone or telemedicine. Each regular psychotherapy session may be recorded to audio and video and you can hear or see these recordings if you wish.

Before starting psychotherapy on the day after each experimental session, you will be asked to guess whether you received MDMA. You will not be told if your guess is



correct. After you finish psychotherapy on the day after an experimental session will answer questions about thoughts and feelings you might have about hurting or killing yourself. The study therapists will ask you these same questions about hurting or killing yourself during each psychotherapy session, and during the second and seventh day of telephone contact with the study therapist. This is so the study therapists can have another way of making sure you are no in danger of hurting yourself.

You will complete a questionnaire about your PTSD symptoms on the third psychotherapy session after an experimental session. If you had tinnitus or chronic pain before the study and mention any changes in these symptoms the study therapists will help you to record the changes.

MEASURING PTSD, DEPRESSION AND OTHER TESTS AFTER EXPERIMENTAL SESSIONS

Approximately three months after the start of the study (six weeks after the third experimental session), the study researcher will ask you about your PTSD and other symptoms. You will also have the same tests of attention, memory and different types of problem solving that you had at the beginning of the study. This visit should last about two and a half hours, and some of the tests may be done by telemedicine or telephone. These tests are so we can tell if your symptoms have changed or stayed the same over time.

After you complete these tests, you will meet with the study therapists and they will ask you about thoughts about hurting or killing yourself. You and the study therapists will learn whether you got the comparator dose or full dose MDMA. The study researcher that measured your PTSD symptoms will not find out.

If you learn that you got the comparator dose, then you will have the option to go on to the next part of the study without finishing Stage 1, described below (Stage 2).

If you will not go on to Stage 2, then you will complete a questionnaire about your experience as a research subject. The study therapists will give you a memory aid card. This is for you to keep track of your health during the months in between your last visit with the researchers and the 12-month follow up visit, described below. The card will help you to remember to tell the researchers about any new problems or medical conditions, or changes in medication that happened during this time. You may have your regular doctor fill out this card for you. Your next study assessment will be the 12-month long-term follow-up.

OPEN-LABEL MDMA SESSION FOR PEOPLE WHO RECEIVED FULL DOSE

If you are one of the seven participants in the full dose group, you will have a third day-long experimental session with the same dose MDMA in Stage 1. After learning that you were in the full dose condition, you will schedule and complete your last experimental session, which will be "open label," meaning you will receive MDMA, but this time you



will know. You will have the same regular psychotherapy visits after this last experimental session.

Approximately six months after the start of the study (two months after the third experimental session), you will meet with the study researcher again. The researcher will ask about your PTSD symptoms and you will fill out a questionnaire on feelings of depression, a sleep quality questionnaire, a dissociation symptoms questionnaire, and a PTSD symptom questionnaire. You will complete the two tests of memory, attention and problem solving. You will also be asked if you have had any thoughts about hurting or killing yourself. This visit should last about 2.5 and 3.5 hours.

OPEN-LABEL MDMA SESSIONS FOR PEOPLE WHO RECEIVED COMPARATOR DOSE (STAGE 2)

If you are one of the five subjects who got the comparator dose, you can take part in three open-label MDMA-assisted sessions scheduled 3 to 5 weeks apart as part of Stage 2. In this part of the study, you will receive an active dose of MDMA during each session. Signing this consent form means you agree to take part in the second part of the study. **The seven people who receive a full dose of MDMA during Stage 1 cannot take part in Stage 2.**

If you take part in Stage 2, you will have 12 more visits with the study therapists. These sessions will be like experimental sessions you had during the first part of the study, except that you will know you are getting an active dose of MDMA. You will also only have one preparatory session rather than three sessions. The study timing and procedures will be similar to Stage 1. In the first experimental session, you will receive an active dose of 100mg MDMA with an optional supplemental dose. If this dose feels optimal you have the option to receive the same dose in the second and third experimental sessions in Stage 2. If it does not feel optimal, you can discuss increasing the dose to 125mg MDMA in either one of the experimental sessions with your study therapists. The study therapists will make the final decision about the dose you will receive in the second and third experimental sessions.

