

Phase II dose-response pilot study of \pm 3,4-methylenedioxymethamphetamine (MDMA)-
assisted psychotherapy in subjects with anxiety associated with advanced-stage cancer.

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Introductory Statement and General Investigational Plan

This protocol is for a randomized, dose-response, Phase II pilot study of (\pm)-3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in twelve subjects with anxiety related to advanced-stage cancer. Subjects will have less than a year of estimated life expectancy and will either not have adequately responded to anxiolytic treatments or will have refused to take anxiolytic medications. The study is being conducted in order to develop our treatment method and to gather preliminary evidence about whether this treatment may be safe and efficacious in this population.

Eight of twelve participants will be assigned to the Experimental Intervention dose condition, and four of twelve will be assigned to the Low Dose condition. Participants enrolled in the study will receive two sessions of MDMA-assisted psychotherapy separated by a two to three week interval, and they will be assessed for up to two months after the second experimental (MDMA) session. Anxiety, quality of life, life function, and pain will all be assessed regularly for the duration of this study. It is expected to take around one year to complete this study.

MDMA is a ring-substituted phenylisopropylamine derivative invented by the E. Merck of Darmstadt, Germany pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the hallucinogen mescaline. It has the chemical name N,-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder and will be administered orally in capsule form (see also FDA Drug Master File 6293). Some investigators have categorized MDMA as belonging to a novel drug class, the “entactogens” (Greer and Tolbert 1998; Nichols and Oberlender 1990; Shulgin 1990). This term refers to MDMA and similar substances possessing a unique set of pharmacological and psychological effects, including increased feelings of rapport with others, increased sensitivity to emotions and increased insights about the self, especially in the context of interpersonal relationships. These effects make MDMA an attractive adjunct in psychotherapy.

Prior to placement into Schedule I, MDMA was used in combination with psychotherapy in the treatment of neuroses, relationship problems, and PTSD (Adamson 1985; Greer and Tolbert 1998; Metzner and Adamson 2001; d’Otalora 2001). It was also used in the treatment of some individuals with chronic pain (Holland 2001; Greer and Tolbert 1998) and in individuals with advanced cancer (Holland 2001; Stevens 2000; Stevens 1999; Stevens 1997). Case reports and narrative accounts of MDMA-assisted therapy indicate that the treatment was often successful (Adamson 1985; Gasser 1994; Greer and Tolbert 1998; Metzner and Adamson 2001; Stolaroff 1997; Widmer 1998). A discussion of MDMA-assisted psychotherapy and a discussion of several case studies appeared in a peer-reviewed journal (Greer and Tolbert 1998).

This pilot study is part of a program of research to evaluate and develop procedures for using MDMA as an adjunct in psychotherapy. This program of research will include studies intended to further develop and standardize MDMA-assisted psychotherapy in

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people with posttraumatic stress disorder (PTSD), anxiety related to a diagnosis of advanced-stage cancer or other terminal illnesses, and potentially other patient populations. If it is found that MDMA-assisted psychotherapy seems safe and efficacious in one or more of the patient populations studied, then MAPS will seek to conduct Phase III studies of MDMA-assisted psychotherapy in larger populations. This is part of a plan to develop MDMA into a prescription medication.

In a teleconference meeting conducted on June 24, 1999, Dr. Cynthia McCormick, Director of the Division of Anesthesia, Critical Care and Addiction Drug Products, stated that the FDA supported a proof of principle study of MDMA-assisted psychotherapy in people with cancer (Memorandum of Telecon Meeting Minutes, July 23, 1999). The meeting was conducted in relation to a study proposed in 1999 by Dr. Charles Grob of UCLA-Harbor Medical Center. Dr. Grob has subsequently obtained FDA permission for his on-going study of psilocybin-assisted psychotherapy in subjects with anxiety associated with cancer.

If data collected from the proposed study of MDMA-assisted psychotherapy in people with advanced-stage cancer indicates that the experimental intervention shows promise of meaningful improvements or significant benefits and can be administered with an acceptable risk/benefit ratio, we will design a second pilot study. This second pilot study will be conducted with a larger sample to increase the statistical power of our findings. In addition, the second pilot study will be used to further refine and standardize MDMA-assisted psychotherapy in these patients. The second study will also aid the further development of an operationalized treatment manual that can be used to evaluate investigator adherence to the principles and practices of MDMA-assisted psychotherapy.

If the results of these pilot studies in people with cancer-related anxiety produce favorable results, the data gathered from these studies will be used to inform the design of two large (N = at least 280) multi-site Phase III studies. MAPS' Clinical Plan (Doblin 2002) estimates that this process will require at least 5 years and will involve at least 600 subjects.

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The Investigator's Brochure

Volume 1 of the Investigator's Brochure has already been submitted to FDA on October 1, 2001, as part of the initial IND application #63,384 for Dr. Mithoefer's MAPS-sponsored pilot study of MDMA-assisted psychotherapy in subjects with chronic posttraumatic stress disorder (PTSD).

Update #1 of the Investigator's Brochure, dated January 20, 2003, and Update #2 of the Investigator's Brochure, dated July 16, 2004, are being submitted as part of this application for Dr. Halpern's MAPS-sponsored pilot study of MDMA-assisted psychotherapy in subjects with anxiety related to a diagnosis of advanced-stage cancer.

The Protocol

This protocol is for a randomized, double-blind dose-response study of MDMA-assisted psychotherapy in people experiencing anxiety as a result of diagnosis with advanced-stage cancer. The study is intended to investigate the safety of MDMA-assisted psychotherapy in these subjects. The study will also measure anxiety, quality of life, and pain in order to determine whether a psychoactive dose of MDMA and/or a minimally active dose, will reduce anxiety, improve quality of life, reduce use of anxiety and pain medications, and increase life functioning.

Study Objectives

The proposed study is primarily intended for two purposes. The first is to explore whether MDMA-assisted psychotherapy can safely be administered to cancer patients with a prognosis of less than 12 months who suffer from anxiety related to the advanced-stage cancer diagnosis who have either failed to respond adequately, if at all, to previous medications for anxiety or who have refused anxiolytic medications. The second purpose is to determine whether this therapy will produce improvements in symptoms of anxiety. Anxiety will be assessed prior to any intervention, immediately after the experimental intervention sessions, at a follow-up evaluation conducted two months after the second experimental session, and in review of a Daily Diary tracking use of anxiolytic and pain management medications. The Spielberger State Trait Anxiety Inventory (STAI; see below under “Measures”) will serve as a primary outcome measure of anxiety. Participants must have a score of 40 or higher on the STAI in order to be enrolled in the study. Improvement will be indicated by lower scores on established outcome measures of anxiety symptoms (STAI, (the primary outcome measure for anxiety), HAM-A, and SCL-90-R) (see Table 3 for the key to abbreviated test names), and reduced use of anxiolytic medications.

A secondary aim of this proposed study is to evaluate whether the experimental intervention translates into meaningful improvements in quality of life. Clinician and participant-rated measures on quality of life will be administered and assessed throughout the study (see Table 1 for the timeline). The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EORTC-QLQ-C30 will serve as a primary outcome measure of quality of life. Additional measures assessing quality of life include hopelessness (BHS), suicidal ideation (SAHD), spiritual well-being (FACIT-Sp), self-expansiveness (SELF), depression (HAM-D and SCL-90-R), symptom prevalence and frequency and associated distress (MSAS), physical performance (KPRS), reductions in extent or intensity of experienced pain and resultant use of pain-relieving medications (VAPS, Daily Diary, and MSAS). (See Table 3 for more details on measures.)

