Study Protocol

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

Study # 63-384

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Aims and Goals

The current protocol is a randomized double-blind placebo-controlled pilot study of the safety and effects of MDMA-assisted psychotherapy on symptoms of chronic, treatment-resistant posttraumatic stress disorder (PTSD). This study follows three FDA-approved Phase I safety studies (one sponsored by MAPS and two by the National Institute on Drug Abuse), is endorsed by the principal investigators of all three of these studies, and is the first FDA-approved scientific study of MDMA-assisted psychotherapy in any patient population.

Findings from this study will be used to guide development of a second pilot study to refine and standardize MDMA-assisted psychotherapy for PTSD patients. If results of both of these pilot studies, plus another small pilot study to be conducted in Israel, are promising, the data gathered will be used to inform the design of two large (N= at least 280) multi-site Phase III studies of MDMA-assisted psychotherapy as a treatment for PTSD. MAPS' Clinical Plan (Doblin 2002) will require at least 5 years and will involve at least 600 subjects.

Specific Hypotheses

The proposed study is intended to test whether MDMA-assisted psychotherapy can be safely administered to people with treatment-resistant PTSD or veterans with PTSD symptoms that have endured for one to five years who are unable or unwilling to undergo conventional psychotherapy or pharmacotherapy for PTSD, and if it will produce improvement in PTSD signs and symptoms four days after each of two experimental intervention sessions and again at a follow-up evaluation conducted two months after the second experimental session. Improvement will be indicated by lower scores on established outcome measures of PTSD symptoms that were used in prior studies which formed the basis of FDA decisions to approve Zoloft and Paxil for the treatment of PTSD, with participants in the MDMA condition expected to have lower scores than participants in the placebo condition. It is also expected that MDMA will not affect cognitive function when measured two months after the second experimental session. The hypotheses to be tested by the proposed study are stated below:

1. Volunteers receiving MDMA-assisted psychotherapy will experience (trends toward) a greater decrease in signs and symptoms of PTSD than controls after each experimental session, as measured by the clinician-rated PTSD Scale (CAPS), the self-reported Impact of Events Scale (IES) and Symptoms Checklist-90-R (SCL-90-R).

2. Volunteers receiving MDMA-assisted psychotherapy will experience (trends toward) a greater decrease in signs and symptoms of PTSD than controls at two months after the second drug-assisted (MDMA or placebo) session.

3. Exposure to MDMA will not be associated with neurocognitive toxicity as assessed by the Repeatable Battery for Assessment of Neuropsychological Status (RBANS), the Paced Auditory Serial Addition Task (PASAT) and the Rey-Osterrieth Complex Figure Test.

The primary outcome measure evaluating efficacy will be the Clinician-Administered PTSD Scale (CAPS). Secondary outcome measures evaluating efficacy will be the Impact of Event Scale (IES) and the Symptom Checklist 90-R.

The assessment of neuropsychological status serves as a means of safety evaluation and is measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Paced Auditory Serial Addition Task (PASAT), and the Rey-Osterrieth Complex Figure. The NEO Personality Inventory is a neuropsychological measure of personality that is also part of our safety evaluation.

Background

MDMA is a ring-substituted phenylisopropylamine derivative with a unique profile of psychopharmacological effects that make it well suited to intensive psychotherapy. MDMA has been hypothesized to represent a new class of psychoactive agents, called entactogens (Nichols 1986; Nichols 1990), producing feelings of closeness to others, empathy, well being, and insightfulness, with little perceived loss of control (Grinspoon and Bakalar 1986; Hegadoren et al. 1999; Nichols 1986; Shulgin and Nichols 1978). There is considerable previous human experience with the use of MDMA in the context of psychotherapy. Before MDMA was classified in 1985 as a controlled substance, a number of therapists employed it as an adjunct to psychotherapy in the United States and Europe (Adamson 1985; Gasser 1994; Greer and Tolbert 1998; 1986; Grinspoon and Bakalar 1986). Although no properly controlled trials were conducted, these therapists concluded that MDMA could be safely administered and was clinically useful in treating various sub-clinical or clinical psychiatric conditions, including posttraumatic stress disorder. More recently, placebo-controlled clinical trials have confirmed reports from therapists that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001a; Tancer et al. 2001; Vollenweider et al. 1998).

Posttraumatic stress disorder (PTSD) occurs in response to a traumatic event or events. It is most likely to occur following an event involving perceived personal threat, such as rape or physical assault (Breslau 1998). Approximately 10% - 20% of people who experience a major trauma go on to develop PTSD, giving it an estimated 8% prevalence in the general population (Kessler et al. 1995). In the National Comorbidity Study, the median time to remission was 36 months with treatment and 64 months without treatment. In either subgroup, more than one-third still had symptoms several times per week 10 years later (Kessler et al. 1995). People with PTSD frequently develop other comorbidities, particularly affective and substance abuse disorders (Kessler et al. 1995). In addition to the psychiatric manifestations, individuals with PTSD have an increased incidence of physical problems and impairments in social and occupational functioning that lead to increased healthcare utilization and decreased quality of life (Brady et al. 2000: Kessler et al. 1999; Solomon and Davidson, 1997). PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. It is also a disorder for which there are, to date, two FDA-approved medications [both selective serotonin reuptake inhibitors (SSRIs)] about which there are still many unanswered questions regarding psychological and pharmacological effects (Montgomery and Bech 2000). The search for more effective treatments and a wider array of treatments is of substantial public health importance.

Treatment goals for posttraumatic stress disorder include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. Developing drugs and 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 may be one means of treating PTSD. Anecdotal reports of past experience with MDMA-assisted psychotherapy suggest that it could serve as such a treatment. On the basis of past reports of successful treatment of PTSD with MDMA-assisted therapy and on the basis of its reported entactogenic effects, we expect that psychotherapy conducted in combination with MDMA should produce symptomatic improvement in this population.

Anecdotal accounts of the use of MDMA in people with PTSD-like symptoms (no formal diagnoses or evaluations were conducted) can be found on the MAPS website at the bottom of the MDMA page (http://www.maps.org/research/mdma/index.html#healing), in the Accounts of Healing section, and include an account of a woman treated for PTSD after rape and sexual abuse (http://www.maps.org/research/mdma/moaccount.html). Other anecdotal reports not dealing specifically with therapy in people with PTSD have also included accounts of people treated for PTSD-like symptoms (Metzner and Adamson 2001).

Further reports of the therapeutic use of MDMA can be found in the testimony from the 1985-1986 DEA Administrative Law Judge hearings on the scheduling of MDMA. Testimony was submitted by Dr. Greer (who had administered MDMA to about 80 individuals and reported apparent benefits to the therapeutic alliance and to outcomes), Dr. Downing (who reported use of MDMA with 8 patients, 5 of whom he considered to have shown accelerated therapeutic progress), and Dr. Ingrasci (who reported successfully conducting approximately 150 MDMA sessions with about 100 patients), and others. Transcripts and documents from of these hearings can be found on the MAPS website at: http://www.maps.org/dea-mdma/ (in Section 6). No formal FDA-approved study of the therapeutic use of MDMA in any patient population has yet to be conducted, despite considerable efforts to obtain permission for such studies.

Samuel Widmer, MD, Peter Gasser, MD, and other members of the Swiss Medical Society for Psycholytic Therapy received permission from the Swiss Ministry of Health to administer MDMA to patients from 1988 to 1993. During this time, 171 patients received MDMA with no significant adverse effects reported. In a follow-up survey, 85.1% of 121 responding patients reported good or slight improvement during therapy, which included 6.8 ± 4.3 (1 - 16) MDMA sessions administered in the context of on-going therapy. Unfortunately, no formalized research was conducted with these patients. Dr. Gasser's report on the follow-up survey was published in the MAPS Bulletin and can be found at: http://www.maps.org/news-letters/v05n3/05303psy.html.

The subject population of chronic PTSD patients was selected in part because these individuals have failed to obtain relief from currently available treatments and because of patient and therapist reports of benefits of MDMA-assisted psychotherapy in treating PTSD, from treatments conducted prior to the criminalization of MDMA in 1985. The qualities that have been associated with MDMA in anecdotal reports (i.e. decreased defensiveness and enhanced therapeutic alliance) seem to have the potential to be particularly useful in the treatment of this disorder. PTSD is a condition that involves

prominent fear responses. Revisiting traumatic experiences in psychotherapy is recognized to be of therapeutic value. Early clinical experience with MDMA is consistent with the hypothesis that it can increase therapeutic effectiveness in this population. The combination of anxiolysis (reduction in fear and anxiety), euphoria, feelings of interpersonal closeness and facilitated recall for past events would seem to have the potential to maximize or amplify the benefits of psychotherapeutic interventions.

MDMA primarily acts as a monoamine releaser, as well as possessing some direct effects on various neurotransmitter receptor sites (for further details, see Chapter 1 in the Investigator's Brochure and Liechti and Vollenweider, 2001). The relationships between the neurochemical and physiological effects of MDMA are poorly understood, but studies of subjective effects in humans indicate that potentially therapeutic actions may be at least partly due to monoamine releasing properties and to moderate activity at the serotonin 5HT2A receptor. An imaging study also noted lower activity in the left amygdala after MDMA (Gamma et al. 2000), suggesting that MDMA inhibits or alters activity in areas of the brain that process fear-related stimuli.

To date, several Phase I trials have been conducted in the United States, Spain and Switzerland. MDMA has been administered to over 100 participants in controlled studies conducted within the United States, and to over 100 more individuals in controlled studies conducted in Europe. When MDMA is used in therapeutic doses in a controlled setting, the risk/benefit ratio is favorable (Cami et al. 2000; de la Torre et al. 2000a; de la Torre et al. 2000b; Grob et al, In Preparation, Data presented to FDA; Grob et al. 1996; Harris et al. 2002; Lester et al. 2000a; b; Liechti and Vollenweider 2000a; b; Liechti et al, 2001a: b; Mas et al. 1999; Pacifici et al. 2001; 2000; Tancer et al. 2001; Vollenweider et al. 1998; 1999). MDMA appears to have risks that are similar to those of other structurally-related sympathomimetic compounds, such as methamphetamine, that have been used clinically for many years.

Since the late 1970s, MDMA has been used by a growing number of individuals in non-medical settings. Illicit use of ecstasy (material sold as MDMA) is most commonly reported at dance events such as "rave" parties and at nightclubs but is not confined to these situations or subcultures. In the United States, prevalence of ecstasy use reported in 2000 was estimated to be 11.6% for young adults (ages 19-28). While a number of serious adverse events, including fatalities, have been reported after illicit use of ecstasy in uncontrolled conditions, these are events are relatively rare when considering the prevalence of ecstasy use (Gore 1999; Baggott, 2002).

There has been no evidence of significant acute or lasting toxicity in Phase I studies. 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 repeated users of illicit MDMA and other drugs (e.g., Croft et al. 2000; Gouzoulis-Mayfrank et al. 2000). In contrast, all available Phase I data indicate that it is unlikely that the MDMA exposures proposed in this protocol cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Tests of neurocognitive function have found that performance is not affected by participation in clinical MDMA trials (Boone et al. In Preparation, see also **Table 2.5** in Investigator's Brochure; Vollenweider et al. 2001; 2000). Vollenweider and colleagues (2000) presented positron emission tomography (PET) data

at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine that found no change in estimated serotonin transporter binding sites four weeks after a dose of MDMA similar to our proposed dose of 125 mg was given to MDMA-naïve volunteers.

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 a novel treatment for chronic PTSD, 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.

