A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

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Study Period	2008-2009

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Introductory Statement

This proposed Canadian pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve patients with treatment-resistant posttraumatic stress disorder (PTSD). This study has been designed as part of an international, multi-site program of research sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org), a USA-based non-profit research and educational organization. MAPS' long-term goal is to develop MDMA into a prescription medication approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA) and Health Canada. MAPS is currently the only organization in the world of which we are aware sponsoring research into the therapeutic potential of MDMA.

MAPS is currently sponsoring under FDA IND #63,384 a nearly completed pilot study of MDMA-assisted psychotherapy in 21 patients with treatment-resistant posttraumatic stress disorder (PTSD), taking place in Charleston, South Carolina under the direction of Dr. Michael Mithoefer. Twenty out of 21 subjects have already completed the protocol. The final experimental session for the 21st subject occurred on July 18, 2008 and the final two-month follow-up evaluation will take place around September 18, concluding the study. Preliminary results are remarkably promising with no drug-related Serious Adverse Events (SAEs) and statistically significant results supporting the efficacy of MDMA-assisted psychotherapy (Wagner 2008, personal communication). A separate longer-term follow-up of participants a year or more after study participation has been approved by our IRB and will be initiated soon.

MAPS is sponsoring two additional ongoing pilot studies of MDMA-assisted psychotherapy in patients with PTSD, one in Switzerland under the direction of Dr. Peter Oehen, and one in Israel, under the direction of Dr. Moshe Kotler, Chair, Department of Psychiatry, Tel Aviv University, Sackler School of Medicine, and former Chief Psychiatrist of the Israeli Defense Forces. Both of these studies are designed for twelve subjects and are scheduled to be completed before the end of 2009. All studies are using the same primary outcome variable, the Clinician Administered PTSD Scale (CAPS), enabling examination of results across all studies, and meta-analyses of data pooled across each pilot study. All of MAPS' studies conducted outside of the US have been approved by regulatory authorities in those countries and have been submitted to FDA and are also being conducted under FDA IND 63,384.

MAPS has also helped initiate and fund an FDA-approved study investigating MDMA-assisted psychotherapy in people with anxiety related to advanced-stage cancer. This study is taking place at Harvard Medical School's McLean Hospital, under the direction of Dr. John Halpern MD, the Sponsor/Investigator. The second of twelve subjects has been enrolled. The first subject has completed the study safely with reports of reduced anxiety and pain (Halpern 2008).

This proposed Canadian pilot study will be the first study of the therapeutic potential of MDMA to be conducted in Canada. In this study, eight of 12 people will receive a dose of MDMA expected to be fully therapeutic (experimental dose) and four of 12 will

receive threshold "active placebo" dose of MDMA during three sessions scheduled three to five weeks apart. PTSD symptoms will be assessed at baseline on entry to the study and six weeks after the third double-blind MDMA-assisted psychotherapy session. Cognitive function will also be assessed at baseline and again six weeks after the third experimental session. Study participants will also receive psychotherapy before and after each day-long experimental MDMA-assisted psychotherapy session.

Participants who received active placebo during the course of the randomized study segment have the opportunity to take part in a second study segment that follows nearly identical procedures, but with participants receiving experimental dose MDMA in an open-label context.

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the psychedelic drug mescaline. It was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s (Freudenmann et al. 2006; Shulgin 1986). In the United States, MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists before it was placed in Schedule 1 in 1985 as a result of extensive non-medical use (Greer and Tolbert 1986; Saunders 1993; Stolaroff 2004). Placement in Schedule 1 prohibited it for use except in a federally-approved research setting.

Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD (Adamson 1985; d'Otalora 2004; Greer and Tolbert 1998; Metzner and Adamson 2001). Case reports and narrative accounts of MDMA-assisted therapy suggest that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways. Specifically, MDMA can "reduce or somehow eliminate fear of a perceived threat to one's emotional integrity" (Greer and Tolbert 1998). Elimination of these "conditioned fear responses" can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. Some clinicians and researchers have asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience (Greer and Tolbert 1998). Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens (Nichols and Oberlender 1990). The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others.