The specific hypotheses to be tested by the proposed study are:

1. MDMA can be administered to participants with advanced-stage cancer without serious adverse events.

2. Participants receiving MDMA-assisted psychotherapy will experience dose-dependent decreases in signs and symptoms of anxiety after each experimental session and at two months after the second MDMA session, as measured by the clinician-rated STAI, HAM-A, and the SCL-90-R anxiety-assessing components.
3. Participants receiving MDMA-assisted psychotherapy will experience dose-dependent decreases in use of PRN anxiolytic medications (for example, benzodiazepines) for treatment of symptoms of anxiety, as indicated by review of anxiolytic medication usage from the participant's Daily Diary.
4. Participants receiving MDMA-assisted psychotherapy will experience dose-dependent improvements in quality of life extending to the final follow-up two months after the second MDMA session, as measured by the BHS, EORTC QLQ-C30, FACIT-Sp, MSAS, KPRS, portions of the SCL-90-R, and the SELF. Participant's Daily Diary and VAPS will also provide data that measure potential improvement in quality of life.
5. Participants receiving MDMA-assisted psychotherapy will experience dose-dependent reductions in pain that will last for at least the duration of the study, as measured by the VAPS and through review of pain-control medication usage in the participant's Daily Diary, with dose and/or frequency of use expected to decrease after MDMA-assisted psychotherapy.

Background and Significance

As described above in the Introductory Statement to this protocol and in IND #63,384, MDMA is a ring-substituted phenylisopropylamine derivative with a unique profile of psychopharmacological effects that make it well-suited as an adjunct to intensive psychotherapy. MDMA has been hypothesized to represent a new class of psychoactive agents, called "entactogens" (Nichols 1986; Nichols and Oberlender 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 Schedule I 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; Greer and Tolbert 1986; Grinspoon and Bakalar 1986; Metzner and Adamson 2001; Stolaroff 1997; Widmer 1997). Although no well-controlled trials were conducted, these therapists concluded that MDMA could safely be administered in an outpatient setting and was clinically useful in treating various psychiatric conditions, including anxiety associated with a diagnosis of advanced cancer. More recently, placebo-controlled clinical trials have confirmed reports from these therapists that MDMA produces an easily-controlled, time-limited alteration of emotion characterized primarily by euphoria, increased well-being, sociability, self-confidence, and extroversion (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001a; Tancer and Johanson 2001; Vollenweider et al. 1998).

Anxiety, depression, chronic pain, and unresolved family issues can become serious physical and mental health problems for individuals living with a terminal illness. End-of-life problems, including pain management, are increasingly understood by caregivers and the public as significant public health concerns (Potter et al. 2003; Randall-David et al. 2003; Shvartzman et al. 2003). Efforts to improve the quality of life for these individuals are clearly a public health priority. Recent efforts to devise more effective medication management for pain control (MacPherson 2002; Thomas and von Gunten 2003), improve family communication and support (Wells et al. 2003), and to diagnose and treat psychiatric conditions that may emerge after diagnosis are all examples of improving care for the terminally ill. The frustration experienced by people with terminal illness with respect to limited treatment options, inadequate pain control, fears of eventual loss of autonomy, fear of stigma associated with receiving psychological counseling, and resentment about dependence on psychopharmacological agents has left some of these individuals with overwhelming suffering in their remaining days of life. These are some of the problematic issues that also underscore the continued drive for legislation supporting physician-assisted suicide. The assisted suicide law in Oregon (the “Oregon Death with Dignity Act;” Oregon Revised Statute § 127.800-897; www.ohd.hr.state.or.us/chs/pas/pas.cfm), a 1994 voter initiative, allows adults who are terminally ill to make requests for assistance in their suicide from their physicians: 171 individuals have ended their life through this mechanism since the program commenced in 1997. This Oregon initiative indicates that approved treatments and supports (including hospice service) clearly fail to meet the needs of some terminally ill individuals. The scientific investigation of more effective treatments and a wider array of treatments is of substantial public health importance.

Pharmacotherapy and psychotherapy are two interventions employed towards reducing the symptoms of anxiety experienced by those with a medical condition that has a poor prognosis for survival. Developing drugs and psychotherapeutic treatments that can aid people with terminal illnesses in revising their assessment and management of stressors that promote the expression of anxiety, panic, and other symptoms of an anxiety disorder may be one means of broadening and improving upon the array of effective treatment options available as well as further alleviating some of the suffering of individuals who experience inadequate relief from standard treatment measures. In their recent report, McClain et al. (2003) support developing additional palliative care interventions to improve the well-being of people with advanced-stage cancer by “... keeping psychological distress of patients who are facing death to a minimum. What is less clear, however, is whether interventions exist that can help raise a terminally ill individual’s sense of spiritual well-being.” 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 anxiety associated with advanced-stage cancer with MDMA-assisted therapy, and on the basis of its reported entactogenic effects (Greer and Tolbert 1998; Holland 2001), we hypothesize that psychotherapy conducted in combination with MDMA will produce symptomatic improvement in patients with advanced-stage cancer.

Moreover, resultant decreased use of anxiolytic agents may better preserve cognition and sensorium, and therefore could significantly improve the individual's quality of life. Chronic use of benzodiazepines for the treatment of anxiety, for example, induces side-effects of compromised sleep architecture, memory difficulties, a plethora of other cognitive impairments, and general lethargy.

The subject population was selected in part because patients with advanced-stage cancer can fail to obtain satisfactory relief from currently available treatments. Furthermore patient and therapist reports of MDMA-assisted psychotherapy conducted prior to the placement of MDMA into Schedule I are suggestive of therapeutic benefits not achievable through other interventions. The qualities that have been associated with MDMA-assisted psychotherapy in anecdotal reports (i.e. decreased defensiveness, decreased stress, and enhanced alliances between subject and therapist, or between the subject and other relatives present) may be particularly useful in the treatment of anxiogenic cognitions, behaviors, and resultant emotions associated with terminal illness. Anxiety disorders involve prominent fear responses including panic attack. In a structured psychotherapeutic environment, review of anxiogenic issues and fears (including the fear of death) affords the opportunity to reduce or eliminate symptoms of anxiety both during the therapy session as well as after. Early clinical experience with MDMA is consistent with the hypothesis that MDMA can increase the therapeutic effectiveness of psychotherapy for people with terminal illnesses. The combination of anxiolysis (reduction in fear and anxiety), euphoria, feelings of interpersonal closeness, and facilitated recall for past events may maximize or amplify the benefits of psychotherapeutic interventions.

Previous Clinical Experiences with MDMA-Assisted Therapy

Prior to placement into Schedule I, MDMA was used in combination with psychotherapy in the treatment of neuroses, relationship problems, and PTSD (Adamson 1985; Greer and Tolbert 1998; Metzner and Adamson 2001; d'Otalora 2001). It was also used in the treatment of some individuals with chronic pain (Holland 2001; Greer and Tolbert 1998) and in individuals with advanced cancer (Holland 2001; Stevens 1997; Stevens 1999; Stevens 2000). Case reports and narrative accounts of MDMA-assisted therapy indicate that the treatment was often successful (Adamson 1985; Gasser 1994; Greer and Tolbert 1998; Metzner and Adamson 2001; Stolaroff 1997; Widmer 1998). A discussion of MDMA-assisted psychotherapy and a discussion of several case studies appeared in a peer-reviewed journal (Greer and Tolbert 1998).