Methods

General Study Design

Twenty-one individuals with chronic PTSD will be recruited for a double-blind, placebo-controlled pilot study in which MDMA or placebo is administered in the context of ongoing psychotherapy. The first 20 individuals will have treatment-resistant PTSD, and the additional participant will be a veteran with war-related PTSD that has lasted for at least a year but no longer than five years. This last subject will not be required to be treatment resistant if he has been unable or unwilling to undergo conventional therapy. Twelve participants will be randomly assigned to receive MDMA, while eight participants will receive inactive placebo. The additional participant will be randomly assigned to receive MDMA or placebo, with a 60% chance of receiving MDMA anda 40% chance of receiving placebo. Following baseline measures and two introductory psychotherapy sessions, participants will receive two MDMA or placebo-assisted sessions spaced 3-5 weeks apart. During these two experimental sessions, participants will receive an initial dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA, or they will receive initial and supplemental doses of inactive placebo. Participants assigned to receive MDMA will undergo a third “open label” session as soon as can be arranged after the blind is broken for the participant 2 months after the second experimental session. Participants assigned placebo who choose to enroll in “Stage 2” will undergo three open-label sessions scheduled as indicated in the tables below. 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, three or four non-drug psychotherapy sessions will be conducted after the second experimental session, and three non-drug therapy sessions will be scheduled after the third “open label” session. Outcome measures will be administered two months after the second MDMA or placebo session in Stage 1 and four to six weeks after the second MDMA session in Stage 2. A final data-collection session will take place at two months after the third experimental session. Participants who consent to the long-term follow-up scheduled to occur at least ten months after completing the study will be assessed with the CAPS by the independent rater and will complete a questionnaire assessing the impact of study participation.

Schedule of Visits: Stage 1

Time: p=post d=days w=week m=month	**Before Visit 4**			**After Eligibility**	**After V. 4**	**1 d p v 5**	**3-7d p v 5**	**Between Visit 4 and Visit 11**			**3-5 w p visit 11**	**1 d p v 11**	**3-7 d p v11**	**Between Visit 11 and Visit 17**			**2 m p v11**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Pre-Study Screening	x																
Baseline Eval.				x													
Psycho Therapy		x	x			x		x	x	x		x		x	x	x	x
MDMA/ Placebo Session.					x						x						
Psycho Logical Measure	x			x			x						x				x
Neuro Psych. Measure				x													x
Metabolic profile	x+																
Electro-Lytes	x																
Liver FCT	x												x*				
Drug Screen & B-HCG	x				x						x						
Medical exam	x												x				
Working Alliance Measure				x		x						x					
RRPQ measure																	x

+ = Liver FCT included in metabolic profile for visit 1.
* = ALT only unless otherwise directed by examining physician

Schedule of Visits – Stage 1 continued

Time: p=post d=days, w=week m=month	**After V 17**	**1 d p v18**	**Between v18 and v22**		**2 m p v18**	**10 m v. 18**
Visit	1-18	1-19	1-20	1-21	1-22	1-23
Psycho Therapy		x	x	x	x	
MDMA Session	x					
Psycho Logical Measure					x	x
Drug Screen & B-HCG	x					

**= Closing session

Primary outcome measures were selected to be well-validated, clinically-relevant, and repeatable. These include observer-rated measures of PTSD symptoms, subject-rated measures of symptoms and discomfort, and neuropsychologist-administered tests of neurocognitive function. Observer-rated and subject-rated measures of symptoms will be made at baseline, at four days after each experimental session, and at two months after the second experimental session. Neurocognitive function will be assessed at baseline and at two months after the second experimental session. A complete medical examination will be performed at baseline and at four days after the second MDMA or placebo session. During experimental sessions, participants will be supervised at all times by trained medical personnel, including a physician who will be present throughout each experimental session. Measures of physiological status and participant distress intended to monitor participant safety will be made at frequent, scheduled intervals. Participants who had received placebo during this study will be offered an opportunity to receive MDMA-assisted psychotherapy upon completion of the study. Participants who consent to the open-label continuation would receive two experimental sessions with 125 mg MDMA, with experimental session scheduled 3 to 5 weeks apart. They would receive one non-drug therapy session prior to the first experimental session, non-drug therapy follow-up sessions after each experimental session, and a final follow-up scheduled two months after the second experimental session. Participants would complete outcome measures two months after the second experimental session.

At least ten months after completing the study, defined as either completing Stage 1 or Stage 2, as applicable, consenting participants may take part in a long-term follow-up that will include re-assessment with CAPS and a questionnaire addressing the positive and negative effects of taking part in the study, any enrollment in new therapies, and use of "ecstasy" subsequent to study participation. The independent rater will conduct the CAPS assessment over the telephone and the questionnaires will be mailed to participants.

Data Analysis

The current study is a Phase II pilot study primarily designed to provide an estimate of the effect size of MDMA-assisted psychotherapy in relieving symptoms of PTSD. As such, this study has sufficient power only to detect large effects. However, it is hypothesized that participants receiving MDMA-assisted psychotherapy will tend to have greater decreases in observer-rated and self-rated symptoms and associated problems at

four days and two months after the final experimental session compared to participants receiving placebo.

The first thirteen participants have been stratified prior to randomization according to whether or not they have been Dr. Mithoefer's patients. Since it is unlikely that many more of Dr. Mithoefer's patients will be enrolled in this study, stratification will cease for the last seven participants. Results will be analyzed for the entire 20 subjects, and they may also include the additional subject. A separate analysis will be conducted comparing results between those subjects who were Dr. Mithoefer's patients and those referred by other psychiatrists and psychotherapists. The purpose of this sub-analysis is to gather some information about whether subjects who have already established a therapeutic alliance with Dr. Mithoefer prior to the start of the study (his patients) will respond more favorably than the other subjects.

Data will be analyzed by mixed analysis of variance (ANOVA), with experimental intervention condition (MDMA versus placebo) serving as a between-group factor and time of measurement, or experimental session (first or second) serving as within-subjects factors. Statistical significance will be set at 0.05. Separate analyses will be performed for systolic blood pressure, diastolic blood pressure, heart rate, body temperature, Subjective Unit of Distress scores, the CAPS-2, the IES, the SCL-90-R, each RBANS scale score, the PASAT, and the Rey-Osterrieth Complex Figures Test scores. Of these measures, it is expected that statistically significant changes will only be detected in heart rate and blood pressure and will last several hours when MDMA-assisted psychotherapy is compared to placebo psychotherapy sessions, but that no other statistically significant changes will be detected. In particular, neurocognitive measures are not hypothesized to suggest potential toxicity in participants receiving MDMA.

The statistics that we will be doing on this project are not complex given the small sample size. Analyses will consist of descriptive statistics, inferential group comparisons, and exploratory correlations. The first step will be to descriptively summarize the data. We will quantitatively characterize the final study by obtaining mean scores and percentiles for all the variables, including the demographic characteristics and outcome variables. The second phase of the data analysis will be to compare the control group with the experimental group. We will perform some exploratory group comparison analyzes to determine if there are any systematic biases in the data. This is not expected to be the case, but since this is not a randomized design, the possibility exists. In order to control for this possible confounding effect, we will use co-variate statistical techniques if a systematic bias does exist. Another method for controlling for any systematic bias is a repeated-measures design where subjects will also serve as their own controls. After the data has been summarized and reviewed, we will undertake the main statistical analyses. A series of ANOVA's will be performed on our main outcome variables. This will include the CAPS, Impact of Events, NEO, neurocognitive toxicity measures, biochemical markers, etc. We will be using a mixed within/between analysis where the control group will be compared to the experimental group and where the subject's baseline will be compared with post treatment scores. We will perform exploratory analyses to compare participants who received supplemental doses with those who received single doses, and within/between analyses comparing PTSD symptoms after the second experimental session and the third, "open label" session. We will perform exploratory analyses that will compare the last CAPS score obtained during participation in Stage 1 and, if applicable, Stage 2, and CAPS score at the

long-term follow-up for any participants assessed at long-term follow-up. All of these analyses will be performed to test for our hypothesized outcomes. Interactions in the data will also be investigated. Finally, since this project is a pilot study, we will also perform exploratory data analysis in attempt to discover any finding that emerge outside of our predicted theories.

Subjects

Who and Why

Participants will be unpaid individuals, male or female, ages 18 through 70, who have been diagnosed with current PTSD using DSM-IV criteria, including a score of 50 or above on the Clinician-Administered PTSD Scale (CAPS), a recognized measure of PTSD severity. PTSD was selected for study because it is among the most debilitating of conditions for which there is evidence that MDMA may be effective. There are only two FDA-approved treatment for PTSD (e.g., Zoloft and Paxil) and these treatments are not effective in all patients. There is therefore a substantial need for improved treatments for this debilitating and degenerative illness.

We will recruit twenty subjects who have failed to achieve remission after treatment with a selective serotonin reuptake inhibitor after at least three months, and after receiving psychotherapy lasting for at least six months, with at least twelve psychotherapy sessions in the course of treatment. We will also accept one veteran whose war related PTSD symptoms have lasted from a year to five years and who does not have access to conventional treatment or who refuses to undergo conventional treatment. Our intention is to recruit participants who, aside from having PTSD, are physically healthy, as confirmed by detailed medical evaluation, and will not be posed untoward risks by exposure to MDMA. Because of the high co-morbidity of mood and anxiety disorders among people with PTSD, it is necessary to include individuals with these additional diagnoses (excluding bipolar affective disorder). As discussed below, we will only include persons who are not taking or can be safely withdrawn from other prescription medications that might present difficult-to-evaluate risks of drug-drug interaction and that might confound any findings of therapeutic benefit.

Total Number/Number per group

Twenty-one men and women will be recruited for study participation. The first twenty who meet inclusion criteria without any exclusion criteria will be included in the study. An additional subject will be a veteran who meets all other initial inclusion criteria but is unable to obtain psychotherapy and is unwilling to undergo pharmacotherapy. Any volunteers who drop out or are excluded between the first and the second experimental intervention (MDMA or placebo) sessions will be replaced. Researchers will, nevertheless, attempt to collect outcome data on PTSD symptoms, neurocognitive function and the experience of being a research subject in drop-outs and excluded volunteers.

Because no previous properly-controlled studies have assessed the efficacy of MDMA-assisted psychotherapy, this pilot study is necessary to estimate the effect size this experimental intervention so that we may later design a larger, properly-powered study.

This pilot study will also allow the researchers to evaluate the instruments used for outcome measures and the timing of these measures. We recognize that this study is under-powered for all but large effects and that trends seen in this study must be interpreted with caution. This pilot study will be followed by a second pilot study to further refine and standardize the therapeutic intervention prior to the initiation of any large Phase III trials.

Inclusion/Exclusion Criteria

Individuals will be included as potential participants if they meet the following conditions:

1. Participants must meet DSM IV criteria for current PTSD (within the past 6 months) in response to crime victimization (CR-PTSD), including childhood sexual or physical abuse, or meet criteria for PTSD in response to combat, with the diagnosis lasting no more than five years in duration. A subject would not be excluded for having more than one traumatic event, but would be excluded if a non-crime-related or non-combat-related traumatic event were a significant contributor to the PTSD symptoms. 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) 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 (Foa et al. 2003; Jaycox et al. 2002; Krupnik 2002; Resick and Schenk 1992). Treatment with an SSRI must have lasted for at least three months, and 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 with PTSD symptoms that have endured for no less than one year but no more than five years. One such subject may be included without prior treatment if he or she is unwilling or unable to undergo psychotherapy or pharmacotherapy.
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 also 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. Mithoefer 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 2 months after the second 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 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. If they desire to do so, they must sign a release for 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 2 months after the second experimental session.
7. Participants must agree that, for one week preceding each MDMA/placebo session:
    c. They will refrain from taking any herbal supplement (except with prior approval of the research team)
    d. 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).
    e. 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 intervention session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA/placebo session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug (MDMA or placebo).
9. Participants must be willing to remain overnight at Dr. Mithoefer'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 a registered nurse (RN) and of the same sex as the participant, and he or she will be trained for assisting in this study. The attendant will be instructed to contact Dr. Mithoefer 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. Mithoefer'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.