MDMA became illegal in the US and then internationally shortly after a rise in use of MDMA outside the confines of psychotherapy. Ecstasy (material represented as MDMA) continues to be used throughout the world. Serious adverse events such as hyperthermia,

hyponatremia or liver damage have occurred in association with ecstasy use, though these are relatively rare given the widespread use of ecstasy. It is notable that the purity and potency of illicit ecstasy is often unknown. Recent surveys of ecstasy tablets indicate that up to 40% are adulterated or contain no MDMA (Baggott et al. 2000; Cole et al. 2002). There is evidence that the use of frequent, high doses of Ecstasy in uncontrolled settings exacerbates its risks. The majority of serious adverse events after Ecstasy consumption have occurred in conditions of high ambient temperature, long periods of strenuous activity (dancing) and insufficient or uncontrolled fluid intake. All of these environmental circumstances may enhance or exacerbate problematic effects of Ecstasy. By contrast, people taking part in MDMA-assisted psychotherapy do not experience these behavioral or environmental factors.

Initial Phase 1 human trials of MDMA in approximately 390 subjects have demonstrated that the drug can be administered safely under controlled conditions. No drug-related Serious Adverse Events (SAEs) have been reported during the course of the ongoing MDMA/PTSD Phase II studies in the US, Switzerland and Israel. Preliminary examination of neuropsychological data from the US study has found no deterioration in condition after MDMA-assisted psychotherapy.

If data from MAPS' pilot studies continue to produce promising results, then MAPS will use the information gathered from these studies to formulate two large (N = approximately 280) multi-site Phase III studies of MDMA-assisted psychotherapy, one to be conducted throughout the United States and Canada and one to be conducted throughout Europe and Israel. MAPS' Clinical Plan (Doblin 2002) estimates that this process will require at least five years and will involve at least 560 subjects.

Background

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder arising after a personally threatening life-event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. The DSM IV (APA 1994) criteria for PTSD include:

A. Exposure to a significant traumatic event accompanied by an intense acute emotional response.
B. Persistent re-experiencing of the event or aspects of the experience.
C. Persistent avoidance of stimuli associated with the event, and/or withdrawal from some aspects of life.
D. Persistent symptoms of increased arousal.
E. The above symptoms must last for more than one month for Acute PTSD and more than three months for Chronic PTSD.

PTSD affects an estimated 8% of the general population at some point during their lifetime (Kessler et al. 1995), as reported in a national survey of mental disorders in the general population of the US. There are still questions concerning what are the best treatments for this debilitating psychiatric disorder (Montgomery and Bech 2000). People

with PTSD face challenges in relationships and with work productivity (Brady et al. 2000). An array of psychotherapeutic options exists for treating PTSD, and two SSRIs (Zoloft and Paxil) are approved as PTSD treatments in the US. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies (Foa et al. 1999; Resick and Schnicke 1992), and at least one study of Paxil indicated that men with PTSD did not respond to this drug (Brady et al. 2000). These findings suggest that there is still substantial need for innovative treatments for PTSD.

Although presently we are not aware of any national surveys of lifetime PTSD prevalence in Canada, it is likely that the percentage of Canadians experiencing PTSD is similar to the 8% to 11% listed in samples from the United States and Europe. Likewise, a large prospective, longitudinal epidemiological study of adolescents and young adults in Germany showed a lifetime prevalence of PTSD, including subthreshold cases, at baseline of 5.6%; by the end of the follow-up period (35-50 months) this had increased to 10.3%. (Perkonigg et al. 2000). A survey of 3062 women in Ontario reported a 10.7% lifetime prevalence rate (Frise et al. 2002). A study of Canadian peacekeepers reported higher rates of prevalence, with peacekeepers with single deployment diagnosed with PTSD at a rate of 10.9% and a 14.8% rate in peacekeepers who were deployed more than once (Richardson et al. 2007). These findings suggest that Canadians have PTSD at rates comparable to the US and Europe and that as expected, certain populations will experience higher rates of PTSD.

PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. Acting Inspector General Jon A. Wooditch testified to the US Congressional Committee On Veterans' Affairs Subcommittee On Disability Assistance And Memorial Affairs that in 2004, the US Veterans Administration spent over $4.3 billion on disability payments to over 215,000 veterans with PTSD (2005). The search for novel and more effective treatments is therefore of major public health and economic significance. In the US National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In either subgroup, more than one-third of the patients still had symptoms several times per week after 10 years (Kessler et al. 1995). Generally, the number of people who do not improve after treatment can be high, between 40% and 60%. In a 2002 comparison of two types of psychotherapy for women with PTSD after sexual assault, 47% of each treatment group still were diagnosed with PTSD with high enough CAPS scores (Resick et al. 2002) and another study reported similar figures (Foa et al. 1999).

PTSD and MDMA-assisted psychotherapy

To date the treatment of PTSD has primarily been a psychotherapeutic treatment, the effect size for psychotherapy being higher than for psychopharmacologic treatment. Cognitive behavioral therapy is considered one of the most effective psychotherapies. Other methods such as psychodynamic therapy and EMDR also proved to be effective in treating some aspects of PTSD symptoms (Ursano et al. 2004). Some people may have to

undergo more than one treatment to reduce or resolve PTSD symptoms (Hamner et al. 2004). However, a recent meta-analysis concluded that all "bona fide" psychotherapies, including all those listed above, are similarly effective with PTSD (Benish et al. 2008).

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy. MDMA possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients (Greer and Tolbert 1998; Metzner and Adamson 2001; Stolaroff 2004; Widmer 1998). Treatment consists of several administrations of MDMA-assisted psychotherapy within the context of a brief to moderate course of non-drug psychotherapy. MDMA-assisted psychotherapy is hypothesized to reduce or ameliorate the hypervigilance and emotional numbing and withdrawal experienced by individuals diagnosed with PTSD.

Anecdotal accounts, an uncontrolled clinical trial, and data from an ongoing controlled trial described above all suggest that MDMA may provide unique benefits to people with PTSD when administered in combination with psychotherapy. It may assist people in confronting memories, thoughts and feelings related to the trauma without increasing fear in response to this confrontation. An increase in self-acceptance and increased feelings of closeness to others may also assist people with PTSD as they work with psychotherapists.

Treatment goals for posttraumatic stress disorder include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. One approach is to discover drugs that directly counteract these neurobiological changes. Paxil and Zoloft are the only two drugs approved by the FDA in the US for treating PTSD, and are known to affect the serotonergic components of PTSD. They may also block the down-regulation of brain-derived neurotrophic factor, but it is not known whether it can arrest and reverse the hippocampal atrophy found in PTSD (Nibuya et al. 1996). Another approach to treatment of PTSD is to develop drugs and/or psychotherapeutic treatments that will indirectly interrupt the destructive neurobiological changes by decreasing or eliminating the stress reactions to triggers and the chronic hyperarousal of PTSD. Reports of past experience with MDMA-assisted psychotherapy suggest that it may also counteract the effects of PTSD. In fact, the biologic and psychotherapeutic approaches overlap and re-enforce each other. Knowledge about the connections between the neurobiological and the therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala (Gamma et al. 2000). This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD (Davis and Shi 1999; Rasmusson and Charney 1997).

To date, Phase I trials have been conducted by eight research teams in the United States, England, Spain, Switzerland, and the Netherlands, with MDMA administered to approximately 390 subjects overall without the occurrence of any serious adverse events (see for example Cami et al. 2000b; Chang et al. 2000; Dumont and Verkes 2006, review;

Kolbrich et al. 2008; Kuypers et al. 2008; Tancer and Johanson 2003; Vollenweider et al. 1998), When MDMA is used in doses similar to those proposed for this study, and in a controlled setting, the risk/benefit ratio is favorable. By and large, MDMA appears to have risks that are similar to those of other structurally-related sympathomimetic compounds (Mas et al. 1999; Tancer and Johanson 2003), such as amphetamine (Adderall), that have been used clinically for many years.

Acute effects reported in controlled studies are in agreement with those reported in earlier uncontrolled studies (Downing 1986; Greer and Tolbert 1986) and anecdotal reports (Adamson 1985; Widmer 1998). These include stimulant-like effects and hallucinogen-like effects. Though to date, no controlled study has confirmed acute changes in feelings of closeness to others or empathy, this effect may be reflected in increased sociability or friendliness (Tancer et al. 2003) and has been informally noted in at least one publication (Vollenweider et al. 1998).