In a psychotherapeutic context, MDMA was reported to produce a lowering of defenses and greater ability to think about and reflect on distressing thoughts and feelings (Naranjo 2001; Greer and Tolbert 2001; Greer and Tolbert 1998; Metzner and Adamson 2001). When spending time with loved ones, individuals who took MDMA in therapeutic contexts often spent time discussing painful or emotionally sensitive topics, such as the impending death of a loved one in the advanced stages of cancer (Stevens 1997; Stevens 1999; Stevens 2000). Reduction in pain was often reported (Greer and Tolbert 1998; Holland 2001; Stevens 1997; Stevens 1999; Stevens 2000). In an uncontrolled study of

MDMA-assisted therapy (described below), couples or groups undergoing MDMA-assisted therapy reported increased intimacy and closeness to others (Greer and Tolbert 1986).

Individuals with PTSD sometimes vividly recalled or re-experienced parts of traumatic events (d'Otalora 2001), sometimes experiencing great distress as they did so, but they were able to return to the state of reduced fear and trust induced by MDMA. While therapeutic contexts often differed across practitioners (compare Naranjo 2001 with Metzner and Adamson 2001), all practitioners used largely client-centered therapies aimed at fostering openness to the emotional and cognitive (insight and recall-related) effects of MDMA.

Greer and Tolbert's (1986) uncontrolled, non-blinded study of MDMA in a therapeutic context found that most of the 29 individuals with mild to moderate psychological difficulties reported obtaining at least some lasting benefits after MDMA-assisted therapy (Greer and Tolbert 1986). During MDMA-assisted therapy, nearly all participants described experiencing both positive and undesirable effects. Positive effects included increased closeness and positive changes in attitude, and undesirable effects included self-dissatisfaction and mild depression. Written follow-up questionnaires, completed two months to two years after the therapy session, found that many participants continued to experience positive life changes, including changes in attitudes and beliefs, strengthened interpersonal relationships, and decreased non-medical or habitual substance use. Given the lack of appropriate controls and unblinded study design, one cannot exclude the possibility that some factor other than MDMA produced these improvements, but the study does demonstrate that individuals with mild to moderate psychological disorders can safely undergo MDMA-assisted therapy without deterioration in mental health, and that they were more likely to have improved quality of life afterwards.

Controlled studies assessing the subjective effects of MDMA in a non-therapeutic context reported that MDMA produced an increase in positive mood and positively experienced alteration in consciousness, anxiety relating to fears of losing control, and alterations in perception (Cami et al. 2000; Grob et al. 1996; Harris et al. 2002; Liechti et al. 2001a; Tancer et al. 2003; Vollenweider et al. 1998). Effects appeared to be similar in individuals who had past experience with ecstasy (e.g. Cami et al. 2000; Grob et al. 1996; Harris et al. 2002; Tancer et al. 2003) and in drug-naïve samples (e.g. Liechti et al. 2001a; Vollenweider et al. 1998). Though MDMA increased both positive and negative mood, participants in these studies tolerated these effects well. These effects are somewhat comparable to effects reported in therapeutic contexts. However, it is expected that individuals undergoing MDMA-assisted therapy may be liable to experience more intense dysphoria, especially in relation to the condition or disorder with which they are grappling. Conversely, individuals struggling with anxiety, grief, fear, or rage, whether as a result of advanced-stage cancer or from a traumatic event, may also reach a greater sense of compassion for the self and others in settings constructed to foster these feelings. It should be noted, however, that the therapy proposed for this study in the experimental MDMA-assisted treatment sessions will have the intention of confronting and working through difficult emotions. Hence, signs of psychological distress 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, fear, or panic, may arise during the experimental sessions and should be understood as an opportunity for addressing and dealing with these events (see the Treatment Manual; Ruse et al. 2004). Hence temporary intensification of anxiety, if it occurs, will be considered an important element of the therapeutic process that may contribute to resolution or improved acceptance of anxiety and other intense emotions associated with the participant's anxiety disorder.

In the current study, MDMA given in combination with psychotherapy within a comfortable setting is expected to reduce anxiety through confronting or accepting fears and concerns relating to deterioration in health and impending death. Anxiety is expected to decrease both acutely during the experimental session and on subsequent assessments performed one week after each experimental session and two months after the second session of MDMA-assisted therapy. It is expected that MDMA will be well-tolerated in this population. Quality of life is expected to increase after a fully active dose of MDMA as a result of reduced anxiety relating to the cancer diagnosis and increased self-acceptance. Participants are expected to use anxiolytic medication less often during the course of the study, and they will experience less pain at least immediately after a fully active dose of MDMA.

Investigators and Institutional Review Board

Principal Investigator

John H. Halpern, M.D., is Associate Director of Drug Abuse Research at McLean Hospital, Belmont MA. He is a licensed physician and will be re-certified in Advanced Cardiac Life Support (ACLS) prior to the first experimental session. Dr. Halpern has completed a multi-year research fellowship at McLean Hospital's Alcohol and Drug Abuse Research Center (ADARC), and he is Associate Director of Substance Abuse Research at the Biological Psychiatry Laboratory. Dr. Halpern is Board Certified in General Psychiatry (ABPN). For more information, please see the CV submitted along with this protocol in the Appendix. Dr. Halpern will administer the informed consent and perform psychiatric screening for all prospective participants. He will conduct all non-drug psychotherapy sessions along with Dr. Naidoo, and he and Dr. Naidoo will conduct both drug-assisted psychotherapy sessions. He will assess vital signs during experimental sessions, following the instructions of the internist. Dr. Halpern will administer outcome measures to participants, and he will store and computerize all data. As Principal Investigator, Dr. Halpern is responsible for all administrative and general issues related to conducting this study.

Additional Investigators

Todd D. Shuster M.D. is a clinical oncologist at the Department of Medical Oncology at the Lahey Clinic Medical Center in Burlington, MA. Dr. Shuster is Board Certified in Internal Medicine, Oncology, and Hematology, and has maintained a fulltime medical

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oncology practice since completion of a Research Fellowship in Hematology/Oncology at the Beth Israel Hospital of Boston in 1995. Dr. Shuster will perform oncology assessments and will medically pre-screen his patients with advanced-stage cancer who are interested in study participation. He will administer pre-screening informed consent, review relevant information such as medical history, and will perform the initial medical examination and the examination occurring during the course of the study. Dr. Shuster will monitor all ongoing study data to ensure that subjects remain qualified for study participation.

Umadevi Naidoo is a psychiatrist working at the Erich Lindeman Mental Health Center. Dr. Naidoo is a board-eligible psychiatrist who has completed a Fellowship in Psychosocial Oncology at the Dana Farber Cancer Institute. She will conduct non-drug and experimental (drug-assisted) therapy sessions with the principal investigator.

Arthur Siegel is Chief of Internal Medicine at McLean Hospital and is Board Certified in Internal Medicine. Dr. Siegel will examine and discuss the medical records and other relevant medical information of each prospective participant to ensure that they meet all criteria for study participation. He will act as on-site medical supervisor during the experimental sessions, remaining on-call and on-grounds during each experimental session, reachable through emergency radio if needed in the case of a medical emergency. Dr. Siegel will monitor all ongoing study data to ensure that subjects remain qualified for study participation.