Individuals will be excluded from study participation if they are:

1. People who indicate that a non-crime or non-combat related traumatic event is a significant contributor to their PTSD symptoms, as assessed by the CAPS.
2. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
3. People with a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder.
4. People with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.
5. 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).
6. People with hypertension, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
7. People weighing less than 50 kg or more than 105 kg.
8. 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.
9. People who would present a serious suicide risk or who are likely to require hospitalization during the course of the study.
10. People requiring ongoing concomitant therapy with a psychotropic drug.
11. People meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.
12. Any person who is not able to give adequate informed consent.

Initial Contact Method and Informed Consent Process

Potential participants will be recruited through referrals made by physicians or psychotherapists (see referral letter), including referrals selected from among the patients of Dr. Mithoefer, and advertisements. Letters of referral specifically request the participation of crime victims experiencing symptoms of PTSD. Prospective participants will contact the investigators for information about the research, usually initially by telephone. Prospective participants will visit the researchers' office, discuss and review the study procedures (including risks, potential benefits, and alternatives) before giving written informed consent. Individuals will be encouraged to ask questions and consider their alternatives. The prospective participant's comprehension of material in the informed consent will be assessed through a 16-item quiz administered after the prospective participant has read the consent form. The investigators will address any misunderstandings identified through incorrect quiz responses, and will use the quiz as a guide for further discussion of the study if necessary. Potential participants can include current and past patients of the researchers. Subjects from the researchers' patient pool must have an interview with another psychiatrist not involved in the design or administration of the study before engaging in the informed consent process. The researchers will be 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. It is anticipated that this study will generate widespread interest and that potential participants from other regions may be willing to temporarily relocate in order to participate in the study. We will accept no one who, because of illness, intelligence, language or cultural differences, appears unable to understand the

nature and risks of the experiment, or who is unable to read (or, if blind, be read to) and follow the informed consent.

Screening Process

The 1998 version of the Clinician Administered PTSD Scale (CAPS: Blake et al. 1990) will be used to provide a DSM-IV CR-PTSD diagnosis. Individuals with a score of 50 or above will be considered eligible for study participation (Weathers et al. 2001). If the subject meets DSM-IV PTSD criteria, the rest of the Structured Clinical Interview for Diagnosis (First et al. 1994) wil7l be administered for the purpose of ruling out exclusionary Axis I diagnoses (i.e., exclusion criteria of substance dependence, psychotic disorder, dissociative disorder, eating disorder, or bipolar disorder). Relevant modules of the SCID II (First et al. 1997) will be administered for the purpose of ruling out the presence of borderline personality disorder, an exclusionary Axis II disorder.

Any subject who appears at imminent risk for trauma and victimization as assessed by information gathered during the screening assessment will be evaluated by the principal investigator (PI) or a study co-investigator. He or she will be counseled in specific risk-reduction strategies, and referred for immediate protection or care as needed. These subjects would not be eligible for study participation. Subjects who do not meet eligibility criteria at this point or who do not wish to participate will be referred for alternative treatment.

There will be no gender exclusions or racial/ethnic exclusions. Because the incidence of crime related PTSD is higher in women, it is anticipated that a majority of the subjects will be female. We will attempt to recruit both men and women into this study. Similarly, it is anticipated that the racial/ethnic composition will be close to that of the regional population. We will attempt to reach individuals of different ethnic or racial backgrounds in our recruitment efforts.

Individuals who meet the psychiatric criteria and agree to participate in the study will receive further medical evaluation. The examination will involve the following procedures: general medical history and physical exam, electrocardiogram (EKG), metabolic profile, assessment of serum electrolytes, thyroid hormone levels and levels of TSH, HIV serology and urine pregnancy test for females. A physician not directly involved in administering the therapeutic treatments will perform the medical examination. Results of HIV serology will be kept confidential, and appropriate referral for counseling will be made if necessary.

After giving written informed consent to participate in the study, participants will receive information on a separate document concerning videorecording of study sessions. Participants can either consent or decline to consent to have their sessions recorded to video.

<u>Study Procedures</u>

Following pre-study evaluation, individuals who meet the study criteria and agree to participate will be scheduled for a baseline assessment battery to be administered within 14 days prior to their first MDMA session. They will also be scheduled for the two introductory psychotherapy sessions that will occur within this same time period. After

these sessions, participants will receive MDMA or placebo during two experimental sessions. If both the participant and the principal investigator deem it is safe and appropriate to do so, participants will receive a supplemental dose of 62.5 mg MDMA or placebo approximately 2 to 2.5 hours after the initial dose. Experimental sessions will be followed by research follow-up sessions and psychotherapy follow-up sessions, as described below.

Study Outcome Measures

The measures that will be used in the course of this study are listed below.

1. Clinician-Administered PTSD Scale, 1998 Revision. (CAPS: Blake et al., 1990). The CAPS is a structured clinical interview designed to assess the seventeen symptoms of PTSD along with eight associated features.
2. Impact of Event Scale (IES; Horowitz et al, 1979). The Impact of Event Scale is a 22-item self-report scale designed to measure the extent to which a given stressful life event produces subjective distress.
3. Subjective Units of Distress. This is a standardized subjective rating scale by which a subject can quickly rate comfort level throughout the session (l-7 scale).
4. Symptom Checklist 90-R: This is a standardized instrument used to measure subjective feeling states. It gives subscales on several dimensions.
5. Working Alliance Inventory (WAI) (Horvath and Greenberg 1989) is a 36-item self-report scale designed to assess the quality of working alliance existing between patient and therapist.
6. Reactions to Research Participation-Questionnaire-Short Form (Revised) (Newman and Kaloupek, 2001). This is a 24-item assessment of participants' experience of study participation, reasons for participation, and perceived costs and benefits of participation. The measure contains items addressing participation due to perceived coercion or undue influence by the investigators.
7. Long-term Follow-Up Questionnaire: This is an 11-item questionnaire designed by the principal investigator (Michael Mithoefer MD) that assesses presence and perceived benefits of study participation, perceived harm from study participation, commencement of new psychotherapy or pharmacotherapy, and use of ecstasy subsequent to study participation.

Neuropsychological Measures that will be used are:

1. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1997) has two parallel forms, with identical administration but different stimulus content, ideal for measuring change in neuropsychological status over time.
2. The Paced Auditory Serial Addition Task (PASAT) (Roman et al. 1991) is a sensitive measure of information-processing speed and efficiency, concentration skills, and immediate memory which has an extensive literature associated with the effects of brain dysfunction.
3. Rey-Osterrieth Complex Figure (Mitrushina et al 1999) consists of a complex two-dimensional line drawing. The subject's task is to copy the design with pencil on paper. The Rey-Osterrieth assesses visuoperceptual skills, spatial organizational skills and memory.

4. NEO Personality Inventory (Piedmont 1998). The NEO is a well-established measure of personality with sound properties of reliability and validity that operationally define personality structure according to a five-factor model.
5. Subject Beliefs on Condition Assignment: All subjects will be asked to indicate whether they believe they have received MDMA or placebo during the experimental sessions.

Safety Monitoring Measures that will be used are:

1. Automated blood pressure and pulse monitoring equipment
2. Thermometer for reading body temperature at regular intervals.
3. Subjective Units of Distress, a 1-item self-report measure of subjective experience of degree of distress, with responses given via 7-point likert scale, with this short measure administered repeatedly throughout the MDMA/placebo session.
4. Standard assay of liver enzymes ("liver panel"), assessed with blood sampled at follow up after the second MDMA/placebo session, as a means of detecting changes in liver function.

As noted in discussing the specific hypotheses of the proposed study, the CAPS will serve as a primary outcome measure, and the IES and SCL-90-R serve as secondary outcome measures. All measures of neurocognitive function and the NEO serve as means of safety evaluation.

The Working Alliance Inventory (WAI) is intended to assess a process variable (therapeutic alliance) that may be related to efficacy. The Subjective Units of Distress (SUD) will also be administered in order to assess a process variable, subject comfort level throughout the experimental session. The Reactions to Research Participation-Questionnaire-Short Form (Revised), another measure of a process variable, will be administered at the final follow-up to evaluate subject reactions to the study itself. The long-term follow-up questionnaire will be administered to assess any positive or negative effects of study participation and use of ecstasy subsequent to study participation.

Baseline Assessment

A battery of psychological and diagnostic assessments will be performed during the two weeks prior to the first experimental session in order to provide baseline measures of PTSD symptomatology, mood state and global functioning. All study measures described above, except WAI and the measure of subject beliefs on condition assignment, will be administered during baseline assessments.

Non-Experimental Psychotherapy Sessions

Following the initial screening and data collection at baseline, all subjects will receive two ninety-minute introductory sessions with the therapists. The WAI will be administered during the second introductory psychotherapy session. There will then be two individual experimental sessions conducted 3-5 weeks apart, each lasting approximately six to eight hours depending upon the participant's response. Three or four sixty to ninety-minute non-drug psychotherapy sessions will be conducted in the time intervening between the two experimental sessions. Participants will also see the investigators in a ninety-minute follow up session a day after each experimental session,

and in two or three more psychotherapy sessions after the second experimental (MDMA or placebo) session but before the study has been completed. A final psychotherapy session will occur at the time of the final research follow-up two months from the second experimental session.

Non-drug psychotherapy sessions will be recorded to video and audio. These recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted therapy. They are intended to record the events occurring during therapy, and will not serve as outcome measures. Full names and addresses, if they appear in these recordings, will be edited out of the recording before the tape is seen by anyone other than the study participant and the investigators present at the session. Facial images will not be removed from the video tapes to be viewed by the sponsor or investigators for review of the therapeutic process and for manual development. However face shots will be obscured on any tapes used for training purposes unless the subject gives his or her written permission (via "Video and Audio Use Permission IC") to retain face shots (for more details of recording, see Appendix B).

The attendant referred to above will be an RN, will always be of the same sex as the subject he or she will be staying with, and will be trained by Dr. Mithoefer to be on duty at the office following each experimental session. The attendants will be selected for their ability to act as reliable and compassionate attendants to the study subjects, and to recognize when to call Dr. Mithoefer in the event that a subject is experiencing physical or emotional distress during the night following an experimental session. A necessary quality for these individuals will be the ability to tolerate being in the presence of other people's emotions without becoming emotionally reactive themselves. Attendants will be taught to be attentive to the subject's needs for food or liquids, and to offer companionship by sitting with them or taking a walk according to the subject's desires. They will be instructed to listen compassionately if the subject wants to talk, but not to attempt to interpret the subject's experiences or otherwise act as therapists. The emphasis will be on listening rather than talking and on being quietly present. The attendant will be taught to avoid initiating long conversations with the subject or being intrusive in any way on the subject's experience, other than to inquire about their physical or emotional needs and their comfort. This role will be further described below under Psychotherapeutic Procedures during Experimental Session.