You will have the same tests of your PTSD and other symptoms, personality and mental health two months after the third open-label experimental session, and some of these tests may be done by telemedicine or telephone. You will have the tests of memory, attention and problem solving in person with the study researcher. You will complete a questionnaire about your PTSD symptoms on every third psychotherapy session after the first and third experimental sessions. You will complete the scale of pain and tinnitus levels if you had them before the study. You will complete a questionnaire about your experience as a research subject.

At the two-month follow-up after your second experimental session, you will receive a memory aid card to help you keep track of your health in between your last visit and a follow up visit 12 months after the final experimental session. The card will help you to remember to tell the researchers about any new problems or medical conditions, or

changes in medication that happened during this time. You may have your research doctor fill out this card for you.



LONG-TERM FOLLOW-UP 12 MONTHS AFTER LAST EXPERIMENTAL SESSION

About 12 months after your last experimental session, you will either complete measurements of your PTSD symptoms over the phone, by telemedicine, or in person. You will complete questionnaires about your other symptoms and you will fill out a questionnaire on the positive and negative effects of being in the study. If you were only in Stage 1, then this will happen 12 months after your third experimental session, and if you were in Stage 2, then this will happen 12 months after the third experimental session in Stage 2.

The same study researcher who asked you about your PTSD symptoms will do so again, either in person or over the telephone. You will also answer the questionnaire about feelings of depression or other symptoms you might have, and questionnaires about your personality, any changes in your PTSD symptoms, any thoughts you have about the good and bad points of MDMA-assisted therapy, and your thoughts about taking MDMA. The study therapists will ask you questions about thoughts or feelings about killing yourself. If you completed the visual scale of pain and tinnitus before the 12-month follow-up, then you will complete it at 12-month follow up to measure changes in tinnitus and chronic pain symptoms if you had them before the study. There are no right or wrong answers to these questions.

The questionnaires may be mailed to you for you to fill out. It will come with an envelope that is already stamped and has only the researcher's address on it. Do not put your name on the questionnaires.

A researcher who is part of the study may ask you about any changes in medication or your mental health, including any benefits or harms, during the follow-up period between your last visit and the 12-month follow-up visit in person or over the phone.

The researchers will use your answers to these questionnaires to see if there are any long-lasting effects of being in the study, such as changes in PTSD symptoms or other life events.

POSSIBLE RISKS OR DISCOMFORTS

MDMA has not been widely tested in humans but as of March 2014 about 960 people have received MDMA in clinical research settings, without any serious unexpected problems happening.



Side effects during the MDMA experience that are less severe but more frequently reported, are:

- Lack of appetite (68%)
- Dry mouth (64%)
- Teeth grinding or tight jaw muscles (60%)
- Decreased concentration (53%)
- Thirst (48%)
- Restlessness (46%)

In two studies of MDMA in a total of 37 people with PTSD, these reactions were commonly reported after a full dose of MDMA:

- Fatigue (77%)
- Anxiety (74%)
- Muscular tightness/tight jaw (62%)
- Insomnia (61%)
- Headache (51%)
- Lack of appetite (48%)

Forty eight to 77% of subjects in previous studies and in a placebo-controlled study of MDMA-assisted psychotherapy in people with PTSD reported nausea, low mood, feeling cold, dizziness, impaired balance, disturbance in attention, restlessness, perspiration, thirst, feeling weak, and need for more sleep (from most to least commonly reported). When any of these side effects occur, they usually last less than four hours, though some people report that some of these side effects can last for more than twenty-four hours, and rarely longer, but no more than four days.