Researcher Addresses

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Arthur J. Siegel, M.D.
Director, Internal Medicine
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Institutional Review Boards

This protocol has been reviewed and approved by the Institutional Review Board of McLean Hospital, a psychiatric hospital affiliated with Harvard Medical School. The IRB at McLean Hospital may be reached through the following address:

Peter Paskevich
McLean Hospital Office of Research Administration

The protocol has also been approved by the Institutional Review Board at the Lahey Clinic. The Lahey Clinic IRB may be reached at the following address:

Mary Oster
Director of Research Administration
Office of Research Administration
The Lahey Clinic Medical Center

Subjects

The researchers will enroll twelve men and women diagnosed with advanced-stage cancer and with 12 months or less of expected remaining life who are experiencing diagnosis-associated anxiety. Participants will either be individuals who have failed to respond adequately, if at all, to anxiolytic medications or who refuse anxiolytic medications. Advanced-stage cancer is defined specifically for each cancer, but generally refers to a condition where the cancer is considered incurable or inoperable. Individuals may be men or woman aged 18 or older. Participants will have symptoms of anxiety and/or panic associated with the diagnosis of cancer (as opposed to a history of an anxiety disorder distinct from the diagnosis of cancer) that are clinically significant enough that the subject has been offered and/or prescribed standard medications or psychotherapy for alleviating these symptoms. Participants must have a score of 40 or higher on the Spielberger State Trait Anxiety Inventory (STAI; see below under “Measures.”) The proposed study aims to enroll individuals who do not respond to anxiolytic medication or who refuse to take anxiolytics.

The first twelve participants who meet inclusion criteria without any exclusion criteria, and who are interested in study participation, will be included in the study. Participants will be referred from within the patient population from the group practice of co-investigator oncologist, Dr. Todd Shuster, at the Medical Oncology Department of the Lahey Clinic Medical Center. Any participants who drop out or are excluded between the first and the second experimental intervention sessions will be replaced.

The investigators 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. The investigators will attempt to reach individuals of different ethnic or racial backgrounds in our recruitment efforts.

Inclusion Criteria

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

1. Have a diagnosis of advanced-stage cancer, as defined for the relevant type of cancer, with an oncologist-estimated 12 months or less of remaining life.
2. Meet DSM IV criteria for Anxiety Disorder Due to a General Medical Condition (Diagnosis Code 293.84) as indicated by the SCID and a score of at least 40 on the STAI.
3. Have failed to respond adequately or at all to medication intended to reduce anxiety, or have refused to take anxiolytic medication.
4. Are at least 18 years of age.
5. Are willing to commit to medication dosing, experimental sessions with overnight hospital stay, follow-up sessions, and to complete evaluation instruments (although they may withdraw from the study at any time without cause).
6. Have completed or independently decided to end all direct cancer treatments, such as chemotherapy and radiation, two weeks prior to the first experimental (MDMA) session. If they wish to initiate or resume treatment for cancer at any point prior to the second experimental (MDMA) session, then they will be withdrawn from the study and will be asked to see the co-investigator oncologist for a final physical examination. Participants will not be withdrawn from the study if they initiate or resume treatment after the second experimental (MDMA) session.
7. Are willing to refrain from taking any psychiatric medications during the study period, except for anxiolytic medications taken as needed on days other than the experimental sessions. If they are being treated with antidepressants or are taking anxiolytic medications on a fixed daily regimen at the time they are first evaluated, these potential participants should independently review their use of these medications with their treatment providers. Such drugs must be discontinued long enough before the first MDMA treatment session to avoid the possibility of a drug-drug interaction (the interval will be at least 5 times the particular drug's half-life). Participants will be withdrawn from the study if they wish to start or resume psychiatric medications prior to the final evaluation session.
8. If in ongoing psychotherapy, those recruited into the study may continue to see their outside therapist, provided they sign a release for the investigators to communicate directly with their therapist. Participants should 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 MDMA treatment session.

9. Participants must agree that, for one week preceding each MDMA treatment session:
 - a. They will refrain from taking any herbal supplement (except when judged by the research team to not affect study measures).
 - b. They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
 - c. They will not initiate any new prescription medications (except with prior approval of the research team).
10. Participants must agree to take nothing by mouth except for routine medications and water after 12 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 treatment session. They must agree not to use nicotine for at least 2 hours before and 6 hours after each dose of MDMA. They must agree not to ingest caffeinated beverages until at least 6 hours after each MDMA treatment session. They must agree to not ingest alcohol-containing beverages for at least 1 day before each MDMA treatment session. They will not take any PRN medications on the morning of the MDMA treatment session prior to arrival to the hospital, although routine daily medications for pain control or nausea may be taken provided this use has been reviewed by the research team and is judged not to pose an undue risk to the safety and well-being of the participant. Non-routine PRN medications for treating breakthrough pain that were taken in the 24 hours preceding the MDMA treatment session may result in rescheduling the treatment session to another date, with the decision at the discretion of the investigators after discussion with the participant.

Exclusion Criteria

Individuals will be excluded from study participation if they are:

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
2. Meet DSM-IV criteria for any Dissociative Disorder, Anorexia Nervosa, Bulimia Nervosa, a primary psychotic disorder or affective disorder (other than Anxiety Disorder Due to a General Medical Condition and Simple Phobia).
3. Meeting DSM-IV criteria for abuse of or dependence on any substance (other than caffeine or nicotine) in the past 60 days.
4. Diagnosed with known primary or metastatic cancer of the CNS.
5. Diagnosed with significant, unstable hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder, that in the clinical judgment of the investigators poses too great a potential for side-effects.
6. Have baseline laboratory values indicative of severely compromised hepatic function. Exclusion will occur if total bilirubin is 2.0 mg/dL or greater

- (approximately twice the upper limit of normal) or if the transaminases ALT (SGPT) or AST (SGOT) are 5 times or greater the upper limit of normal. Five times the upper limit of normal for alanine aminotransferase (ALT) and for aspartate aminotransferase (AST) is 175 U/L.
7. Diagnosed with significant peripheral vascular disease, hepatic disease, renal insufficiency, or preexisting or past evidence of hyponatremia.
 8. Diagnosed with hypertension, even if well-controlled with medication. A systolic blood pressure of 140 or greater and/or a diastolic blood pressure of 90 or greater will exclude the potential participant from this study.
 9. Weighing less than 45 kg.
 10. Reporting a history of use of “ecstasy” (illicit drug preparations purported to contain MDMA) at any time within the previous 3 months.
 11. Reasonably judged to present a serious suicide risk or who are likely to require psychiatric hospitalization during the course of the study.
 12. Requiring ongoing concomitant therapy with a psychotropic drug other than PRN as needed anxiolytic medications and pain control medications.
 13. Is unable to fully understand the potential risks and benefits of the study and give informed consent.
 14. Is enrolled as a participant in any other medical research protocol.

Prescreening and Informed Consent

Potential participants will be identified through the oncology practice at the Lahey Clinic Medical Center. Prospective participants will first give written informed consent before undergoing the medical examination and completing the Spielberger State-Trait Anxiety Inventory (STAI). Candidates will have been diagnosed with advanced-stage cancer that is not currently being actively treated with cytotoxic, biologic, hormonal (other than LHRH agonist injections for hormone refractory prostate cancer), or radiation therapy. As part of the screening process (“Day –1” – See Table 1 below), information regarding the type of malignancy, sites of disease spread, prior treatment, and expected prognosis will be collected.

Each prospective candidate’s general medical condition will be assessed in the Medical Oncology Department by Dr. Shuster to determine suitability for study participation. This “pre-study screening” exam (see Table 1 for timeline) will be performed by co-investigator oncologist Dr. Shuster at the Lahey Clinic. Screening will last for up to 30 minutes and will involve gathering information regarding the type of malignancy, sites of disease spread, prior treatment, and expected prognosis. The medical examination will involve the following procedures: general medical history and physical exam, metabolic profile, assessment of serum electrolytes, Dr. Shuster will perform the medical examination. After an individual consents to participate in the study, Dr. Shuster or Dr. Halpern will perform additional medical tests to further establish participant eligibility. These include ECG, thyroid hormone levels and levels of TSH, HIV serology, and urine pregnancy test for females of childbearing potential. Results of HIV serology will be kept confidential, and appropriate referral for counseling will be made if necessary.