Sessions Employing the Experimental Intervention

Drugs and Dosing

Twelve individuals will receive 125 mg MDMA and eight individuals will receive lactose placebo in gelatin capsules on two occasions, 3-5 weeks apart. The additional participant enrolled in the study will have a 60% chance of receiving 125 mg MDMA. An initial dose of 125 mg MDMA has been selected for use in this study on the basis of prior reports of therapeutic effectiveness and tolerability. Doses equal to or greater than 125 mg have been well-tolerated in previous studies of MDMA in humans (Cami et al, 2000; Freedman et al. 2005; Grob et al, In preparation; Harris et al. 2002; Lester et al. 2000; Mas et al, 1999; Tancer et al, 2001; Tancer et al. 2003; Vollenweider et al. 1998). The supplemental dose of 62.5 mg was chosen on the basis of prior reports of such doses extending potentially therapeutic effects of MDMA in psychotherapy (Stolaroff 2004) and in an uncontrolled study (Greer and Tolbert 1986). The cumulative dose of 187.5 mg

has been exceeded by single doses in some previous research studies without any adverse events (Grob et al., unpublished see p. 52 of initial submission to FDA, IND #63,384). MDMA will be supplied by David Nichols, Ph.D., Department of Medicinal Chemistry and Pharmacognosy, Purdue University. This MDMA is of confirmed identity and purity and has been used in all three Phase I clinical trials conducted in the United States.

Currently three studies of MDMA-assisted psychotherapy will use supplemental dosing. This includes two studies of MDMA-assisted psychotherapy in people with PTSD. One study is to take place in Israel and has gained final approval from the Israeli Ministry of Health, an Israeli ethics committee, and the Israeli Anti-Drug Authority. The other study will take place in Switzerland. The protocol and informed consent have gained full approval from the local ethics board and the protocol design has obtained approval from the national health agency Swissmedic, with only the supply of MDMA remaining to be approved. Additionally, in December 2004, FDA permitted a study of MDMA-assisted psychotherapy in people experiencing anxiety as a result of advanced-stage cancer and short estimated life expectancy that will use supplemental dosing.

Condition assignment will be randomized. The first thirteen participants have been stratified prior to randomization according to whether or not they have been Dr. Mithoefer's patients, but owing to the low likelihood of many other patients of Dr. Mithoefer's being enrolled in the study, the last seven participants will not be stratified. The blind will be broken for each subject upon completion of the study. If there is an adverse event or other emergency, the blind may be broken for an individual participant.

All experimental (MDMA or placebo) sessions will begin at 10:00 AM and will take place in the clinical treatment office of Dr. Michael Mithoefer, located in South Carolina. Participants will have had nothing by mouth except alcohol-free liquids since 12:00 AM the evening before. Participants will not have consumed caffeine or nicotine for two hours before or six hours after drug administration. They will be asked to arrive at 9:00 AM for collection of a urine specimen for drug screening and, for females, a pregnancy test. These results must be negative for the participant to continue with the experimental session. Prior to drug administration, the researchers will verbally confirm that the participants have not recently ingested any medications (including herbal, over-the-counter, or prescription) that are not approved by the researchers or allowed in the protocol. After preliminary measurements (described in Monitoring for Acute Toxicity below) have been made and the researchers have discussed goals for this session and general procedures, participants will ingest gelatin capsules containing drug or placebo along with a glass of water. Subjects will remain overnight in the clinic until after the non-drug psychotherapy session the next morning. A subject's decision to withdraw from the study at any time will be respected as is accepted practice in human research. In the event of withdrawal during an experimental session the subject will not be permitted to leave the clinic until Dr. Mithoefer has assured that he or she is in a safe and stable condition. Rules of withdrawal apply to the entire 2 experimental sessions while subjects are potentially on study medication. If they do withdraw from study participation, they will not leave the clinic until the study staff feels it is safe for them to do so, and when they leave, a friend or family member will drive them home. If transport is unavailable, the study staff will assist the subject in finding transport from the clinic.

Measures during Experimental Intervention Session

Measures made during the experimental sessions are primarily made for safety monitoring and are described below for "Monitoring for Toxicity." In addition, the investigators will make audio and video recordings of each experimental session. Comparison of information gathered from these recordings may be qualitatively or quantitatively examined in an attempt to gain a better understanding of the effects of MDMA within a psychotherapeutic context, but the recordings themselves will not be treated as outcome measures. Audio and video recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted therapy. For more details on audio and video recordings, see Appendix B.

Psychotherapeutic Procedures during Experimental Session

The MDMA or placebo sessions will be supervised and facilitated by the principal investigator, male investigator/psychiatrist (Michael C. Mithoefer MD.) accompanied by an experienced female registered nurse (Ann T. Mithoefer.). Both Michael and Ann Mithoefer will be present throughout the sessions. The sessions will be conducted following the principles developed by Stanislav Grof, MD for LSD psychotherapy (Grof, 1980, pp. 123-147) and for Holotropic Breathwork (Grof 2000: pp. 178-183) and adapted for MDMA-assisted psychotherapy by Metzner and by Greer and Tolbert (Metzner and Adamson 2001; Greer and Tolbert 1998). Both therapists have been trained and certified in Holotropic Breathwork facilitation by Grof, and have years of experience working therapeutically with this model in non-drug Holotropic Breathwork sessions. The principal investigator also has extensive experience treating PTSD in his psychiatric practice using both medications and psychotherapy. More detail on the psychotherapeutic approach to be used in this protocol can be found in a treatment manual draft for MDMA-assisted psychotherapy (Ruse et al. 2002). The protocols will be exactly the same for each experimental session.

At the beginning of the session, the researchers will discuss with the subject his or her intentions for the session, including intentions regarding working with psychological issues related to their PTSD. After the session begins, subjects will recline in a comfortable position with eyes closed or wearing eyeshades if preferred. They will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material. (Bonny and Savary 1990; Grof 2000: pp.186-191; Grof 1980; Unkefer 1990). After the first hour, if the participant has not spoken spontaneously, the investigators will check in with him/her about the nature of the experience. Approximately 2 to 2.5 hours after the initial dose, the investigators will assess whether a supplemental dose can be administered. If the investigators believe that it is safe and appropriate to do so, and if the participant agrees to a supplemental dose, then the participant will receive a supplemental dose of either 62.5 mg MDMA or placebo. The supplemental dose will be administered in the same manner as the initial dose. For the rest of the experience, as appropriate, the investigators will engage with the participant to support and encourage emotional processing and resolution of whatever psychological material is emerging. The investigators will also encourage periods of time in which the participant remains silent with eyes closed and with attention focused inward in order to allow for the further unfolding of the inner experience.

Electrolyte containing fluids will be available ad lib throughout the session within the limits described in “Monitoring for Toxicity." Food will be available during the latter part of the session. Foods provided will include crackers or bread, fruit and vegetables, and soups. After the conclusion of the session, dinner will be made available by the attendant, with breakfast offered the next morning.

After approximately eight hours, if all medical parameters are acceptable and the subject is alert, ambulatory and emotionally stable, the session will be ended. During the last 30 - 60 minutes of the session, the attendant (an RN) will join the investigators and the subject in order to become familiar with the subject's state of mind, and any wishes the subject might have in the way of food or activity during the evening. If the subject so desires, an additional designated support person (a spouse, partner, relative or friend) may join in this meeting. After the researchers leave (when they have judged the subject to be emotionally and medically stable), the subject will spend the rest of the evening and night in Dr. Mithoefer's offices where he or she will have a private room to sleep in. The room will be an office designated for that purpose and will be furnished with comfortable furniture and a sofa-bed. All records pertaining to the study and any other sensitive material will be securely stored in a separate area of the clinic. The attendant will be on duty during this time and will have a separate room in which to rest. The clinic has a kitchen with eating area, two bathrooms, several offices, and a yard with an outdoor table and chairs. Since the office is in a quiet, attractive area, the subject, accompanied by the attendant, may spend time in the yard, walk in the neighborhood to enjoy nature. Subjects will, however, be encouraged to use much of the time for rest and for a period of reflection and integration in a quiet atmosphere. The subject may request that a spouse, partner or friend also remain with them during the night, but this must be approved by Dr. Mithoefer after he has met this support person and has discussed the possible advantages and pitfalls with the study subject.

During the night following the experimental session, Dr. Mithoefer will be at home within ten minutes drive of the office, and the attendant will be instructed to call him if the subject is experiencing emotional difficulties or any other problems. Dr. Mithoefer will be willing to return to the office to meet additional needs or provide requested support to the subject, and will be available throughout the night of the experimental session. (At all other times during the study 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 participant will be given a wallet card with a pager number to call immediately if any problems occur.)

When the researchers return to meet with the subject for the scheduled ninety-minute therapy session occurring on the following morning, the attendant will go off duty. After this psychotherapy session, a person previously selected by the subject will provide a ride home. If the subject is unable to locate an individual willing or able to take them home, or if the designated person is unable to assist the subject due to unforeseen events, the investigators will assist the subject in finding an alternative means of returning home.

Starting on the day of the non-drug psychotherapy session following each experimental session, one of the investigators will contact the subject via telephone on a daily basis for one week. The investigators will use clinical judgment to assess the psychological well-being of the subject during this period of time. If there are any indications of continuing

anxiety or distress, the investigators may arrange to work on reducing the distress at a specially scheduled non-drug therapy session, through continuing contact, or at the next regularly scheduled non-drug therapy session. The subject may also initiate contact with the investigators at any time throughout the study.

Monitoring for Toxicity

There is now a considerable body of information indicating that the likelihood of significant toxicity from the doses of MDMA used in this kind of setting is very low. Phase 1 studies conducted in the United States and Europe have failed to demonstrate toxicity (Cami et al. 2000; Grob et al. 1996; Harris et al. 2002; Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Tancer and Johanson 2001; Vollenweider et al. 1998). Doses of up to 2.5 mg/kg were employed in one of the studies conducted in the US (Grob et al., In Preparation), with eight subjects receiving doses equal to or exceeding the dose of 125 mg proposed in this study. In another US Phase I study (personal communication, Tancer, 2001), over twenty subjects were administered doses larger than 125 mg.

Likewise, psychiatrists in the US and Europe reported using MDMA in a large number of patients before the drug was made illegal. The therapists did not report any severe adverse effects occurring during or after MDMA-assisted psychotherapy sessions (Adamson 1985; Greer and Tolbert 1986; Gasser 1994; Metzner and Adamson 2001; Widmer 1997).

A controlled study of the effects of two doses of 100 mg MDMA given four hours apart failed to report any adverse events (Pacifici et al. 2002), and an uncontrolled psychotherapy study employed supplemental doses frequently half the size of an initial dose (Greer and Tolbert). Anecdotal accounts of psychotherapists who conducted MDMA-assisted psychotherapy prior to its scheduling indicate that supplemental dosing was used (Stolaroff 2004).

Although serious untoward reactions are unlikely, the researchers will closely and continuously monitor participants during experimental sessions. To date, there have been no adverse events requiring the assistance of an additional emergency medicine physician occurring during any of the 31 experimental sessions. Of these 31 sessions, MDMA was administered in 23. All increases in blood pressure, pulse or temperature have resolved uneventfully without clinical intervention. The researchers have extensively communicated with the FDA to ensure that sufficient personnel and equipment are available to manage even very unlikely acute adverse effects. Throughout all the sessions, participants will be attended by Michael Mithoefer, M.D., and Ann Mithoefer, BSN. Michael Mithoefer is board certified in internal medicine and psychiatry and is now re-certified in Emergency Medicine as of October 27, 2005. He had previously been board certified in Emergency Medicine and practiced emergency medicine for 10 years before going into psychiatry. Dr. Mithoefer also maintains Advanced Cardiac Life Support certification throughout the study. Ann Mithoefer was a nurse in a cardiac care unit before going into psychiatric nursing. In addition, the researchers will hire a currently practicing emergency department nurse to be present in an adjoining room during at least the first five hours of each experimental session. The investigator, assisting investigator, and emergency medicine nurse will provide a team of one experienced emergency physician and two registered nurses to respond in the unlikely event of a medical emergency.