There has been no evidence of significant or lasting toxicity in subjects participating in Phase I studies of MDMA. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e. g.Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Reneman et al. 2001; Thomasius et al. 2003). In contrast, all available Phase I data indicate that it is unlikely that the MDMA exposures proposed in this protocol will cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. As described in more detail below, more recent retrospective and prospective studies suggest that receiving MDMA in a controlled, therapeutic setting bears little to no attendant risks of serotonin system neurotoxicity or of functional consequences of this possible toxicity. Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to serve as an innovative treatment for PTSD, particularly in people who fail to respond to currently available therapies, and that the modest risks of administering MDMA within a therapeutic context are greatly outweighed by the possibility that this treatment may offer significant benefits.

Previous Clinical Experience with MDMA

Prior to its scheduling and international regulation, MDMA was used in psychotherapy to treat neuroses, relationship difficulties, and PTSD (Adamson 1985; d'Otalora 2004; Gasser 1994; Greer and Tolbert 1986; Greer and Tolbert 1998; Stolaroff 2004; Widmer 1998). Anecdotal and narrative accounts of MDMA-assisted psychotherapy reported successful treatment of PTSD. People reported reduced PTSD symptoms and improved quality of life. It should be noted that during this period in time, MDMA may have been given to thousands of individuals without any fatalities or serious adverse events (Holland 2001; Rosenbaum and Doblin 1991). Greer and Tolbert's (1986) uncontrolled, non-blinded study of MDMA in a therapeutic context found that most of the 29

individuals with mild to moderate psychological difficulties reported obtaining some lasting benefits after MDMA-assisted therapy (Greer and Tolbert 1986).

As described in the Introductory Statement, a sponsor-supported pilot study of MDMA-assisted psychotherapy in 21 people with PTSD is almost completed in Charleston, South Carolina. This study employs the CAPS as a primary outcome measure, with PTSD symptoms measured by a blinded, independent assessor at baseline, a week after each experimental (MDMA or placebo) session, and two months after the final experimental session. To date, all participants in this study have tolerated MDMA, and preliminary data indicates that MDMA is associated with greater improvement in PTSD than placebo. A recent analysis conducted by the independent rater detected a significant decline in CAPS score in the MDMA condition when compared with placebo (see attached report).

The ongoing study in Switzerland comparing the effects of 125 mg MDMA followed by a supplemental dose of 62.5 mg with 25 mg MDMA and a supplemental dose of 12.5 mg in people with PTSD has enrolled six of 12 subjects. The design of the study permits the investigator to provide up to two additional open-label sessions to individuals who do not respond to three experimental dose MDMA-assisted psychotherapy sessions. In these additional sessions, the investigator is permitted to administer either 125 mg followed by a supplemental dose of 62.5 mg or a higher dose of 150 mg followed by 75 mg supplemental dose. To date, one participant has received two additional experimental sessions with 150 mg MDMA and supplemental dose without incident. This study is estimated to conclude before the end of 2009.

The ongoing study in Israel comparing the effects of 125 mg MDMA followed by a supplemental dose of 62.5 mg with 25 mg MDMA followed by a supplemental dose of 12.5 mg in people with PTSD is currently designed to have two experimental sessions. One subject out of 12 has completed the study. This study is estimated to conclude before the end of 2009.

The potentially therapeutic effects of MDMA were initially investigated starting in 2000 in a MAPS-sponsored dose-response pilot study in Spain in women survivors of sexual assault with treatment-resistant PTSD. Unfortunately, the study in Spain was halted in 2002 due to political pressure from the Madrid Anti-Drug Authority. Prior to its suspension, six women were enrolled in this study without any adverse events or signs of deteriorating mental health, and with some mild signs of improvement, with single doses ranging from 50 to 75 mg. MAPS is currently exploring the possibility of starting a new pilot study in Barcelona, Spain, under the direction of the PI from our initial study.

Summary

The proposed pilot study will employ a randomized, double-blind, active placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive two MDMA-assisted sessions with either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of

62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later.

After undergoing three introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions scheduled three to five weeks apart, during which they will randomly receive either the experimental or active placebo dose of MDMA. Participants will undergo one non-drug-psychotherapy session 24 h after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session. PTSD symptoms will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session.