Risks from MDMA

Changes in vision, hearing or other senses: In other studies where MDMA was given to volunteers, most people reported experiencing minor changes in vision and hearing, such as sounds seeming closer or farther away than usual, or objects seeming brighter than usual, with these changes lasting 2 to 3 hours. People also reported unusual feelings in their bodies, such as tingling or numbness (12%-33% in healthy controls, 7% of people with PTSD given full dose MDMA). These studies did not report exactly how many people experienced perceptual changes.

Blood pressure and heart rate. These effects of MDMA usually last 4 to 6 hours. At the dose in this experiment, the increases in blood pressure and heart rate are likely to be moderate. Average increase in systolic blood pressure is 35 mmHg (measurement unit for blood pressure) and average diastolic blood pressure increase is 20 mmHg. Heart rate may increase by 20 beats per minute (BPM).



Blood pressure rose well above normal levels in a few people (a little less than 5% MDMA was given in previous studies, but these people did not report any discomfort and did not require any treatment. Although these increases in blood pressure are similar to what happens after heavy exercise, they could cause serious problems in people with pre-existing heart or blood vessel defects. These serious problems could include irregular heart beat, heart attack or stroke. We will screen all potential participants for preexisting heart problems before they are allowed to be in this study. This doesn't guarantee that no heart problems will occur, but it does greatly reduce the risk of this happening.

Anxious or jittery feeling: Some people in previous studies (16%) felt over-stimulated or anxious. It usually lasted less than 30 minutes. Due to your PTSD, you may be more likely to have severe anxiety or panic attacks. Panic attack was reported by 4% of participants with PTSD. Letting yourself accept and feel those emotions deeply can be part of the psychotherapy. If you are not able to deal with these experiences in a way that helps you, the study therapists will work with you to deal with these feelings. It is possible that if such periods of heightened emotion do not clear up or grow weaker during the session, you could be at increased risk for suicide or other self-harm afterwards. You will be encouraged to ask the attendant to call the study therapists immediately if you have any thoughts about hurting or killing yourself so they can help you resolve them safely. If necessary, they may prescribe anti-anxiety medication or medication for sleep.

If you are in immediate danger of hurting or killing yourself or hurting someone else, then the study therapists may require you to stay in a nearby hospital.

Serious problems and death: There have been some serious problems, and even deaths, associated with the use of Ecstasy, an illegal substance that may contain some MDMA, outside of controlled clinical or laboratory settings. Serious problems have included high fever, drinking too much liquid, convulsions, and liver damage. Some recreational users of Ecstasy have become severely anxious, depressed or paranoid (thinking that other people are against them). Since you will be taking moderate amounts of uncontaminated MDMA in a controlled setting with trained therapists who will be closely monitoring your physical and psychological reactions, these problems are not expected to occur during or after the experimental session, but this does not guarantee that they could not occur. If they do occur, the study therapists are prepared to respond to these problems. There has been one case of irregular heartbeat in a controlled, clinical study of MDMA in a person with PTSD.

Insomnia & drowsiness: In previous studies, less than 23% of subjects without PTSD have reported insomnia (difficulty sleeping), and feeling tired, irritable, or drowsy for as long as 3 days after MDMA. Sixty-one percent of people with PTSD reported some insomnia, and 4% of people in two completed and one ongoing study in people with PTSD reported insomnia lasting more than 7 days.



Mood: Some after-effects of MDMA may be noticeable up to 2 or 3 days later. In people with PTSD, 39% reported low mood and 17% reported some rumination (persistent worries). In healthy people, a few people feel that their mood is better, but 14% feel it is worse.

Immune System: You will probably have a less active immune system for 2 or 3 days after MDMA. This may make you more likely to become sick with a cold or other infection during this time. The study describing this finding did not say how many people in the study showed these changes.

Addiction: There is a small chance that you could become addicted to MDMA. One study found that up to 6% of people using Ecstasy for recreational purposes were dependent on it. However, a study of people who had received MDMA for the first time in a legal laboratory setting found that they did not want to try MDMA again outside of the laboratory, and in two completed studies in 37 people with PTSD, only one person reported trying ecstasy after being in the study. People who have had problems with drug abuse in the last 6 months should not take part in this study.