Blood pressure and pulse will be measured at the outset of each experimental session, once every 15 minutes for 6 hours, and then every 30 minutes for 3 more hours. If at any time the blood pressure exceeds 160 systolic or 110 diastolic or pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. Body temperature will be measured at the outset and then hourly for 6 hours. The physician may also call for more frequent measurements in the event of clinically significant changes. The SUD (a brief self-report measure of volunteer distress) will be repeated at 60-90 minute intervals.

Both non-drug sessions and experimental sessions will be conducted in the psychiatric offices of Michael Mithoefer MD. The offices are located 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. Benadryl, injectable epinephrine and other standard emergency drugs and equipment will be available on-site as a means of treating any potential allergic reactions or other medical emergencies. Available emergency medications include antihypertensive agents (such as nitroprusside and labetolol), pressor agents, anxiolytics, and intravenous fluids. In addition to drugs, the crash cart will contain a defibrillator (with telemetry capability), an oxygen tank, a 12-lead electrocardiogram (EKG) device, a suction device, a pulse oxometer, an IVAC pump and intubation equipment (including laryngoscope, and endotracheal tubes). We will have equipment for placing an arterial line and monitoring arterial pressure. The researchers have established (in communication with the FDA) contingency plans for responding to those adverse events that appear most likely, based on a comprehensive review of case reports of toxicity in illicit MDMA users reported in the Investigator's Brochure (See Appendix). With these personnel and equipment, the researchers would be able to stabilize a subject in the office and then transport them by ambulance if hospital admission were required. The researchers have contacted the Charleston County Emergency Medical Services and learned that, in 2001, the average response time for an ambulance to arrive at a location in the sector where the research will be conducted was 8 minutes, 55 seconds. Transportation time to the East Cooper Medical Center Emergency Room should take no more than 10 minutes.

An assay of the liver enzyme ALT will be performed at research follow-up four days after the second MDMA/placebo session so as to detect any change or decline in liver function. Participants will be closely monitored for any change in emotional or cognitive function in the weeks following each session employing the experimental intervention.

Written notice will be given to the IRB and the FDA within five days of the occurrence of a life-threatening adverse event, and within 15 days of the occurrence of any serious but not life-threatening events.

The Data Safety Monitoring Board (DSMB) will be composed of three individuals, at least one of whom is psychiatrist and another a psychotherapist. The DSMB will have scheduled meetings after the first five subjects have completed their first experimental sessions, again after these same subjects have completed their final follow-ups, after subjects 6-10 have completed their final follow-ups, and after subjects 11-15 have completed their final follow-ups. DSMB meetings will also be held to review every report of a serious adverse event, or more frequently if the DSMB so chooses. After each

meeting, the DSMB will present a report to the sponsor, the IRB and the FDA recommending whether the study should be continued as is, modified, or halted. Any new findings deemed relevant to study participation will be communicated to each potential participant during informed consent.

We feel that these precautions and the contingency plans described in the appendix represent a very cautious approach to the remote possibility of a serious complication.

Research Follow Up

The follow-up will begin 3 to 7 days after the first experimental (MDMA or placebo) session. There will be a total of three research follow-up interviews. The first two will be done 3 to 7 days after the first and second experimental sessions, respectively. The CAPS, IES and SCL-90-R will be administered as outcome measures to be compared with baseline scores. All outcome measures will be administered by Mark Wagner PhD, a consultant experienced in administering psychological and neurocognitive assessments. He will have no involvement in the experimental sessions and will be blinded to what occurs during the sessions. A research follow-up will also be done at two months after the second experimental session. The measures of cognitive function administered during baseline (RBANS, PASAT and Rey-Osterrieth Complex Figure) will be administered again at the last research follow-up, and the measures of PTSD symptoms will be administered again.

The research and experimental intervention aspects of this project will be kept as separate and distinct as possible. Dr. Wagner, the psychologist obtaining all information gathered during research follow-up, will not be involved in monitoring the subjects during the experimental sessions, and will, therefore, be naïve to complaints of medication side effects. He will also be blind to whether participants have been assigned to the MDMA or placebo condition.

Participants will also be reassessed for psychological and physical status by the physician-investigator immediately following this session and weekly for at least 3 weeks after each session.

Participants' reasons for consenting to participate in the study, their experience during and after participation and perceived costs and benefits of participating will be assessed during the final research follow-up through the RRPQ, a self-report measure of responses to research participation. Responses to this measure will be examined throughout the study to determine whether participants feel that they were unduly influenced or coerced into participating, and further actions will be taken to reduce undue influence if it is consistently detected through RRPQ responses.

At the end of the study, participants will be asked to complete and sign a video recording permission form regarding whether or not they will allow people in sponsor's training program for teaching MDMA-assisted therapy to view video recordings of their session, with our without identifying information.

Therapy Follow-up

Participants will see the investigators one day after each of the two experimental (MDMA or placebo) sessions. During these 90-minute follow-up sessions, participants will be encouraged to describe their experiences during the experimental sessions and to freely express any thoughts, feelings, questions or concerns they have. The WAI, the measure of quality of working alliance administered during the second introductory session, will be administered again at each therapy follow-up session. Participants will also be asked to indicate whether they believe they received MDMA or placebo at each follow-up session. The primary purpose of these sessions will be to support the participant in further processing, understanding and integrating of the experience. It will also be an opportunity for the investigators to gather information, in an unstructured format, about the effects of MDMA or placebo and to provide data with which to evaluate after the conclusion of the study whether the blind was maintained for subjects.

Third Open-Label Experimental Session

After each participant has completed the Visit 17 follow-up session, the blind will be broken for that subject, as per previous revisions of the protocol.

- If a subject has received MDMA and has undergone both experimental sessions without any clinically significant adverse event, then the subject will be offered participation in a third, open-label, MDMA-assisted experimental session. Procedures for this third MDMA-assisted session will be the same as in the first two experimental sessions, except that all participants will receive MDMA. Subjects will undergo a therapy follow-up session 24 hours after the open-label MDMA-assisted therapy session identical to therapy-follow-up sessions occurring after other experimental sessions. Subsequently there will be two additional non-drug psychotherapy sessions scheduled to occur approximately one and two weeks after the MDMA-assisted session to facilitate integration of material arising during the open-label session. These non-drug therapy sessions will follow procedures identical to those described for previous non-drug therapy sessions, except that participants will not complete the process measure of therapeutic alliance. All outcome measures will be administered two months after the open-label MDMA-assisted psychotherapy session, including CAPS, IES and SCL90R. For the reasons detailed below, neurocognitive assessments will not be administered again.
- Participants who receive placebo and enroll in the open-label continuation ("Stage 2") described below will be offered a third open-label session unless the investigators believe it is contraindicated or the participant declines. The third session will take place four to six weeks after the second open-label MDMA session. It will be preceded by one introductory session to re-acquaint the participant with study procedures, and it will be followed by non-drug psychotherapy follow-ups 24 hours, and approximately one week and two weeks later. PTSD symptoms will be assessed two months after the third MDMA session. In both cases, PTSD symptoms will be assessed four to six weeks after the second MDMA session."

Open Label Continuation for Placebo Subjects

Participants who received placebo during the course of the study may enroll in an open-label continuation of the study wherein they will undergo three MDMA-assisted psychotherapy sessions and a continued course of therapy follow-up sessions. Participants will give written informed consent to take part in this second stage of the study, with consent given separately from the initial consent. If the participant consents to take part in this open-label continuation (or "Stage 2") of the study, he or she would undergo three experimental sessions with an initial dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA. The participant would undergo one preparatory non-drug psychotherapy session prior to the first experimental session, and he or she would receive non-drug psychotherapy follow-up sessions according to a similar schedule described for the first stage of the study. This schedule includes a non-drug psychotherapy session conducted a day after each experimental session, two non-drug psychotherapy sessions occurring between the first and second MDMA experimental sessions, and two non-drug psychotherapy sessions occurring within 3 weeks of the second MDMA experimental session. The final outcome measures from Visit 17 in the initial study would serve as baseline measures for the second stage (the open-label continuation), and outcome measures would not be repeated until two months after the second experimental session in the second stage of the study. An exception to this would be situations in which more than 30 days have passed between visit 17 and visit 18 (the first experimental session in the open-label continuation). In this case outcome measures would be repeated in visit 17.1 as indicated in the table of visits for Stage 2 below. Participants will not receive a second medical examination after the second MDMA-assisted session in Stage 2. Procedures for non-drug psychotherapy sessions, experimental sessions, weekly telephone contact and research follow-up sessions will be the same except that outcome measures will only be administered four to six weeks after the second experimental session and again two months after the third experimental session. Non-experimental and experimental sessions will be recorded to audio and video. These recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted therapy. Full names and addresses are unlikely to appear on the video or audio tapes. However, if they do, they will be edited out. Face shots will not be excised from recordings viewed by the investigators or sponsor. (For more details on recording, see Appendix B.) Due to generally high scores found so far in participants completing Stage 1, the WAI, a process measure of therapeutic alliance, will not be administered again during Stage 2. Since performing a third neurocognitive examination is costly, and three forms do not exist for the RBANS so performance could reflect a learning curve produced from prior experience with the measures, neurocognitive function will not be assessed for a third time on the final follow-up.

If, after the second open-label session of Stage 2, the subject has undergone both MDMA-assisted sessions without any clinically significant adverse events, then he or she will be offered participation in a third, open-label, MDMA-assisted experimental session. Procedures for this third session will be the same as for the previous two as described above. The third MDMA-assisted session will be scheduled four to six weeks after the second MDMA-assisted session. Follow-up non-drug psychotherapy visits will also be identical in procedure to previous psychotherapy follow-ups, including a non-drug therapy session occurring 24 hours after the MDMA-assisted session, and two non-drug

psychotherapy sessions, as described above. Repeat outcome measures will be administered two months after the third MDMA-assisted session.

Schedule of Visits-Stage 2

Time: **d=days w=week m=month p = post**		**After v 17**	**+ 1 d v18**	**Between v18 and v22**		**3-5 w after v18**	**+1 day v22**	**Between v22 and v27**		**4-6 w p v 22**	**4-6 w p v 22**	**4-6 w p v 22**	**1 d p v27**	**Between v27 and v31**		**+8 w p v27**
Visit	17*	2-18	2-19	2-20	2-21	2-22	2-23	2-24	2-25	2-26	2-27	2-28	2-29	2-29	2-30	2-31
Baseline Eval.	x															
Psycho Therapy	x*		x	x	x		x	x	x		x		x	x	x	**
MDMA Session.		x				x						x				
Medical Examination	x^															
Psychological Measures	x									x						x

*Participants enrolled in Stage 2 less than one month after completing Stage 1 will have their introductory psychotherapy session for Stage 2 at the final follow-up for Stage 1(visit 17), , and the PTSD symptom measures done in visit 17 will also serve as baseline measures for Stage 2. People starting Stage 2 more than one month after visit 17 will have an additional introductory psychotherapy session and will have PTSD symptoms measured during a separate visit scheduled after the final Stage 1 follow-up. The additional visits referred to above will be numbered 17.1 and 17.2 for the evaluation and the psychotherapy visits respectively
** Closing session
^ Only participants who have completed Stage 1 more than a month prior to being enrolled in Stage 2 will receive a second medical examination to ensure that they still meet subject eligibility criteria.

