Summary of Study Protocol

Phase II clinical trial testing the safety and efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in the treatment of chronic posttraumatic stress disorder.

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Sponsor: **Multidisciplinary Association for Psychedelic Studies (MAPS)**

Note: References are not listed in this summary. References appear in the full protocol, literature review and update and the 1/20/03 response letter.

Introduction

The current protocol is a randomized, double-blind, placebo-controlled, pilot study of the safety and efficacy of MDMA-assisted psychotherapy in patients with chronic, treatment-resistant posttraumatic stress disorder (PTSD). This pilot study is the first FDA-approved study of the use of MDMA in any patient population.

The proposed study is intended to gather preliminary evidence about whether MDMA-assisted psychotherapy can be safely administered to treatment-resistant PTSD patients, and whether it will produce improvement in PTSD signs and symptoms both immediately after experimental treatment and again at a follow-up evaluation conducted two months after the second of two experimental treatments. It is expected that MDMA will not adversely affect cognitive function when measured by a battery of commonly accepted neuropsychological tests and that no significant acute or chronic adverse effects will occur as a result of the treatment. Improvement will be evaluated by commonly accepted measures of PTSD symptoms (primarily the Clinician Administered PTSD Scale), with participants in the MDMA condition expected to show greater reductions in symptoms than participants in the placebo condition.

Should this study generate promising results, a subsequent pilot study would be conducted to standardize the therapy, to finalize development of a treatment manual and associated checklist for determining therapist compliance with the manual, and to gather data to adequately power any subsequent Phase III safety and efficacy studies.

Study Design

Twenty individuals, men and women, with chronic, treatment-resistant PTSD will be recruited for a double-blind, placebo-controlled pilot study in which MDMA or placebo will be administered in the context of ongoing psychotherapy. Throughout the course of the study, all subjects will receive about fourteen hours of non-drug psychotherapy and two 6-8 hour experimental treatment sessions. Following baseline measures and two introductory psychotherapy sessions, participants will receive the first experimental treatment session, with the second session taking place 3-5 weeks later. During these two experimental sessions, twelve participants will be randomly assigned to receive MDMA (125 mg/session) on both occasions, while eight participants will receive inactive placebo on both occasions. One day after each experimental session, a non-drug psychotherapy session will occur. In addition, three or four non-drug psychotherapy sessions will be conducted between the two experimental sessions and again after the second experimental session. A final data-collection session will take place two months after the final experimental session.

Both non-drug psychotherapy sessions and MDMA/placebo experimental sessions will be conducted by the principal investigator (Michael C. Mithoefer MD.) accompanied by an experienced female registered nurse (Ann T. Mithoefer), in the medical offices of Michael

Mithoefer MD. The offices are located in Mount Pleasant, SC., 2.6 miles from the nearest emergency room. The office will be equipped with a "crash cart" containing the emergency drugs and equipment necessary to respond to any complications. In addition, there will be a currently practicing, board certified, emergency physician and emergency nurse present in the adjacent room for the first 5 hours of each MDMA/placebo session.

Inclusion Criteria:

1. Age 21 – 65
2. DSM IV diagnosis of current, crime related, chronic PTSD and CAPS score of > 49
3. Must have failed previous treatment including:
   At least 3 months of drug treatment with an SSRI and
   At least 6 months with at least 12 visits of psychotherapy of one of the following:
   Cognitive Behavioral Therapy or Insight Oriented Therapy or Stress Inoculation Training
   A current CAPS score of > 49 will be the definition of previous treatment failure.
4. Must be willing for the PI to communicate fully with any outside therapist or physician.
5. Must be able to give adequate informed consent.
6. Women of childbearing age must be on effective birth control.
7. Any patient recruited from Dr. Mithoefer's patient base must be willing to meet with another psychiatrist once to discuss their decision to enter the study and again after the first MDMA/placebo session to discuss their decision to continue.