There may be unknown side effects or risks from the use of MDMA.

Possible Brain Damage

Experiments in rats and monkeys show that high and repeated doses of MDMA can change brain cells that release a chemical called serotonin; in mice only, the affected cells release dopamine. The changes include loss of the part of the cell (called "axons") that connects different brain areas. Rodents given repeated, high doses of MDMA are less sensitive to a later dose of MDMA, are more likely to become overheated when placed in a warm room, and some studies find they perform worse in difficult tests of memory. Recent studies in monkeys and rodents suggest that the doses in studies finding damaged axons are too high to reflect typical human doses of ecstasy or MDMA used in studies.

Many studies found that people who had used Ecstasy many times in recreational contexts were not able to recall words, pictures or patterns as well as people who did not use Ecstasy and performed less well on tests of planning and impulse control. These differences are not big, but they have lasted for at least a year after people had stopped taking Ecstasy. Not all studies have found Ecstasy users to have difficulty recalling words or pictures or to have impulse control problems. When compared with people who do not use Ecstasy, studies found Ecstasy users were more likely to report feeling generally anxious or depressed. Many of these studies found that using alcohol or other drugs was also associated with feeling anxious or depressed. At least two studies found that people who are anxious, depressed or have psychological problems before taking any drugs are more likely to take Ecstasy than people without these problems.



Only one study has looked at brain scans of people before they got MDMA and again after they have received one or two moderate doses of MDMA, and did not see any changes in the brain, though it is possible that there were changes that were too small to notice. Other studies looked at people before and after they decided to take a few tablets of ecstasy in a recreational setting, and only saw one small change in the amount of blood found in a specific part of the brain, and did not see signs of brain injury. The decrease in blood volume might be from temporary lowering of a type of brain receptor, or it might be a sign of reduced function in this area. Findings from these studies suggest that the amount of MDMA you will receive in this study will not produce any lasting changes in your brain, though this is not guaranteed.

Studies of people receiving one or two doses of MDMA in a medical laboratory setting have not found any lasting changes in memory or planning. Studies comparing people before and after they decided to take a few Ecstasy tablets in a recreational setting with people who did not take them found less improvement in memory in the people who took Ecstasy, and no other changes in thinking or planning. A study of MDMA-assisted psychotherapy in the US found that memory and learning were the same in people who got MDMA and people who got placebo. It is believed that the amount of MDMA you will receive will not produce any lasting changes in memory or planning ahead, though this cannot be guaranteed. You will not get a second dose of MDMA if they believe you are showing signs of memory problems.

Other Risks:

You should not drive or use machinery immediately after each experimental session (up to 24 hours afterwards). This is because the study medication may cause drowsiness, lack of co-ordination or slower reaction time.

If you are tested for drugs of abuse within three days of each experimental session, you may test positive. The study therapists will provide you with an information card in case you are tested for drugs of abuse, and if you are tested for drugs of abuse while you are in this study, you can have the person(s) testing you call the study therapists to verify that you are in this study.

The interviews you will have during the course of the study involve no specific risks or discomforts beyond those of a standard clinical interview situation. You may feel upset at the review of your emotional experiences, or you may feel boredom or fatigue. The medical evaluations involve some blood tests. The risks of blood drawing include temporary discomfort from the needle stick, bruising and, rarely, infection at the site of the needle stick. Fainting could also occur.

It is possible that after you stop taking psychiatric medication (as for depression or anxiety) as part of the study, you may start to have symptoms again. If this happens, you should talk with your outside therapist and the study therapists. If you have to start taking medication again, then the study therapists will have to take you out of the study.