Long-Term Follow-up

Participants may take part in a long-term follow-up involving re-assessment of their PTSD symptoms and assessing the impact of study participation. The long-term follow-up will be scheduled to occur at least ten months after completing Stage 1 for all participants in the MDMA condition and any in the placebo condition who did not enter Stage 2, and for at least ten months after completion of Stage 2 for all participants who took part in this open-label study continuation. The independent rater will re-administer the CAPS, and participants will complete the NEO, the IES, and a questionnaire concerning experiences since taking part in the study. The questionnaire will include questions about the presence, type and duration of perceived benefits to participating, presence and type of perceived harm from study participation, initiating new psychotherapy, new use of psychiatric medication, and any use of ecstasy after taking part in the study. The CAPS will be administered over the telephone or in person, and the questionnaires will be mailed to participants. Participants will be provided with a return envelope listing the principal investigator's office postal address as both main and return address. The investigators will administer a separate consent for the long-term follow-up to all new participants on the final study visit of Stage 1 or Stage 2, and they will mail consent materials to all previous participants. The long-term follow-up will allow the investigators to assess the longevity of any changes in PTSD symptoms and to see how taking part in the study has affected participants' lives. If there are any placebo

participants who decline to take part in Stage 2, the investigators can also make informal comparisons between those who received MDMA and those who received no MDMA during the study.

Time and Events: M-P1 (63,384) Long-Term Follow-Up				
	V1	V2	V3	V4
	Pre-study	Consent	Questionnaires	CAPS Assessment
	After main study		After consent	After questionnaires
	M. Ballard/Mithoefer	M. Ballard	M. Ballard	Mark
Check contact info	X			
Mail Consent	X			
Consent		X		
Mail Questionnaires		X		
Custom Questionnaires			X	
NEO			X	
IES			X	
CAPS				X

Costs to Participants.

There will be no costs to the study participants. The sponsor will cover all costs of study participation. Charges for treatment of the participant's condition that are unrelated to the research study or any of its procedures will continue to be billed to the health insurance provider of the participant or to the participant him or herself. It is anticipated that there will not be any charges for treatment that is unrelated to the study except in the case of participants who previously received therapy from the principal investigator and who will continue to receive ongoing treatment that is not related to participating in the study.

Treatment and Compensation of Study Related Injury

Treatment of a study-related emergency would first be billed to a participant's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a participant's health insurance. Most study-related emergencies can be treated by the investigators as described under "Monitoring for Toxicity and within the Appendix. If the investigator cannot treat a study-related emergency, then there are contingency plans for the transport of participants to the nearest hospital, East Cooper Medical Center.

Risks to Participants

Risks and Discomforts Associated with Drawing Blood

Blood specimens will be obtained from the subjects during the evaluation and follow-ups as listed above. Temporary discomfort may arise as a result of sampling blood. Participants may experience temporary discomfort at the blood drawing site. There is also a remote possibility of inflammation or infection at the blood drawing site. Blood samples will be used for the most part to determine whether the participant is healthy and can safely take part in the study. Hence the temporary discomfort is outweighed by the need to ensure that participants are healthy, meet all inclusion criteria at screening, and are not experiencing adverse effects after the MDMA or placebo sessions.

Risks and Discomforts Associated with Screening Procedure

Medical data will be collected via history and physical examination, and via measurement of vital signs. Submitting to a full medical examination may be time consuming, and may be distressing or uncomfortable for some. Because medical examinations are part of the screening procedure, they cannot be omitted from the study design.

Psychological and neuropsychological data will be obtained through interviews and neuropsychological testing. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. Because psychiatric interviews and discussion of PTSD symptoms are used during screening, they cannot be avoided. The investigators have experience working with people with PTSD, and they will seek to reduce anxiety and distress during these interviews.

Risks and Discomforts Associated with Non-Experimental and Experimental Psychotherapy

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

Risks and Discomforts Associated with the Experimental Intervention

In doses similar to those proposed for this study, MDMA produces sympathomimetic effects similar to the effects of a moderate dose of methamphetamine or other stimulants (Cami et al. 2000; Grob et al. In Preparation; Grob et al. 1996; Harris et al. 2002; Lester et al. 2000; Liechti et al. 2001a; Tancer et al. 2002; Vollenweider et al. 1998). The

amount of MDMA used in this study is not likely to produce changes in blood pressure or heart rate greater than 40% of resting values. These changes should last no more than six hours. These changes have been well-tolerated by volunteers in previous studies and should not pose large risks to our participants, who have been carefully screened for cardiovascular and related problems. In less than 5% of volunteers, increases in blood pressure were higher. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of participants and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity.

MDMA also may produce mild alterations in perception and altered perception of time (Cami et al. 2000; Vollenweider et al. 1998). Women may be more sensitive to these effects of MDMA (Liechti et al 2001a). Some participants receiving MDMA report experiencing periods of increased anxiety (Harris et al. 2002; Tancer and Johanson 2001; Vollenweider et al. 1998). Psychological distress could arise at any time after the onset of the effects of MDMA, from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress may last for as little as 15 minutes or for as long as 5 hours. In previous Phase I studies, these symptoms have been modest, self-limiting, and responded well to reassurance from investigators. In the proposed study, participants will have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected. During the preparatory sessions, participants will be made aware of the fact that difficult emotions, including grief, rage and fear or panic, may arise during the MDMA sessions and should be understood as presenting an opportunity for addressing and dealing with these traumatic events. If significant anxiety persists more than a few hours after the expected end of the experimental session, contingency plans (described in appendix) include the continued presence of the investigators, support and assistance provided by an individual close to the participant, and the possibility of administering anti-anxiety agents.

Side effects of MDMA are modest and generally have not been associated with serious discomfort by volunteers in previous studies (Cami et al. 2000; Liechti et al 2001a; Tancer 2001; Vollenweider et al. 1998). Decreased appetite, jaw clenching, and dry mouth are commonly reported during peak MDMA effects, while fatigue may be felt up to several days afterward. Less commonly, mild anxiety and depressed mood are reported one and three days after MDMA administration (Harris et al. 2002; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Vollenweider et al. 1998). Some of these effects are very likely to occur, but proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects, so that they will not be unduly troubled by them.

MDMA may produce modest changes in immune functioning, lasting two to three days. A research team in Spain has studied the immunological effects appearing after the administration of one or two doses of 100 mg MDMA (Pacifici et al. 2000; Pacifici et al. 2001). They reported a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-Gamma and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1

cytokines and increase the amount of Th2 cytokines measured in blood. The mechanism of this MDMA-induced immunomodulation is unclear but may involve MDMA-induced glucocorticoid release or sympathomimetic activity. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine (Pacifici et al. 2000; Pacifici et al. 2001). Because of their limited duration, these changes are not likely to have clinical significance beyond a possibly increased risk of the common cold or similar illness for several days. Previous Phase I studies have not reported any indication of increased risk of illness occurring after MDMA administration. Individuals who are positive for HIV or have other immunocompromising diseases will be excluded from the protocol.

MDMA may cause modest changes in cerebral blood flow lasting several weeks after drug exposure. These changes have been hypothesized to be the result of short-term down-regulation of serotonergic receptors controlling cerebral vasodilatation (Reneman et a. 2002; Reneman et al. 2000). MDMA induced decreased regional and global cerebral blood flow (CBF) 10 to 21 days after administration (Chang et al. 2000), as reported in a study of 10 ecstasy users given two separate ascending doses of MDMA at a two-week interval, with comparisons made at baseline and after the administration of both doses. Doses per administration in this study ranged from approximately 17 mg (0.25 mg/kg) to approximately 175 mg (2.5 mg/kg). The authors did not find differences in regional or global CBF when 21 MDMA-experienced volunteers (with a reported 211 ± 340 exposures) were compared to 21 nonusers (data are presented in the same paper), suggesting that effects on CBF do not last indefinitely. There are no known consequences of these changes and neurocognitive performance was not altered in these volunteers.

Serious MDMA toxicity is rare even in uncontrolled settings, considering the millions of users taking ecstasy of unknown identity, potency, and purity (Baggott, 2002; see Investigator's Brochure). Many users routinely consume estimated MDMA doses that are several times higher than those proposed in the current protocol without any apparent toxicity. Under unsupervised and nonmedical conditions, the most common serious adverse event involves hyperthermia, which often appears to be influenced by prolonged physical exertion (dancing) and other unsafe conditions of use, such as high ambient temperature. In addition to hyperthermic syndromes, other rare adverse events include dysphoric responses, hyponatremia, and hepatotoxicity. In the proposed clinical study, volunteers will be carefully monitored for signs and symptoms of these unlikely events. Contingency plans for responding to these events are described in an appendix.

Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth, but the meaning of these findings are in dispute. Women who are able to bear children will be required to use effective contraception during the study and pregnant women will be excluded from participation, with pregnancy tests performed before each drug administration.

MDMA is classified as a Schedule I compound, largely on the basis of its growing popularity at night clubs and parties in the early to mid-1980s. Whether or not MDMA's abuse potential will negatively affect people with PTSD exposed to MDMA when given along with psychotherapy is an open question for which there is no direct data. However, instead of experiencing euphoria, people with PTSD undergoing MDMA-assisted

psychotherapy during the experimental sessions are likely to experience painful and frightening emotions and memories related to the original traumatic incident. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging experimental intervention will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings.

There is no evidence that MDMA-naïve healthy volunteers exposed to MDMA in previous Phase 1 clinical studies have been motivated to seek out and use MDMA in non-medical settings. For example, Liechti et al. (2001) reviewed the effects of MDMA in 54 male and 20 female volunteers who had participated in clinical studies. Liechti and colleagues stated that "none of the participants expressed any interest in taking MDMA as a recreational drug" after participation in an MDMA study.

There is known to be significant comorbidity for substance abuse among individuals with PTSD, though specific data on the relationship between MDMA use and PTSD have not been reported. Currently, there is no definite evidence concerning the causal relations between the two disorders, and it is unclear whether PTSD precipitates substance abuse or whether people with pre-existing substance abuse are at greater risk for PTSD. The most commonly accepted hypothesis for the relationship between PTSD and substance abuse is that of self-medication (Meisler, 1996). Since individuals undergoing the proposed experimental intervention will be encouraged to confront traumatic events during the experimental intervention rather than defending against them or avoiding them, it seems likely that these individuals will subsequently be less inclined to choose to self-medicate through the self-administration of MDMA.