Baseline assessments of symptoms of PTSD and depression conducted by an independent rater will be compared with assessments made six weeks after the third double-blind (experimental) session. Baseline assessment of neurocognitive function will be compared with assessments made six weeks after the third double-blind (experimental) session. The blind will be broken after completing this assessment. Participants in the active placebo condition will have the opportunity to enroll in an open-label study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD symptoms and depression six weeks after the third open-label session.

Principal Investigator

Ingrid Pacey MBBS FRCP[C] is a practicing psychiatrist in Vancouver, BC. She has worked as a psychiatrist for 36 years. She has a private practice in Vancouver, BC. She has performed Holotropic Breathwork, a therapeutic breathing practice capable of producing alterations in consciousness, in people with PTSD. She has also written papers on Holotropic Breathwork and has taught others the technique. She worked as a clinical supervisor in the UBC Student Women's Office from 1992 to 1996.

Co-Investigators

Andrew Feldmár, M.A., has practiced psychotherapy as a psychologist for almost 40 years in Vancouver, Canada. He has given workshops, lectures and seminars on psychotherapy and topics of psychotherapeutic interest. See his work in Hungary as presented on the website of the Feldmár Institute: http://www.feldmarinstitute.hu/. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. The independent rater will be Karen Tallman Ph.D, a clinical psychologist who has worked as a clinical psychologist for 15 years and has conducted psychiatric diagnostic and competency assessments. She has a private practice and has worked at the Short Term Assessment and Treatment Centre at Vancouver General Hospital.

Ethics

The trial will not be initiated until appropriate Health Canada and Institutional Review Board (IRB) approval of the protocol and the informed consent document has been obtained. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. The IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. The protocol will also be submitted to FDA under MAPS' IND 63,384.

This trial will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, and applicable standard operating procedures (SOPs). The trial will be conducted under a protocol reviewed and approved by an IRB; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

Informed Consent of Subject

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.
The information about the trial must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject's legal rights, the information should include that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject should have the opportunity to inquire about details of the trial and to consider participation.
The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).

The principal investigator or the co-investigator therapist will provide a copy of the signed informed consent to the subject, and will maintain the original in the investigator's study file.

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive approval from an ethics board before use.

The subject should be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name appears on any other document (e.g. pathologist report), it will be obscured before the copy of the document is supplied to the sponsor.

Written consent to take part in this study includes giving the investigators permission to view the participant's recent medical records to assess study eligibility. Information necessary for study participation includes physical examination, tests of metabolic and liver function, thyroid panel and psychiatric diagnostic interview.

Recruitment and Screening

Candidates for study participation will be Canadian residents recruited by letters of referral sent to psychiatrists and psychotherapists and through word of mouth. One of the investigators will interview prospective participants by telephone to learn if they meet basic eligibility criteria. If the prospective participant is interested in taking part in the study, the investigators will provide the prospective participant with consent materials through postal mail or situated on a website, for review and consideration. If, after review, an applicant remains interested in taking part in the study, then he or she will meet with the investigators to complete the consent process. Applicants will complete a quiz addressing questions relating to information contained in the consent forms, with the investigators going over quiz responses with the prospective participant to ensure that he or she correctly understands study procedures, risks and benefits.

Study Objectives

The study seeks to examine whether a fully active (experimental) versus active placebo dose of MDMA-assisted psychotherapy will reduce or attenuate PTSD symptoms and whether there is sufficient safety for this innovative treatment.

Primary Efficacy and Safety Objectives: The primary objective of this study is to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with treatment-resistant PTSD. Symptoms of PTSD will be assessed via Clinician-Administered PTSD Scale (CAPS). The Posttraumatic Diagnostic Scale (PDS) will be used as a secondary measure of PTSD symptoms. The investigators will analyze changes in PTSD symptoms during the start of the study, six weeks after the third experimental session. Scores on the PDS will also be compared at the start of the study, six weeks after the third experimental session.

The investigators will administer the CAPS to participants who received active placebo and opted to enroll in the open-label study segment six weeks after their final experimental open-label session. They will compare CAPS scores six weeks after the third experimental session and six weeks after the third open-label session, and they will also compare scores at the start of the randomized session with scores six weeks after the third open-label session.

The investigators will also gather information on physiological effects and side effects after MDMA.