As part of the pre-study screening at the Lahey Clinic, prospective candidates will complete the STAI, a commonly used measure of anxiety. If an individual attains a STAI score of 40 or higher and if they meet all study criteria without meeting any exclusionary criteria, then the prospective participant will be provided with the informed consent for review at home, and contact information for reaching Dr. Halpern. If she or he is still interested in taking part in the study, the prospective participant will contact Dr. Halpern via telephone to discuss the study procedure, answer questions about the study and the informed consent, and arrange for an initial visit to take place at appropriate research facilities of or made available to the Biological Psychiatry Laboratory at McLean Hospital, where additional screening and written informed consent will occur. The pre-screening conversation will last 15 to 30 minutes and will be reviewed again at the beginning of the first scheduled meeting (see Table 1 for timeline) at McLean Hospital.

All medical health data – including medical history, physical exam, electrocardiogram (ECG), and laboratory values – will be reviewed by the principal investigator, the co-investigator oncologist, and the co-investigator internist prior to accepting the candidate into the study. All three investigators must agree that all inclusion criteria have been met and that no exclusion criteria are present prior to this acceptance into the study. Any change in health status during the course of the study will necessitate a re-review by these three investigators to ensure that the inclusion/exclusion criteria are being met at least through the second experimental treatment session.

Screening

Each prospective participant will next meet with Dr. Halpern at an appropriate research facility of or made available to the Biological Psychiatry Laboratory at McLean Hospital. This baseline evaluation (“Day 0” on Table 1) is expected to last approximately two to three hours. After face-to-face discussion of the study procedures and alternatives to study participation and any other questions that may arise while reviewing the contents of the informed consent, the potential participant will be given a written quiz on the contents of the informed consent. Wrong answers on this quiz will not disqualify the individual from study participation but will be used as a tool to clarify understanding the contents of the information contained in the informed consent. After obtaining informed-consent and providing a copy to the participant, Dr. Halpern will commence with the baseline evaluation by first administering the SCID, a structured psychiatric interview (First et al. 1997) to provide a DSM-IV diagnosis of Anxiety Disorder Due to a General Medical Condition and to rule out the presence of exclusionary Axis I diagnoses (i.e., substance dependence, psychotic disorder, dissociative disorder, major affective disorder, or eating disorder). Prospective participants will also complete the STAI again to confirm a score \geq 40. Other outcome measures administered at this baseline meeting include observer-rated measures of symptoms of anxiety, depression, hopelessness, and quality of life; subject-rated measures of symptoms and quality of life; and psychiatrist-administered tests of mental status and diagnosis (see Table 1 for schedule and Table 3, in “Measures” for details on measures). Participants will also be instructed on keeping the Daily Diary and measures of daily pain. Specifically, the Daily Diary logs daily use of all medications and need for symptom-specific medications for acute symptoms of anxiety and/or pain. The

Daily Diary will also ask the participant to rate their prior 24 hours of pain each day using the VAPS. Completing the Daily Diary is expected to take six to eight minutes. A urine sample will also be obtained for drug testing. Any remaining medical tests (such as EKG or laboratory tests) that have not been completed at the Lahey Clinic will be collected at this baseline evaluation visit at McLean Hospital. If it is more convenient for the participant to have these laboratory tests performed at the Lahey Clinic, this may be done in coordination with Dr. Shuster, provided all tests have been completed with sufficient time for all elements of the medical assessment to be reviewed by the investigators prior to the first scheduled treatment session day.

Potential participants who do not meet eligibility criteria at this point or who do not wish to participate will be referred for alternate standard treatment.

Methods

The proposed study is a randomized, double-blind dose-response study of MDMA-assisted psychotherapy in people with advanced-stage cancer and diagnosis-related anxiety. Upon enrollment, participants will be randomly assigned to one of two conditions, Low Dose or Experimental Intervention dose (see Table 2). The McLean Hospital Pharmacy will generate and maintain the randomization code and procedure. Four of the twelve participants will be assigned to the Low Dose condition, and eight of twelve participants will be assigned to the Experimental Intervention dose. Condition assignment will be maintained throughout the course of the study, since this study does not employ a crossover design.

Group assignment will be randomized using a table of random numbers generated by and placed on file at the McLean Hospital Pharmacy. The group assignment of each participant will be provided in a sealed envelope to investigators and a copy will be maintained at the McLean Hospital Pharmacy. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, as when pharmacological intervention is necessary, the blind may be broken for an individual participant.

Participants in the Low Dose condition will receive an initial dose of 25 mg MDMA followed 2.5 hours later by a supplemental dose of 12.5 mg on both experimental sessions, for a total of 37.5 mg MDMA on each session. On the first experimental session, participants in the Experimental Intervention condition will receive an initial dose of 83.3 mg MDMA followed 2.5 hours later by 41.7 mg MDMA, for a total of 125 mg overall. On the second experimental session, participants in the Experimental Intervention condition will receive an initial dose of 125 mg MDMA followed 2.5 hours later by a supplemental dose of 62.5 mg, for a total of 187.5 mg. For more details, see "Drugs and Dosage."

The study includes six conventional (non-drug assisted) psychotherapy sessions with Dr. Halpern and Dr. Naidoo, with all sessions lasting one hour, two experimental (MDMA-assisted) sessions, with the second experimental session scheduled two to three weeks

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after the first experimental session (See Table 2 in “Drugs and Dosage” below), and six administrations of outcome measures lasting from 60 to 90 minutes. A participant will have completed the study approximately three and a half months after screening, and two months after the second experimental session.

Timeline

The timeline for participation in the study is outlined below in Table 1. Visits are to be scheduled within the week that the below numbered days fall within.

Table 1. Schedule of Visits Timeline

DAY STUDY MEASURE	-1	0	7	14 S ^a	15	21	28 S ^a	29	35	36	84
Pre-study Screening	x										
Informed Consent		x									
Baseline Evaluation		x									
SCID		x									
SCL-90-R		x									x
SELF		x									x
MMSE		x		x		x	x		x		x
HAM-D		x		x		x	x		x		x
HAM-A		x		x		x	x		x		x
STAI	x	x		x		x	x		x		x
EORTC QLQ-C30		x		x		x	x		x		x
FACIT-Sp		x		x		x	x		x		x
SAHD		x		x		x	x		x		x
BHS		x		x		x	x		x		x
MSAS		x		x		x	x		x	x	x
Psychotherapy			x		x	x		x	x		x
MDMA Treatment Session				x			x				
Metabolic profile	x									x	
Liver FCT	x									x	
Drug Screen		x		x			x				
Medical exam	x									x	
KPRS	x									x	
Daily Diary & VAPS		x	x	x	x	x	x	x	x	x	x
Number of days from first MDMA session				0	1	7	15	22	28	29	70
Conducted at Lahey Clinic	x									x	
Conducted at McLean Hospital ^b		x	x	x	x	x	x	x	x		x

^a “S” indicates study day with experimental treatment session.

^b Day 35 and Day 84 may alternately be performed at the participant’s home if the participant requests doing so because declining health precludes travel to McLean Hospital.

Psychotherapy

All participants will undergo an introductory psychotherapy session prior to the first experimental session, where they will review their cancer-related anxiety and discuss what will occur during the experimental session. Psychotherapy with Dr. Halpern and Dr. Naidoo will also occur on the day after each experimental session, and one week after each experimental session, with the participant and investigators exploring and discussing the events of the experimental session. Participants will also receive a psychotherapy session approximately one week after each experimental session. The final psychotherapy session will occur eight weeks after the second experimental session. (See Table 1). If any additional psychotherapy sessions are conducted, participants will complete outcome measures before that session as well. If the participant's health precludes traveling to McLean Hospital after the second experimental session, then meetings for administration of measures and psychotherapy (on Day 35 and Day 84) can be conducted at the participant's home.