As with any medical procedure, there are potential risks associated with the use of



telemedicine. These risks include, but may not be limited to:

- In rare cases, information transmitted may not be good or clear enough (e.g. poor resolution or choppy video connection) to allow for appropriate medical decision making by your therapy team or the researchers;
- Delays in medical evaluation and treatment could occur due to problems or failures of the equipment or internet service;
- In very rare instances, security protocols (the computer software and settings that maintain security) could fail, causing a breach of privacy of personal medical information;

Reproductive Risks:

Effects of MDMA on the growth and development of an unborn baby are not known, therefore you will not be allowed to enter the study if you are pregnant.

Women who are able to become pregnant must use one of the allowed birth control methods, such as birth-control pills or shots, IUD, and diaphragm used along with spermicide and with partner use of condom while they are in the study. The study doctors will explain these methods to you and will help you decide which might be best for you, and they can suggest to you where you can get more information and advice.

You will be tested at the start of the study and again before each experimental session to see if you are pregnant. If, at any time during the study, you suspect that you may be pregnant or are concerned that you may become pregnant, you must advise the study therapists immediately. If you should become pregnant during the study, the study therapists will help you get proper advice while you are pregnant and you will need to let them know about the health of your baby when he or she is born.

NEW FINDINGS

If any new information becomes available about MDMA while you are participating in this study, the study therapists will tell you about it as soon as possible.

POSSIBLE BENEFITS

Your symptoms of PTSD may improve while taking part in this study. There is no guarantee that you will benefit from being in this research study. Information learned from this study may help researchers to improve treatment for PTSD in the future.

COSTS

The sponsor of this study, Multidisciplinary Association for Psychedelic Studies (MAPS), will cover the costs that are directly related to this study. This includes the costs for all psychotherapy sessions, for the psychological and laboratory testing, for medical examinations, and for the experimental drug. You, your private medical insurance (if any), and the public health insurance plan will not be charged for any procedures done solely for the purpose of the study.

You or your insurance will remain responsible for on-going treatment unrelated to the study.



REIMBURSEMENT FOR PARTICIPATION

The Sponsor, MAPS, will not pay for meals and lodgings or travel expenses.

The sponsor is paying your study therapists and study researchers for the time, effort and expenses to conduct this study.

ALTERNATIVES

One alternative to being in this study is to decide not to participate. You may decide to try other treatments for PTSD. There are other medications, such as Paxil (paroxetine) or Zoloft (sertraline) and anti-anxiety medications such as Xanax (alprazolam) and other forms of psychotherapy that you could try. If you are currently receiving psychotherapy and/or medication, you could continue with these.

CONFIDENTIALITY

All information collected will be treated and handled as confidentially as possible, except where disclosure is required by law. Although complete confidentiality is something the study team will try for, absolute confidentiality cannot be guaranteed.

As part of this research, the study doctors will collect the results of your study-related tests and procedures and may also access your personal medical records for health information such as past medical history and test results. When not in use, information will be stored in a locked office and will be kept for 25 years after study completion, as required by Canadian clinical trial regulations. Audio and video recordings will be stored for up to 25 years after their creation.

Some people need access to the information to monitor the study. Any paperwork copied will have any information that could be used to identify you removed first. Session recordings will not have your name or initials printed on them, only a number.

Medical records, including audio and video recordings, which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes.

Medical records may be looked at, at the study site, by

- Representatives of the sponsor, MAPS
- Health Canada and similar agencies in other countries, as the U.S. Food and Drug Administration (FDA)
- Governmental agencies in other countries; and
- IRB Services

Information from this study will be submitted to the sponsor, and to Health Canada and to governmental agencies in other countries (e.g. U.S. FDA). Information sent from the study site will not contain your name.



Results from this study may be presented in meetings or in publications. Your identity will not be disclosed in those presentations, which will mostly give averages of data.

All records in [REDACTED] are subject to subpoena by a court of law.

Audio and video recordings: Any information that could directly identify you will be withheld from recordings (except unique voice or image identity). Access to recordings will be limited to research purposes.