Secondary Objectives: The secondary objective of this study is to investigate the effects of MDMA-assisted psychotherapy on symptoms of depression in people with PTSD. Depression will be assessed via the Beck Depression Inventory (BDI). The investigators will examine changes in BDI scores at baseline, six weeks after the third experimental session.

The investigators will administer the BDI to participants who received active placebo and enrolled in the open-label study segment, comparing scores at the start of the open-label segment and scores six weeks after the third open-label session. They will compare depression symptoms six weeks after the third experimental session and six weeks after the third open-label session, and they will also compare study baseline scores and scores six weeks after the third open-label session.

The investigators will also compare scores at the open-label study segment baseline with scores six weeks after a participant's final open-label session.

General Investigational Plan

Study Population and Characteristics

The study will enroll twelve (12) participants aged 21 years or older. The study will enroll both men and women. Eight of 12 participants will be randomly assigned to receive the experimental dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg 1.5 to 2.5 hrs later and four will be randomly assigned to receive the active placebo dose of 25 mg followed by a supplemental dose of 12.5 mg 1.5 to 2.5 hrs later. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Inclusion Criteria

Participants who meet the following criteria will be considered for inclusion in this study:

1. Participants must meet DSM IV criteria for current PTSD. They must have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
2. They must either:
    a. have had at least one unsuccessful attempt at treatment with a selective serotonin uptake inhibitor (SSRI), mirtazapine or a monoamine oxidase inhibitor (MAOI) and one unsuccessful treatment with any form of psychotherapy for which there exist a controlled trial indicating efficacy in the treatment of PTSD. This includes cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety management, and insight-oriented psychotherapy, and eye movement desensitization (EMDR) [5, 29-31]. Treatment with an SSRI must have lasted for at least three months, or the participant must have refused to

take SSRIs. Psychotherapy must have lasted for six months and included at least twelve sessions. Treatment will be deemed to have been unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.

b. Be a veteran who meets all criteria listed above in 2a and with PTSD symptoms that have persisted for no longer than ten years.

3. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of subjects with other mood and anxiety disorders is essential because there is marked frequency of co-existence of other psychiatric disorders among people with PTSD (Brady et al. 1994; Faustman and White 1989).
4. Participants must be willing to commit to medication dosing, experimental sessions, and follow-up sessions and to complete evaluation instruments.
5. Participants must be willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. If they are being treated with psychoactive drugs at the time they are recruited into the study, the prospective participant will be encouraged to discuss medication withdrawal with his or her outside treating physician, and will be required to give Dr. Pacey permission to do so as well. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA/placebo session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life). No new medications may be started until after the evaluation session, which will occur six weeks after the third experimental session. An exception to this may arise in the case of designated rescue medication that may be administered in the event of a crisis during or after the experimental session.
6. Participants who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. They must sign a release if they want to permit the investigators to communicate directly with their therapist. They may not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session six weeks after the third experimental session.
7. Participants must agree that, for one week preceding each MDMA/placebo session:
    a. They will refrain from taking any herbal supplement (except with prior approval of the research team)
    b. They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
    c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).
8. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each active placebo dose/experimental

dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.

9. Participants must be willing to remain overnight at Dr. Pacey's clinic after each experimental session until the non-drug session occurring the next morning**.** An attendant will be present to assist with personal needs if requested and offer dinner and breakfast. The attendant will be an individual with previous training in managing psychological distress, including distress occurring after use of psychedelic drugs and of the same sex as the participant, and he or she will be trained for assisting in this study. The attendant may be anyone with some training or background in health care, particularly in psychiatric health care. The attendant will be instructed to contact Dr. Pacey at the request of the participant or if there are signs that the participant is under physical or psychological distress. At the participant's request and with Dr. Pacey's approval, a significant other can remain with the participant for support between the end of the experimental session and the non-drug session the next morning.
10. Participants will be asked to locate an individual willing to drive them home the morning after the experimental sessions, after the non-drug therapy session. If a participant is unable to locate someone to transport them home, the investigators will assist the participant in obtaining transport from the clinic to the participant's home or any other location where he or she is staying temporarily.
11. Participants must be willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.
12. Female participants of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.
13. Participants must be literate. They must be proficient in reading documents written in English.