During the introductory psychotherapy session, the investigators and the participant will review the participant's anxiety and will discuss any other issues or goals the participant has for the initial experimental session. Participants will learn more about the procedures occurring during and after each experimental session, and the investigators will discuss the effects of MDMA and what might occur during an experimental session. The participant will also learn more about the rules and restrictions concerning the experimental sessions. The investigators and participant work together to formulate a goal or goals for the experimental sessions.

Psychotherapy follow-up sessions will be conducted in the morning on the day after the experimental sessions at McLean Hospital (see "Day 15" and "Day 29" on Table 1). The investigators and participant will review the events of the experimental session. They will seek to integrate the thoughts, feelings or insights that arose during the experimental session. Psychotherapy occurring after the first experimental session may also involve preparation for the second experimental session, if all involved have concluded that it is safe and appropriate for a second experimental session to occur. The participant will be instructed to not drive a motor vehicle or operate heavy machinery during this day. The participant will arrange a ride home from the facilities, and if he or she is unable to do so, the investigators will assist in locating transport from the research facilities. At time of discharge (or as soon as possible), a duplicate videotape of the prior day's experimental session will be provided to the participant (see "Experimental Sessions" below for more details on videotaping of sessions). This duplicate videotape will be edited to remove any portions of the videotape that the participant instructed to not be copied and to remove any silent/non-relevant portions of videotape (such as of the participant reclining with eye shades on and listening to recorded music).

Participants will undergo psychotherapy with the investigators approximately one week after each experimental session ("Day 21" and "Day 35" on Table 1). Each of these psychotherapy sessions will occur after the completion of outcome measures. The

participant and the investigators will continue to review, discuss and explore the events of the preceding experimental session. Psychotherapy will continue to focus on reducing anxiety, but may also address other issues that arose during or after the experimental sessions. Psychotherapy conducted a week after the second experimental session may encompass the events of both the first and the second experimental sessions. As noted above, the participant may request additional psychotherapy sessions during the course of the study.

The final meeting between the participant and the investigators will occur approximately eight weeks after the second experimental session. After a final administration of all outcome measures, the investigators will speak with the participant about his or her anxiety level and quality of life in the interval between psychotherapy sessions. The investigator and participant may re-examine the goals set out for each experimental session, or they may return to the discussions and work that occurred during the previous psychotherapy session.

Administration of Outcome Measures (Research Follow-Up)

Outcome measures will be administered on six occasions; once prior to the initial psychotherapy session, on the day of each experimental session prior to drug administration, prior to each psychotherapy session scheduled a week after an experimental session, and on the final day of the study, two months after the second experimental session. No outcome measures, except for the Daily Diary and pain measures, will be administered prior to psychotherapy sessions conducted the day after each experimental session. Observer-rated and participant rated outcome measures will be administered during each approximately 60 to 80 minute research follow-up session, with research follow-ups occurring in appropriate research facilities of or made available to the Biological Psychiatry Laboratory at McLean Hospital. Daily Diaries will also be reviewed during these meetings. These instruments will include the participant-rated BHS, EORTC QLQ-C30, FACIT-Sp, MSAS, SAHD, SELF, STAI, and SCL-90-R, and the investigator-rated HAM-A and HAM-D (See Table 3). Participants will complete outcome measures on days when any additional sessions are scheduled (see “Psychotherapy.”) More details about each measure can be found in “Measures” below. Daily Diaries will also be reviewed at these meetings. The Spielberger State-Trait Anxiety Inventory (STAI) will serve as the primary outcome measure of anxiety, and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) will serve as the primary outcome measure of quality of life.

Participants will also be reassessed for psychological and physical status by the physician-investigators immediately following and one week after each session. This will occur during psychotherapy sessions. Physical assessment and examination will also be completed by the co-investigator oncologist one-week post completion of the second experimental intervention session (on “Day 36” on Table 1). The second medical examination will include a complete physical examination and a second metabolic profile and serological assessment of liver function. Any change in health status not related to

the progression of the participant's advanced-stage cancer discovered during this second physical examination will be treated as an adverse event and will be reported as such.

Experimental Sessions

Participants will undergo two experimental sessions with Dr. Halpern and Dr. Naidoo. Each experimental session will last for six to eight hours and will include an overnight stay at the research facilities. After the investigators have determined that the participant can undergo the experimental session, each participant will receive an initial dose of MDMA, as described in "Drugs and Dosage" below. The participant will lie or sit comfortably while listening to a musical program designed to facilitate introspection and deep emotions. Blood pressure and pulse will be measured at the outset of each treatment session, once every 15 minutes for 4 hours, and then every 30 minutes for 2 more hours if the established thresholds for normal blood pressure and pulse have not been exceeded. Body temperature will be measured at the outset and then every thirty minutes for 6 hours with an automatic temperature sensor and telemetry device worn on the skin. The physician may also call for more frequent measurements in the event of clinically significant changes (for more details on measures of physiological effects, see "Monitoring for Toxicity" below). Approximately 2.5 hours after the initial dose, and at the discretion of the investigators, a second supplemental dose of MDMA will be administered, as described in "Drugs and Dosage" below. The supplemental dose will always be one half of the initial dose. Participants may have a significant other, such as a spouse, close friend or relative, accompany them during part or all of the experimental session and including the overnight stay at the research facilities. More details on each experimental session are provided below. The experimental session ends six to eight hours after the administration of the initial dose of MDMA. If the acute psychological and physiological effects of MDMA are no longer present and the participant appears well and in good mental and physical health, then the investigators will leave the facilities, to return the next day when a psychotherapy session will be conducted.

All MDMA treatment sessions will begin at 11:00 AM and will take place at an appropriate research facility of or made available to the Biological Psychiatry laboratory at McLean Hospital, located in Belmont, Massachusetts. 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 of childbearing potential, a pregnancy test. At this time, they will also complete measures of anxiety, quality of life, performance, and pain (as outlined in Table 2 below). Urinary pregnancy test results must be negative for the participant to continue with the experimental session, and urinary drug screens should be negative for all substances (marijuana, phencyclidine, opiates, cocaine, and amphetamines). A positive result from this drug screen may result in the participant being withdrawn from the study (for evidence of use of a non-prescribed drug) or having the experimental treatment session rescheduled to another day (a positive result for opiates will require careful review with the investigators to confirm that this result is due to the participant's standard and routine use of opiates for pain control and is not due in

whole or in part to additional opiates taken as a P.R.N. for breakthrough pain in the prior 24 hours). Prior to MDMA 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 Toxicity” below) have been made and the researchers have discussed goals for this session and general procedures, participants will ingest gelatin capsules containing MDMA along with a glass of water, as described in “Drugs and Dosage” below.

Each experimental session will be videotaped. Comparison of information gathered from these videotapes may be qualitatively or quantitatively examined in an attempt to gain a better understanding of the effects of MDMA within a psychotherapeutic context. Participants will also be provided with an edited copy of the treatment session videotape, with lengthy periods of silence removed from the recording, for their personal use to aid in reviewing, recalling, and deepening the therapy between experimental treatment sessions as well as after the second experimental treatment session. Only one copy will be provided, and this copy will clearly be labeled “Confidential, not for duplication or broadcast,” will have the contact information for the principal investigator, and will expressly forbid any viewing by any third-parties, other than the participant, people of the participant’s choosing, and the participant’s outside therapist.