Telemedicine: Some of the study visits may be conducted by telemedicine or telephone from different locations for the purpose of improving your access to care and making scheduling more efficient. The information may be used for diagnosis, therapy, follow-up and measuring symptoms, and may include any of the following:

- Live two-way audio and video that may be recorded
- Sending recorded audio and video of therapy sessions or assessments

Electronic systems used will include measures to protect confidentiality of your identification and video data.

You will be asked to give an additional consent at the end of the study in order for your audio or video recordings to be viewed by others, such as researchers working with the sponsor or therapists learning how to perform MDMA-assisted psychotherapy, but you do not have to agree to this in order to participate in the study. You may request to hear or see these recordings.

You have the right to check your study records and request changes if the information is not correct.

By signing this information and consent form, you consent to the collection, access, use and disclosure of your information as described above.

TREATMENT AND COMPENSATION FOR INJURY

In the event of a study-related injury, the Sponsor will cover any costs that arise from treating the injury that is not covered by the provincial health plan or your private medical insurance (if any). Injuries that are not related to participation in the study will not be covered.

LEGAL RIGHTS

The above section does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this Subject Information and Consent Form.

VOLUNTARY PARTICIPATION

Your decision to take part in this research study is completely voluntary. There will not be any penalty or loss of benefits to you if you decide not to participate.



In addition, you may withdraw from the study at any time. If you choose to do this, your study therapy team before you wish to withdraw. This notice will allow your doctor to inform you if there are any potential medical risks of withdrawal. You may be asked to return to the clinic to answer questions or complete tests.

WITHDRAWAL

The study therapists, the sponsor company, Health Canada and the US Food and Drug Administration (FDA) has the right to stop the study at any time, with or without your consent, for any of the following reasons:

- If you have an adverse event (unwanted effect or health problem) from the study drugs
- If for any other reason the study doctor judges that it is not in your best interest to continue in the study,
- If you need a treatment not allowed in this study, such as restarting medication for depression or anxiety,
- If you do not keep appointments and follow study rules
- If you do not take the study drug as instructed,
- If you become pregnant,
- If the study is canceled by the FDA, Health Canada or the sponsor company

QUESTIONS

If you have any questions about this study, its procedures, risks, benefits or your alternatives or rights or if at any time you feel you have experienced a research-related injury, contact:

[REDACTED]

[REDACTED]

In case of an emergency, please contact [REDACTED] at phone number [REDACTED] OR [REDACTED] at phone number [REDACTED] and go to the nearest hospital emergency department.

Please contact the Director, Human Research Protection Program, IRB Services, who is not affiliated with the research or the research team, if you:

- have questions about your role and rights as a research participant
- wish to obtain more information about clinical research in general

- have concerns, complaints or general questions about the research, or
- wish to provide input about the research study



You can do so in the following ways:

In writing: 300-372 Hollandview Trail, Aurora, ON L4G 0A5

By phone: 1-866-449-8591

By email: subjectinquiries@irbservices.com

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

SUBJECT'S STATEMENT OF CONSENT

Your participation in this study is voluntary. You may refuse to take part in or you may stop taking part in this study at any time. You should call the study doctors if you decide to do this. Your decision will not affect your current or future regular medical care or any benefits to which you are entitled at this site. The study doctors and/or the sponsor may stop your participation in this study at any time without your consent if they decide it is in your best interest or if you do not follow the study doctors' instructions.

You will need to have someone drive you home on the day after the experimental session. If you cannot find anyone to take you home, the study doctors will find someone to drive you.

You have read the information in this consent form and it has been discussed with you. All of your questions so far about the study and your participation in it have been answered. You freely consent to participate in this research study.

You will not donate blood while you are in the study and for at least 30 days after.

By signing this consent form, you have not waived any of the legal rights which you otherwise would have as a subject in a research study. **You will be given a copy of the consent form signed by you and the person administering this consent.**

The study therapists have my permission to tell my regular doctor about my being in this study:

YES NO



	SUBJECT
Printed name	
Signature	
Date	

	PERSON ADMINISTERING CONSENT
Printed name	
Signature	
Date	