In the currently proposed study, diversion is not an issue because MDMA will only be administered under supervision of a psychiatrist and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

Potential Neurotoxicity Associated with Ecstasy Use

Extensive studies in animals indicate that high or repeated dose MDMA exposure can damage serotonergic axons originating in the dorsal raphe nucleus of the brainstem, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site density (See Baggott and Mendelson 2001; Green et al. 1995; O'Callaghan and Miller 1994 and Chapters 4 and 5 in the Investigator's Brochure). Although some regrowth occurs, seemingly permanent redistribution of axons was noted in a study with squirrel monkeys (Hatzidimitriou et al. 1999). Similar changes can be induced by methamphetamine and some other psychostimulants (Miller and O'Callaghan 1996; Molliver et al. 1990; O'Callaghan and Miller 1994; Sabol et al. 1995; Seiden and Kleven 1989; Seiden and Sabol 1996). There is controversy over the extent to which analogous changes occur in humans. Imaging studies comparing ecstasy users with non-users have found evidence of lower binding to serotonin transporter re-uptake (SERT) sites (McCann et al. 1998; Obrocki et al. 2000; Reneman et al. 2001a; Reneman et al. 2001b; Semple et al. 1999). Because these studies use novel experimental techniques to compare self-identified drug users and non-users, it is not always clear what is being measured or how apparent differences relate to MDMA exposure (Kish 2002). More importantly, there has been no evidence of these changes in clinical studies. Vollenweider and colleagues measured

serotonin transporter density using positron emission tomography (PET) with the same radioligand employed in one of the previous studies [11 C]McN5652 (McCann et al. 1998) before and after a clinical administration of approximately 105-120 mg (1.5-1.7 mg/kg) MDMA (Vollenweider et al. 2001; 2000). Comparisons were made in a pilot study with six MDMA-naïve healthy volunteers, and later in a second study with additional volunteers (n = 8). Vollenweider and colleagues failed to find any lasting differences in scans made before and after MDMA administration. These findings indicate that it is unlikely that MDMA will produce significant serotonergic toxicity at the dosage that will be used in the proposed study.

If long-term serotonergic changes do occur in some humans, it is not known if these changes have clinically significant consequences. Studies of illicit ecstasy users have suggested that repeated MDMA use may be associated with lowered neurocognitive performance, including measures of verbal memory (Bhattachary and Powell 2001; Bolla et al. 1998; Gouzoulis-Mayfrank et al. 2000; McCann et al. 1999; Morgan 1999; Reneman et al. 2000; Rodgers 2000; Zakzanis and Young. 2001a) and executive function (Gouzoulis-Mayfrank et al. 2000; Verkes 2000; Wareing et al. 2000; Zakzanis et al. 2001b). There is continuing controversy over whether these findings reflect pre-existing differences or the effects of other drug use (particularly cannabis). The possible decreases are clinically insignificant, and do not appear to disrupt the lives of most ecstasy users examined in these studies. As is also the case with imaging studies, conclusions drawn from examining regular ecstasy users may be inappropriately applied to the administration of one or two doses of MDMA in a controlled environment. A yet-unpublished study failed to find decreased memory in ecstasy users reporting a lifetime dose of 20 to 40 tablets, with decreased memory function only appearing in ecstasy users reporting a lifetime dose of 80 or more tablets (Gouzoulis-Mayfrank, data presented at the 2001 National Institute on Drug Abuse MDMA Conference). A Phase I study comparing 14 ecstasy users at baseline and again after two separate administrations of MDMA, at doses per administration ranging from 0.25 mg/kg (approximately 17 mg) to 2.5 mg/kg (approximately 175 mg) (combined dose of 0.75-4.75 mg/kg, or approximately 52.5-332.5 mg) in a controlled setting failed to find differences between performance on an extensive battery of neurocognitive tests given at baseline and after MDMA administration (Boone et al. In Preparation, also see Investigator's Brochure). Measures employed in this study included assessments of verbal recall and executive function. It would thus appear that while regular ecstasy use may be related to subtle decline in some areas of cognitive function, administration of MDMA at therapeutic doses does not appear to produce differences in neurocognitive function. Lastly, some recently published studies failed to find reduced memory function in ecstasy users when compared with cannabis user controls (Simon et al. 2002). Based on the above data, and additional data listed in the Investigators Brochure, it appears very unlikely that two doses of 125 mg of MDMA will have any lasting untoward effect on neurological functioning.

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials (McCann et al. 2001). Relying on a commonly used calculation for estimating pharmacological effects across species and data from studies in rats and monkeys, the researchers claim that humans should be even more sensitive to the effects of MDMA than smaller animals with higher metabolisms. However, their use of interspecies scaling may be inappropriate in this case. Interspecies scaling models may not be suited for estimating effects of extensively metabolized drugs, and there is some evidence that calculations using less than three different species are not as accurate as

those using three or more species (Mahmood and Balian 1996). Vollenweider et al. (2001) compare published pharmacokinetic data for humans and rats and conclude that human exposure to MDMA after 125 mg is significantly less than the lowest known consistently neurotoxic MDMA dose in Sprague-Dawley rats, 20 mg/kg, sc, (Battaglia et al. 1988; Commins et al. 1987). At these doses, human MDMA plasma area under the curve (AUC) are approximately 30% of the rat AUC. Similarly, human Cmax are approximately 10% of rat Cmax. The same research team that has used interspecies scaling to calculate a neurotoxic dose in humans has found no signs of neurotoxicity when 2.5 mg/kg was administered once every two weeks to squirrel monkeys over a period of four months (Vollenweider et al. 1999b, citing personal communication from Ricaurte to Swiss Federal Ethical Committee). Taken together, these findings suggest that the dose of 125 mg MDMA is very unlikely to produce serotonergic neurotoxicity in humans.

We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. Similar conclusions have apparently been drawn by the Food and Drug Administration, which has permitted this research and several Phase I clinical trials by other research groups in the United States. Moreover, a series of letters in the journal Neuropsychopharmacology discussed the risks of neurotoxicity in MDMA studies (Gijsman et al. 1999; Lieberman and Aghajanian 1999; McCann and Ricaurte 2001; Vollenweider et al. 2001; 1999a), leading two of the journal editors to conclude that there is no evidence that the MDMA exposures in the studies of Vollenweider and colleagues (similar to those currently proposed) were neurotoxic (Aghajanian and Lieberman 2001). A team of researchers in Spain have also been permitted to conduct human trials with MDMA in the treatment of PTSD associated with sexual assault (Bouso 2001).

Nevertheless, the risks of neurotoxicity arising from MDMA administration will be discussed with all participants prior to and during the informed consent process. The investigators will monitor each participant for psychological and neurocognitive status throughout the study.

Alternative treatments and procedures:

The alternative to participating in the research study is to decide not to take part in the study. The decision not to participate in this research study will not in any way alter or compromise the care offered to individuals receiving therapy from the investigator or any physician involved in this research study.

The investigators will discuss alternatives to study participation, including other available treatments, with all potential participants.

There are a number of recognized treatments for PTSD. Treatment often includes both psychotherapy and medication. Most commonly recommended psychotherapeutic treatment for PTSD include anxiety management (stress inoculation training), cognitive therapy, exposure therapy and psychoeducation. Psychodynamic psychotherapy and Eye Movement Desensitization and Reprocessing are also used to treat PTSD.

The only drugs that are currently FDA approved for treatment of PTSD are sertraline and paroxetine. Sertraline has been shown to decrease the hyperarousal and avoidance symptoms, but not the re-experiencing symptoms, of PTSD. Paroxetine has been shown to have an effect on all three categories of symptoms in approximately 62 % of patients. Other medications commonly used are other SSRIs, nefazedone, venlafaxine, tricyclic antidepressants, benzodiazepines, buspirone, zolpidem and mood stabilizers.

The alternative to having non-experimental and experimental sessions recorded to video is not to consent to have sessions recorded to video disc. While audiorecording of sessions is included as part of study methods in the informed consent, consent to session videorecording is made on a separate document.

Confidentiality of Records

Every effort will be made to strictly safeguard the confidentiality of all participants. Despite this, privacy cannot be guaranteed. Data collected from each participant will be identified only by the participant's initials on the source document and by a randomly generated numeric code on all secondary documents and databases. Any materials or questionnaires mailed to participants will be sent along with stamped envelopes using the office address of the principal investigator both as main and return address, and questionnaires will only be marked with a newly assigned subject number, and participants will be instructed not to place their name on the questionnaire. The investigators will retain a key associating these new numbers with those assigned to participants upon study enrollment. All measures, records, audio and video recordings will be kept in a locked file drawer in a locked office. Access to measures will be limited to regulatory agencies, researchers assessing the participant for changes in symptoms, and individuals analyzing data. Researchers with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Participants will sign forms for the release of information to any of the individuals who will need to obtain this information. Interested parties might include the prescribing physician or psychiatrist.

Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information. Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. While it is possible that individuals may be identified on audiotape or video recording through means other than their names, restricting access to audiorecordings or video recordings greatly reduces the opportunity for identification.

Risk-Benefits Analysis

While there are a number of available means for the treatment of PTSD, the search for a wider array of potential treatments is crucial. Not all individuals with PTSD respond to the currently available treatments. MDMA-assisted psychotherapy may prove to be yet another treatment option for people with PTSD. If it is found to be safe and efficacious in this population, then a potentially greater number of people will be able to improve their quality of life through the reduction or alleviation of PTSD symptoms.

Our participants will be individuals suffering from PTSD that is refractory to treatment or who are unwilling or unable to attain or tolerate conventional PTSD therapies, and they will receive 10 to 11 non-drug psychotherapy sessions throughout the course of the study, in addition to the two experimental sessions. Hence participants will not be denied an available treatment when taking part in this study. If they are interested in doing so, participants who have yet to undergo other therapies prior to entry into this study may undertake those therapies after study completion. Some participants may be better able to tolerate MDMA-assisted psychotherapy than other psychotherapies. It is possible that, as hypothesized, MDMA-assisted psychotherapy will reduce PTSD symptoms. Since PTSD disrupts all aspects of life, including social and occupational function, even small decreases in symptom severity, frequency or intensity would benefit study participants. If this pilot study demonstrates improvement in PTSD symptoms, then future research may assist in the development of a novel treatment for PTSD.

There is good evidence that administering two doses of 125 mg MDMA in a clinical setting poses a low risk to the subjects. Previous studies examining the effects of MDMA in humans found that it has been well-tolerated, and no lasting toxicity has been reported in clinical trials with MDMA (Cami et al. 2000; Grob et al.; Grob et al. 1996; Lester et al. 2000; Tancer et al. 2001; Vollenweider et al. 1998). There is no evidence for long-term changes in serotonin function or neurocognitive function after a small number of MDMA administrations conducted during a clinical trial (Boone et al., In Preparation; Vollenweider, 2001; 2000). Case reports of therapeutic work carried out before the scheduling of MDMA indicate that MDMA can be safely administered to people reporting symptoms of PTSD (Adamson 1985; Gasser 1994; Greer and Tolbert 1986; Grinspoon and Bakalar 1986). In conclusion, MDMA has been safely administered in numerous Phase I studies of MDMA and in therapeutic settings, and low risks are presented by the administration of a small number of doses of MDMA in a clinical setting.

Reports and anecdotal accounts indicate that, before MDMA was placed in Schedule 1, therapists conducting MDMA-assisted psychotherapy administered an additional dose of approximately one half the size of the initial dose to prolong the therapeutic effects of the drug (Stolaroff 2000), and this procedure was well-tolerated. Participants in an uncontrolled study of MDMA-assisted psychotherapy were offered a supplemental dose of MDMA during the course of therapy (Greer and Tolbert 1986). There is limited formal data concerning the risks associated with the addition of a second smaller dose of MDMA, but studies of the effects of two doses of 100 mg, either administered four or 24 hours apart (Farre et al. 2004; Pacifici et al. 2001) suggest that a smaller supplemental dose would slightly elevate subjective and physiological effects. Prolonging the therapy session is expected to offer the potential benefit of improving PTSD symptoms, since there will be more time to rely on the anxiolytic and insight-fostering effects of MDMA.

The possibility of developing a novel means of reducing or alleviating symptoms in treatment-refractory posttraumatic stress disorder outweigh the low risks of three experimental sessions in a controlled laboratory setting, each administering 125 mg doses of MDMA with supplemental doses of 62.5 mg after 2 to 2.5 hours.