Exclusion Criteria

Prospective participants will be excluded from the study if they have the following conditions or characteristics:

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
2. People with a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder.
3. People with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.
4. People with evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (Participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).
5. People with hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions

(Rosendorff et al. 2007), peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
6. People weighing less than 48 kg
7. People with prior use of "Ecstasy" (illicit drug preparations purported to contain MDMA) more than 5 times or at any time within the previous 6 months.
8. People who would present a serious suicide risk, or who are likely to require hospitalization during the course of the study, with suicide risk ascertained via face to face interview and through the use of the Adult Suicidal Ideation Questionnaire (ASIQ).
9. People requiring ongoing concomitant therapy with a psychotropic drug.
10. People meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 6 months.
11. Any person who is not able to give adequate informed consent.

Planned Duration of Study

The randomized, double-blind, active-placebo controlled study segment will last approximately four months from screening and baseline evaluation up until the evaluation six weeks after the third experimental session..

The open-label study segment for participants assigned to active placebo will last an additional four months from the single introductory and review psychotherapy session to the evaluation two months after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

Drug Description and Dosage

Upon enrollment in the study, the participant will be randomly assigned to the active placebo or experimental dose condition. The two therapist-investigators and the independent assessor will remain blind to condition assignment. If there is an adverse event or other emergency requiring knowledge of the participant's condition assignment, the blind may be broken for an individual participant.

Participants in the active placebo condition will be assigned to receive three experimental sessions with an initial dose of 25 mg MDMA followed 1.5 to 2.5 hours later by a supplemental dose of 12.5 mg MDMA. Participants assigned to the experimental dose condition will receive three experimental sessions with an initial dose of 125 mg followed 1.5 to 2.5 hours later by a supplemental dose of 62.5 mg MDMA. Eight of 12 subjects, or 66.6%, will be assigned to the experimental dose condition, and four of 12, or 33.3%, will be assigned to the active placebo condition.

Participants in the active placebo condition will be offered the option of undergoing a study segment using nearly identical procedures to those in the randomized study segment but with participants receiving experimental dose MDMA within an open-label context.

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental condition are identical to those in use in the studies of MDMA-assisted psychotherapy currently underway in the US, Switzerland and Israel. Previous researchers have also used doses within this range (Cami et al. 2000a; Freedman et al. 2005; Grob et al. 1996; Harris et al. 2002; Kuypers et al. 2006; Liechti et al. 2001). Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA (Cami et al. 2000b; de la Torre et al. 2000a; Freedman et al. 2005; Grob 2001; Mas et al. 1999; Tancer and Johanson 2003). Prior to the time MDMA was placed in schedule 1 identical or similar doses and regimens were used in psychotherapy (Greer and Tolbert 1986; Metzner and Adamson 2001; Stolaroff 2004). The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose.

Active placebo MDMA doses have been selected on the basis of their ability to produce minimal but detectable subjective effects (Grob 2001; Harris et al. 2002) and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is not expected to produce a significant reduction in anxiety or a significant increase in access to emotionally upsetting material, though this dose may produce slight alterations in consciousness, such as increased relaxation or tension (Harris et al. 2002).

Table 1
Drug Doses for proposed study

	Initial Dose	**Supplemental Dose**	**Cumulative Dose**
Active Placebo	25 mg	12.5 mg	37.5 mg
Experimental Dose	125 mg	62.5 mg	187.5 mg

Method
The researchers will employ a randomized, double-blind, active-placebo controlled design to compare symptoms of PTSD and depression before and after receiving MDMA-assisted psychotherapy with an experimental or active placebo dose of MDMA. The double-blind study will consist of twelve 60 to 90 minute "conventional" or non-drug augmented psychotherapy sessions and three experimental sessions of MDMA-assisted psychotherapy, and two assessments of symptoms of PTSD and depression. An independent rater not involved with performing psychotherapy will assess symptoms of PTSD with CAPS and PDS, and depression with the BDI at study baseline and six weeks after the third experimental session.

The investigators will break the blind individually for each participant after the assessments six weeks after the third experimental session.

Participants who learn they are assigned to active placebo can enroll in the open-label study segment. Active placebo condition participants enrolled in Stage 2 will have three sessions with experimental-dose MDMA.