Psychotherapy During Experimental Session

The MDMA treatment sessions will be supervised and facilitated by the principal investigator, psychiatrist (John H. Halpern, M.D.) accompanied by an experienced female co-investigator/co-therapist (Umadevi Naidoo, M.D.). Both co-therapists will be present throughout the treatment sessions. The sessions will be conducted following the principles developed by Grof for LSD psychotherapy (Grof, 1980, pp. 123-147) and adapted for MDMA-assisted psychotherapy by Metzner and Adamson (2001) and by Greer and Tolbert (1998). The principal investigator has extensive experience treating anxiety and other psychiatric conditions in his psychiatric practice using both medications and psychotherapy. The co-investigator also has an extensive history of treatment within her practice and, in particular, has expertise in palliative care. General details on the psychotherapeutic approach to be used in this protocol can be found in a draft treatment manual for MDMA-assisted psychotherapy for PTSD (Ruse et al. 2002) and for anxiety associated with advanced-stage cancer (Ruse et al. 2004). The treatment method will be the same for each experimental session.

At the beginning of the session (11:00 A.M.), the co-therapist researchers will discuss with the participant his or her intentions for the session, including intentions regarding working with psychological issues related to their episodes of anxiety for which they may have previously taken PRN anxiolytic medications or antidepressants. After the session begins, participants 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 experimental session 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). The music will consist of instrumental music, as for example the recording “Santosh” by P.C. Davidoff and Friends. Dr. Halpern will maintain a limited but varied selection of instrumental recordings, including classical music, jazz, and other forms of instrumental music, and the participant may request a specific musical style for his or her session. 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. For the rest of the experimental session, 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 introspectively on his or her sense of self and life-history in order to increase the psychological insights mediated by the MDMA treatment.

Electrolyte-containing fluids will be freely available throughout the session within the limits described in “Monitoring for Toxicity” below. Food will be available during the latter part of the session. Foods provided will include crackers or bread, fruit and vegetables, and soups.

At the participant’s request and after making arrangements with the investigators, a spouse, partner, relative, or friend may join the participant and investigators during the experimental session in order to offer support.

After approximately six to eight hours, if all medical parameters are acceptable and the participant is alert, ambulatory, and emotionally stable, the session will conclude and videotaping will stop. The co-investigator internist, Dr. Siegel will at this time also review the collected vital sign data with Drs. Halpern and Naidoo and may, if warranted, check on the participant to confirm health status. Participants will remain at McLean Hospital for an overnight stay, allowing for continued observation. A psychiatric resident will be hired for overnight availability and coverage during this time. The support person may also remain overnight if approved by the investigators. Staff at McLean Hospital will be available to treat any adverse event occurring during the overnight stay. 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 and their support person will be given the pager number of the principal investigator or the covering physician to call immediately if any problems occur.

Drugs and Dosage

The two doses of MDMA chosen for the Low Dose condition have been selected on the basis of their ability to produce minimal but detectable subjective effects (Grob et al. unpublished; Harris et al. 2002) and thus serve as an active placebo. The cumulative dose of 37.5 mg is not expected to produce any of the predicted subjective effects or improvements in anxiety, quality of life, or pain. The initial and supplemental dose of MDMA for Session 1 in the Experimental Intervention was selected so as to make the cumulative dose equal to that of the initial dose for Session 2 (125 mg), with the initial

dose serving as a comparison for dose-response analysis. On the basis of previous research (Grob et al. unpublished; Mas et al. 1999; Lamers et al. 2004; Tancer and Johanson 2001), this dose is expected to produce most of the expected effects of MDMA without producing the full array of effects. The maximum initial dose of 125 mg MDMA in Session 2 has been selected for use in this study on the basis of prior reports of therapeutic effectiveness and tolerability (Greer and Tolbert 1998). Doses equal to or greater than 125 mg have been well-tolerated in previous studies of MDMA administered to humans (Cami et al, 2000; Grob et al, Unpublished; Harris et al. 2002; Lester et al. 2000; Mas et al, 1999; Tancer and Johanson, 2003; Tancer and Johanson 2001; Vollenweider et al. 1998). 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, data cited on p. 52 of Dr. Mithoefer’s protocol, IND# 63,384). With participants carefully monitored for any indicators of adverse events, this dose should prove tolerable and will produce the full array of subjective and physiological effects.

Table 2. Dose Regimen

	Session 1		Session 2 ^a	
	Dose ^b 1	Dose 2 ^c	Dose 1	Dose 2 ^c
Low Dose Group N = 4	MDMA 25 mg	MDMA 12.5 mg	MDMA 25 mg	MDMA 12.5 mg
Experimental Intervention Dose Group N = 8	MDMA 83.3 mg	MDMA 41.7 mg	MDMA 125 mg	MDMA 62.5 mg

^a Session 2 is scheduled 2-3 weeks after safe completion of Session 1.

^b All doses administered are encapsulated with uniform shape, size, and weight. Doses are taken orally with water.

^c Dose 2 is administered 2.5 hours after Dose 1, if ongoing assessment of safety and subject participation supports continuing the experimental session.

Each participant will receive an initial dose of MDMA followed 2.5 hours later by a supplemental dose of half the initial dose. The supplemental dose will be administered only if observation indicates that the participant is tolerating the first dose, and if both the researchers and the participant agree to proceed. The advantages of splitting the total amount of MDMA to be administered during a session include extending the duration of the session without increasing the peak effects of the predicted treatment and reducing the initial amount of MDMA administered to a patient population that may be more sensitive to dose-dependent effects than a healthy, normal population.

Each dose will consist of the specified amount of racemic MDMA mixed with inactive compound. Staff at the McLean Hospital Pharmacy will weigh out the appropriate amount of MDMA in gelatin capsules along with an inactive compound, such as lactose to ensure that the investigators cannot distinguish Low Dose and Experimental Intervention dose capsules by weight or appearance. Each participant will receive the

same number of capsules during an equivalent session (first or second experimental session) so as to maintain the blind for condition assignment. Both Low Dose and Experimental Intervention Dose participants receive an identical number of capsules. MDMA will be administered p.o. along with 250 to 300 mL water.

Participants will receive MDMA on two experimental sessions spaced 2-3 weeks apart and described above in “Methods” on “Day 14” and “Day 28” (see Table 1). During these two experimental sessions, eight participants will be randomly assigned into the Experimental Intervention MDMA Group and will receive, in Session 1, 83.3 mg MDMA followed 2.5 hours later by an additional dose of 41.7 mg MDMA, and in Session 2, 125 mg MDMA followed 2.5 hours later by an additional dose of 62.5 mg MDMA. Four other participants will also be randomly assigned into the Low MDMA Group and will receive, in Session 1, 25 mg MDMA followed 2.5 hours later by an additional dose of 12.5 mg MDMA, and in Session 2 they will receive 25 mg MDMA followed 2.5 hours later by an additional dose of 12.5 mg MDMA.

Assessment/Measures

Outcome measures were selected primarily because they are well-validated, clinically-relevant, and repeatable. These include observer-rated measures of symptoms of anxiety, depression, hopelessness, and quality of life; subject-rated measures of symptoms, quality of life, daily pain, and daily diary (logging medication use); oncologist-rated measures of physical health, review of laboratory values, and physical functioning; and psychiatrist-administered tests of mental status and diagnosis. Observer-rated and subject-rated measures of symptoms of anxiety and depression will be made at baseline, on the morning of each experimental session (“Day 14” and “Day 28”), one week after each experimental session (“Day 21” and “Day 35”), and at two months after the second experimental session (“Day 84”). This will be the case for all measures except for SCID, administered only at baseline, and SCL-90-R and SELF, administered only at baseline and two months following last experimental session. Observer-rated and participant-rated measures of hopelessness, desire for a hastened death, spiritual well-being, measures of quality of life, and of symptom prevalence, frequency, and distress will also be administered at these same times. Participants will be asked to keep a daily diary that logs daily use of all medications and need for symptom-specific medications for acute symptoms of anxiety and/or pain. Participants will also be asked to rate their prior 24 hours of pain each day using the VAPS. The measures that will be used in the course of this study are in Table 3 and listed below.