Exclusion Criteria:

1. Pregnancy or nursing
2. Anyone at imminent risk for trauma or victimization as assessed by information gathered during the screening assessment and evaluated by the PI.
3. Anyone judged to be at risk for suicide or likely to require hospitalization
4. Anyone judged to be at risk for serious destabilization or for relapse of a comorbid condition as a result of tapering off current psychotropic medications.
5. Any of the following psychiatric diagnoses as determined by Structured Clinical Interview for Diagnosis (SCID) during screening evaluation: Psychotic disorder, Bipolar Affective Disorder type I, Dissociative Identity Disorder, Eating Disorder with active purging, Substance Abuse or Dependence during the previous 60 days (with the exception of nicotine or caffeine)
6. Anyone with evidence or history of significant medical problems [cardiovascular (including hypertension), pulmonary, renal, gastrointestinal (including abnormal liver enzymes with or without other evidence of liver disease), neurological hematological, immune compromise or endocrine (with the exception of hypothyroidism on stable thyroid replacement)]
7. History of or current hyponatremia
8. Weight < 50 kg. Or > 105 kg.
9. Anyone who has taken Ecstasy > 5 times in their lifetime or at all within 6 months.

Initial Contact Method and Informed Consent Process

Potential participants will be recruited through a letter to psychiatrists and other psychotherapists in Charleston, SC and communities within a 4 hour radius. Prospective participants will be asked to contact the investigators initially by phone at which time a brief structured telephone screening interview will occur (see enclosed script). Potential subjects who are in treatment will be required to discuss the study with their therapist before agreeing to take part in the study. Dr. Mithoefer will be required to contact their therapist and prescribing physician (if they are on medications) to discuss issues of safety before accepting a patient into the study. Prospective participants will visit the researchers' office to discuss and review the study procedures (including risks, potential benefits, and alternatives) before giving written informed consent.

Potential participants can include current and past patients of the researchers. The researchers will be particularly careful when discussing the study with these individuals to ensure that the pre-existing patient-physician relationship does not unduly influence their decision concerning study participation. In addition subjects from the researchers' patient pool must have an interview with another psychiatrist (as described above) before signing the informed consent.

Patients who meet the psychiatric criteria and agree to participate in the study will receive further medical evaluation (history, physical exam, laboratory tests, EKG) to screen for any medical exclusions. A physician not involved in administering the therapeutic treatments will perform the medical examination.

Outcome measures

Outcome measures were selected to be well-validated, clinically-relevant, and repeatable. Measures of efficacy include observer-rated measures of PTSD symptoms [Clinican Administered PTSD Scale (CAPS)], patient-rated measures of symptoms and discomfort [Symptom Check List 90 (SCL 90), Impact of Events Scale (IES), Subjective Units of Distress (SUD)]. Measures of safety include complete medical exams and neuropsychologist-administered tests of neurocognitive function [The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), The Paced Auditory Serial Addition Task (PASAT), Rey-Osterrieth Complex Figure, NEO Personality Inventory]**.**

Observer-rated and patient-rated measures of symptoms will be made at baseline, at four days after each experimental session, and at three months after the first experimental session. Neurocognitive function will be assessed at baseline and at three months after the first experimental session. Therapeutic alliance will be measured by the Working Alliance Inventory (WAI) at the second psychotherapy session and on each non-drug psychotherapy session occurring one day after receiving MDMA or placebo. A complete medical examination will be performed at baseline and at four days after the second treatment session.. Measures of physiological status and participant distress intended to monitor participant safety will be made at frequent, scheduled intervals.

All screening and outcome measures will be performed by Dr. Mark Wagner, PhD, a neuropsychologist who will be serving as an outside consultant, will not be involved in treatment, and will be blinded to the therapy received by the subjects. He will also act as an outside consultant for data analysis at the end of the study.