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Appendix A: Procedures for Treating Serious Adverse Events

Description of potential adverse events and procedures described to address these unlikely events are presented in order of relative likelihood. Contingency plans for responding to these events were all negotiated with and approved by the FDA, and are described below.

Hypertension

Thus far, hypertension is the only adverse event to have occurred after the administration of MDMA in a controlled, laboratory setting (Grob et al. In preparation; Mas et al. 1999; Vollenweider et al. 1998). Typical physiological effects of MDMA include modest elevations in blood pressure and heart rate, with blood pressure and heart rate returning to normal five hours after drug administration. Clinically significant elevation in systolic blood pressure (30 mm Hg above baseline) has been recorded in less than 5% of volunteers across all human trials conducted so far. Clinically significant increases in systolic blood pressure have lasted for up to two hours and have returned to normal without any intervention. Clinically-significant elevation in blood pressure and heart rate usually begins 30 minutes to an hour after drug administration, and has lasted from 20 minutes to 2 hours, with blood pressure and heart rate returning to normal within approximately five hours after drug administration. None of the cases of elevated blood pressure have required medical intervention.

Individuals with evidence of cardiovascular disorders, including hypertension, will be excluded from study participation. Blood pressure and pulse will be measured at the outset of each MDMA or placebo session, then once every 15 minutes for the first 6 hours, and then every 30 minutes for the next 3 hours. If at any time the blood pressure exceeds 160 systolic or 110 diastolic or the pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. During this time, the physician-investigator will continually evaluate the participant for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular or neurologic emergency. If needed, additional care will also be provided by the board-certified emergency room physician and licensed emergency room nurse who will be on standby in the next room. The investigator will make a clinical judgment about whether additional monitoring or treatment is required. If a participant exhibits systolic > 220 or diastolic > 120, he or she will be considered to be in hypertensive crisis, and will receive immediate treatment to lower blood pressure. Reasons for transport to the intensive care unit (ICU) would include, but not be limited to, severe headache in the setting of hypertension, or angina or neurologic deficits regardless of blood pressure. A crash cart will be immediately available and will contain nitroprusside and other antihypertensives in addition to the usual resuscitation drugs and equipment. This will allow treatment to be instituted without transferring the participant if that should become necessary. The physician-investigator may, at any time, make a clinical judgment to transfer the participant to the ICU in the nearest local hospital for further observation and care.

Any participant who, during the first MDMA session, experiences sustained blood pressure of > 220 systolic or > 120 diastolic or heart rate > 75% predicted maximum will not be given a second experimental session.

Psychological distress

Reports of MDMA-assisted psychotherapy conducted prior to the scheduling of MDMA indicate that some people receiving MDMA in a therapeutic context experienced periods of increased anxiety and even panic. In the proposed study, participants will have the intention of confronting and working on their traumatic experiences and accepting and working through difficult and painful emotions. Hence, signs of psychological distress, panic or other unpleasant psychological reactions are possible. Psychological distress could arise at any time after the onset of the effects of MDMA until the last effects have dissipated (approximately 3 to 5 hours after drug administration), with anxiety or distress potentially lasting for as little as 15 minutes to as long as 5 hours.

The potential for destabilizing psychological distress will be minimized by excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders), by preparing people before the experimental session, by creating an atmosphere of trust during the experimental session, by close monitoring, by daily contact with subjects for the period of a week after the experimental session, and by providing non-drug integrative psychotherapy sessions. Subjects will remain in the offices of the principal investigator for the evening and night of each experimental session. The clinic will be staffed by a trained attendant (an RN) to respond to the needs of the subject. The attendant will be instructed to contact Dr. Mithoefer upon request or at the appearance of signs of a potential adverse event. The overnight stay in a private room in Dr. Mithoefer's clinic and the presence of the attendant should further reduce psychological distress.

People diagnosed with bipolar affective disorder – 1 or with psychotic disorders will not be enrolled in the proposed study.

During the preparatory sessions, participants will be made aware of the fact that difficult emotions, including grief, rage and fear or panic, may arise during experimental sessions. Every effort will be made to help participants resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the session, including empathic listening on the part of the investigators and performance of diaphragmatic breathing by participants.

If, by the end of the 6 to 8 hour experimental session, the participant is still severely agitated or experiencing great psychological distress, the following measures will be taken:

- If a subject is anxious, agitated, in danger of any self harm or is suicidal at the end of the MDMA/placebo session, the investigators will remain with the subject for at least two more hours. During this time, the investigators will employ affect management techniques described in the manual, will talk with the subject to help him or her gain cognitive perspective of their experiences, and will help them implement the self soothing and stress inoculation techniques they 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 investigators will be available to stay with the subject for at least two additional 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 subject until the time of his or her appointment with investigators the next day. The investigators 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

Participants hospitalized after a severe panic reaction will be suspended from study participation until after recovery or stabilization, at which time the investigator will carefully evaluate the subject's emotional status. If this response occurs during the first experimental session, the investigator may elect to forego the second administration and drop the subject from the study. This decision will be made after discussion with the data safety monitoring committee and the submission of a report to the IRB and the FDA.

For those subjects engaged in an on-going therapeutic relationship, we will actively involve their outside therapists in the management of any psychiatric complications of treatment.

In the event of a participant's experiencing severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an MDMA session, the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication." If a participant should become psychotic or suicidal, arrangements will be made for him or her to be admitted to the nearest inpatient psychiatric facility of their choice. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

Angina or Myocardial infarction

If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored as described above. He or she will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the participant has had an acute myocardial infarction (AMI), he or she will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in individuals who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have EKG evidence of AMI (J Am Coll Cardiol 34:890, 1999).

Stroke

If any participant has neurologic deficits, whether or not they are associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored as

described above. He or she will be transported to the hospital for a head CT scan and further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the 3 hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines (Neurology 47:835, 1996).

Hyponatremia

Hyponatremia (low blood sodium or high blood water) has occurred after use of ecstasy in uncontrolled settings, perhaps as a result of MDMA effects and user behavior (drinking excessive water in order to stave off dehydration) (Henry and Rella 2001). A modest dose of MDMA (47.5 mg) has been demonstrated to induce arginine vasopressin (AVP) release in humans (Forsling et al. 2001). Researchers and therapists have not generally monitored for hyponatremia after MDMA administration. However, hyponatremia has not been reported either in case reports of MDMA-assisted therapy conducted before the scheduling of MDMA or in recently conducted clinical trials.

History of hyponatremia or detection of hyponatremia on initial physical examination will be cause for exclusion from the proposed study. Participants will be given electrolyte solutions such as Gatorade instead of water in order to decrease the likelihood of dilutional hyponatremia. They will not be allowed to drink more than 3 L. of fluids, and fluid intake will be appropriately spread out across the session. If there are any signs or symptoms of hyponatremia, a stat serum sodium will be drawn and fluids will be withheld until the results are obtained. If the serum sodium is less than 125mEq/L, serum and urine osmolality and sodium will be measured, and the subject will be transported to the East Cooper Medical Center, where further intervention can be provided.

Hyperthermia

Cases of hyperthermia in ecstasy users are probably due in large part to an interaction between drug effects, high ambient temperature found at some dance events and prolonged or vigorous exercise (Henry and Rella 2001). No cases of hyperthermia have been reported in studies wherein MDMA was administered to humans in a controlled environment. Hyperthermia is unlikely to arise in the proposed study because participants will not be exercising and will be in an environment with controlled ambient temperature, which will be kept comfortably cool.

Body temperature will be taken every 60 to 90 minutes throughout each experimental session. If temperature rises more than 1° C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the subject. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, ice packs will be used, blood will be drawn for stat CBC, electrolytes, BUN, creatinine, glucose, CPK, PT, PTT, platelets and liver enzymes, and urine will be collected for urinalysis. If there are significant abnormalities in these tests, if the temperature continues to rise, or if an elevated temperature is associated with delirium or muscle rigidity the participant will be transferred to the ICU at the East Cooper Medical Center.

If, during the first MDMA session, a participant's temperature rises more than 1 ° C. and does not rapidly come down after the above adjustments have been made in blankets,

clothing, ambient temperature and ventilation, then that participant will not be given a second experimental session.

In order to avoid dehydration, participants will be encouraged to drink at least 750 - 1500 ml. of Gatorade or a similar fluid during the session depending on their size, level of activity and body temperature.

Hepatotoxicity

Cases of hepatotoxicity have been reported in ecstasy users, and in vitro studies show that MDMA can impair liver cell viability, with effects possibly exacerbated by hyperthermia (Carvalho et al, 1999), but their results suggest that this is very unlikely to occur in the proposed clinical study. The peak liver exposure to MDMA in the proposed clinical study should be approximately one-eleventh the concentration shown to impair cell viability in these in vitro studies. Hepatotoxicity has not been reported to occur in any of the clinical studies where MDMA was administered to research participants.

Liver enzymes will be measured four days after the second experimental session as a means of monitoring for any signs of potential hepatotoxicity. Any participant who shows abnormalities on any of the liver enzyme determinations will receive further evaluation and follow-up by a gastroenterologist.

Reproductive/Developmental Toxicity

One of two studies of polydrug-using ecstasy users found a possibly increased incidence of developmental abnormalities when pregnant women used illicit drugs including ecstasy (McElhatton et al. 1999). There is some contention as to whether the developmental abnormalities reported in the study conducted by McElhatton and colleagues are, in fact, the result of ecstasy consumption. Pregnant women will be excluded from participation in the proposed study and urine pregnancy tests will be performed before each drug administration.

Appendix B: Procedures used for Audio and Video Recording

Recording to video will be done with two unobtrusive cameras operated remotely by the investigators, already present as co-therapists for the experimental and non-drug psychotherapy sessions. One camera will be adjusted to capture a fairly tight shot of the subject, including full-face shots and partial or full body shots. The other will capture a wider view including the subject and the two investigators. Remote operation will include stopping and starting recording, as with a foot-operated switch or pedal. Two copies of the video tapes will be made routinely, one to be stored by the investigators, and the other by the sponsor. Both will be kept in locked cabinets in secure locations. A third video tape copy will be made for any subject who requests it.

Full names and addresses are unlikely to appear on the video or audio tapes. However, if they do, they will be edited out of the recording before the tape is seen by anyone other than the study participant and the investigators present at the session. Facial images will not be removed from the copy of the video recording to be viewed by the sponsor or investigators for review of the therapeutic process and for manual development. However face shots will be obscured on any tapes used for training purposes unless the subject gives his or her written permission (via " Video and Audio Use Permission IC") to retain face shots.

Audio recording of experimental and non-drug psychotherapy sessions will be done using a laptop computer controlled by one of the investigators, with control allowing him to stop or start recording. The recordings will be written on an external hard drive connected to the laptop, not onto the laptop hard drive itself. The external hard drive will be kept in a locked office. The recordings will then be burned onto CDs in the investigators office. One copy will be stored by the investigators in a locked cabinet, another copy will be sent to the sponsor if requested and will also be stored in a locked cabinet at the location of the sponsor. During experimental sessions, but not during non-drug psychotherapy sessions, an additional audio recording will be made with a portable cassette deck. The purpose of this is to enable the participants to have a cassette recording for themselves at the end of each experimental session, rather than having to wait until the CDs are made by the investigators.

The participants will be informed on the consent document that they have the right to require audio and/or video taping to be stopped at any time and for any existing audio or video recordings to be erased.

At the end of the study, participants will be asked to complete and sign a video recording permission form regarding whether or not they will allow people in sponsor's training program for teaching MDMA-assisted therapy to view video recordings of their session, with our without full facial images.