Safety Monitoring Measures for the Experimental Sessions

1. Automated blood pressure and pulse monitoring every 15 minutes for 4 hours, and then every 30 minutes for 2 more hours if the established thresholds for normal blood pressure and pulse have not been exceeded
2. Thermometer for reading body temperature at the outset and then hourly for 6 hours.
3. Subjective Units of Distress administered repeatedly throughout the treatment session.
4. Plasma electrolytes measured immediately after the first experimental treatment session as a means of detecting possible hyponatremia.
5. Standard assay of liver function ("liver panel"), assessed with blood sampled at follow up after the second experimental treatment session, as a means of detecting changes in liver function.

Psychotherapeutic Procedures during Experimental Sessions

The experimental treatment sessions will be supervised and facilitated by the principal investigator (Michael C. Mithoefer MD.) accompanied by an experienced female registered nurse (Ann T. Mithoefer). Both therapists will be present throughout the sessions. The sessions will be conducted following the principles developed by Stanislav Grof, MD for LSD psychotherapy and for Holotropic Breathwork and adapted for MDMA-assisted psychotherapy by Metzner and by Greer and Tolbert. These methods, as well as the methods to be used in introductory and follow-up therapy sessions, are described in appendix A and in the accompanying treatment manual.

After approximately eight hours, if all medical parameters are acceptable and the patient is alert, ambulatory and emotionally stable, the session will be ended. He or she will then be allowed to leave via a pre-arranged ride with a friend or family member. The principal investigator or a covering psychiatrist familiar with the study will be on call 24 hours a day, seven days a week to handle any concerns or emergencies related to the protocol. The patient will be given this physician's pager number to call immediately if any problems occur. All subjects will be required to have a partner, family member or friend who will be with them for at least 24 hours after each treatment session. The subject will be required to allow this person to meet with him/her and the therapists at the end of each MDMA. session and will be given the number to reach Dr. Mithoefer 24 hours a day.

If at the end of a treatment session a subject is anxious, agitated or otherwise in emotional distress, in danger of self harm or is suicidal the therapists will remain with the patient for at least two more hours. During this time the therapists will employ the affect management techniques described in the treatment manual, will talk with the subject to help him or her gain cognitive perspective regarding their experiences, and will help implement the self soothing, stress inoculation techniques that were taught in the introductory sessions. If this situation should occur at the end of one of the ninety minute follow-up sessions at least one of the therapists will be available to stay with the patient for at least two hours.

If a subject remains severely anxious, agitated or in danger of self harm or suicide, or is otherwise psychologically unstable at the end of this two hour stabilization period Dr. Mithoefer will decide between one of two options:

A. A psychiatric nurse, therapeutic assistant or therapist (whose availability we will have arranged ahead of time) , will stay with the patient until the time of his or her appointment with the study therapists the next day. The therapists will then meet with the subject daily until the period of destabilization has passed. At any time during this process Dr. Mithoefer may make the clinical judgment to proceed to option B.
B. Hospitalization for stabilization

Relationship with Outside Therapists

For those subjects engaged in an on-going therapeutic relationship, Dr. Mithoefer will communicate with their outside therapists before enrolling the subjects in the study and then again after each experimental session to inform the other therapist about the patient's experience and any therapeutic gains or potential problems. Dr. Mithoefer will also call the outside therapists about any significant developments between MDMA/placebo sessions. In the event of any psychiatric complications of treatment, Dr. Mithoefer will actively involve these therapists in patient monitoring and management and will engage in a frequent and scheduled series of communications with them.

Adverse Effects Reporting and Safety Monitoring Committee

Any serious adverse events will immediately be reported to the IRB and to the FDA by telephone. Written notice will be given to the IRB and the FDA within seven days of the occurrence of a life-threatening adverse event, and within 15 days of the occurrence of a serious but not life-threatening event. There will be quarterly meetings of the Safety Monitoring Committee which will consist of the PI and two other physicians who are not otherwise involved in the study. Minutes of these meetings will be kept and a report of each meeting will be submitted to the IRB and the FDA. In the event that there appear to be a significant number of adverse events, meetings of the safety monitors will be held more often.