Table 3. Test Measures

Assessment	Abbreviation	Measure of	Time Needed	Clinician Rated	Participant Self-Rated	Screening or Outcome Measure
Beck Hopelessness Scale	BHS	Pessimism / hopelessness	5-10 minutes		X	Outcome
Daily Diary	--	Anxiolytic and Pain-control Rx	5 minutes		X	Outcome
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire ^a	EORTC QLQ-C30	Global quality of life - five functional scales, and nine symptom scales	10-15 minutes		X	Outcome
Functional assessment of chronic illness therapy— spiritual well-being scale	FACIT-Sp	Spiritual well-being	5 minutes		X	Outcome
Hamilton Anxiety Rating Scale	HAM-A	Anxiety	5-10 minutes	X		Both
Hamilton Depression Rating Scale	HAM-D	Depression	5-10 minutes	X		Outcome
Karnofsky Performance Rating Scale	KPRS	Physical functioning ability	5 minutes	X		Outcome
Memorial Symptom Assessment Scale	MSAS	Symptom prevalence, frequency, and distress	10-15 minutes		X	Outcome
Mini-Mental Status Exam	MMSE	Cognition examination	10 minutes	X		Both
Schedule of Attitudes Toward Hastened Death	SAHD	Desires for a hastened death	5-10 minutes		X	Outcome
Self-Expansiveness Level Form	SELF	Transpersonal identity	10 minutes		X	Outcome
Spielberger State-Trait Anxiety Inventory ^a	STAI	Anxiety	5-10 minutes		X	Both
Structured Clinical Interview for DSM-IV	SCID	Past and present psychiatric health	50 to 120 minutes	X		Screening
Symptom Checklist-90-	SCL-90-R	General current mental health	12-15 minutes		X	Both

Revised		and quality of life				
Visual-Analog Pain Scale	VAPS	Rating of subjective pain experienced	2 minutes		X	Outcome
Total estimated time to complete all screening measures: 82-165 minutes						
Total estimated time to complete all outcome measures: 94-132 minutes.						

^a Primary outcome measures

1. Beck Hopelessness Scale (Beck and Steer 1988; Beck et al. 1974) assesses suicidality along 3 axes of hopelessness: feelings about the future, loss of motivation, and expectations. Extensive normative data has been published on the BHS. The BHS has 20 true/false questions.
2. Daily Diary. Participants will keep a daily log of all medications taken while actively enrolled in the study protocol. The forms provided to participants will also remind them to contact the investigators prior to initiation of any drug or medication not already reviewed during the intake evaluation. The VAPS (see Visual Analog Pain Scale below) will also be completed daily.
3. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Aaronson et al. 1993) has satisfactory psychometric properties and currently is one of the most widely accepted measures of quality of life. This instrument has 30 items yielding scores for 5 subscales (physical, role, emotional, social, and cognitive functioning) and 3 symptom subscales (fatigue, pain, and nausea/vomiting). This will be the primary outcome variable for quality of life.
4. Functional Assessment of Chronic Illness Therapy— Spiritual Well-Being Scale (Cella et al. 2002a; Cella et al. 2002b) has two subscales: one measuring sense of meaning and peace, and the other assessing the role of faith in illness. Total combined score offers a measure of spiritual well-being. It has been found to be a psychometrically sound measure of spiritual well-being for individuals with cancer and with other chronic illnesses. Questions do not refer to specific religious beliefs or practices and are not biased for or against any particular religious group. The FACIT-Sp has 12 questions with 5 possible answers, each.
5. Hamilton Anxiety Rating Scale was developed in 1959 (Hamilton 1959) and has since become a widely used and accepted outcome measure for the evaluation of anxiety; it is well-validated and has been administered to a wide population. The HAM-A has 14 items; each is rated on a 5-point scale ranging from 0 (not present) to 4 (severe). A score of 14 or greater is associated with clinically significant symptoms of anxiety.
6. Hamilton Depression Rating Scale, developed in 1960 (Hamilton 1967; Hamilton 1960), is also a widely used and accepted outcome measure for the evaluation of depression and is well-validated, having been administered to patients across hundreds of studies. A score of 10 to 13 indicates mild depression; 14-17– mild to moderate depression; and greater than 17 – moderate to severe depression. We will use the 17-item version of the HAM-D, which, like the HAM-A, is rated on a 5-point scale ranging from 0 (not present) to 4 (severe).

7. Karnofsky Performance Rating Scale is a clinician-rated measurement of quality of life (Karnofsky and Burchenal 1994), scored from 0 to 100: 100 – normal/no complaints/no evidence of disease; 90 – able to carry out normal activity/minor signs or symptoms of disease; 80 – normal activity with effort/some signs or symptoms of disease; 70 – cares for self/unable to carry on normal activity or do active work; 60 – requires occasional assistance but is able to care for most of his/her needs; 50 – requires considerable assistance and frequent medical care; 40 – disabled/requires special care and assistance; 30 – severely disabled/hospitalization is indicated although death not imminent; 20 – very sick/hospitalization necessary, active supportive treatment necessary; 10 – moribund/fatal processes progressing rapidly; 0 – dead.
8. Memorial Symptom Assessment Scale (Portenoy et al. 1994) is a self-report inventory of 32 symptoms commonly associated with medical illness. For each symptom present during the prior week, the subject rates on a 4 point scale how often it was experienced, how severe it was usually, and how much the symptom caused distress or bothered the subject. Scoring of the MSAS yields several validated subscale scores: the 10-item MSAS Global Distress Index is considered a measure of overall symptom distress; the 12-item MSAS Physical Symptom Subscale; the 6-item MSAS Psychological Symptom Subscale; and the Total MSAS Score, which is the average of the symptom scores of all 32 symptoms in the MSAS instrument.
9. Mini-Mental Status Exam is a clinician-administered instrument of 10 items, with a score from 0 to 30. Scores are age- and education-dependent; generally a score equal to or greater than 27 is considered normal (Folstein et al. 1975). A diagnosis of dementia is made when the MMSE score is less than 24, there is evidence of cognitive impairment from subject history, and there is evidence of functional impairments.
10. Schedule of Attitudes Toward Hastened Death has primarily been administered to individuals with AIDS or with cancer (Breitbart et al. 2000; Rosenfeld et al. 1999). This instrument explores desire for death, including an active desire for death, optimism/pessimism towards one's future quality of life, social and personal factors that may influence willingness to consider assisted suicide or euthanasia, passive hopes for a more expedient death, and behaviors that might reflect a desire for death. The SATHD has 20 true/false questions.
11. Self-Expansiveness Level Form assesses the transpersonal construct of “self-expansiveness,” which is defined as “the amount of True Self which is contained within the boundary demarcating self from not-self through the process of self-conception” (Friedman 1983). It is a paper and pencil test of 18 self-descriptive statements which are rated on a five-point Likert scale by the subject as to how willing he/she identifies with test items. There are three subscales: Personal, Middle, and Transpersonal. Criterion, convergent, discriminant, and factorial validity has been established for this test measure.
12. Spielberger State-Trait Anxiety Inventory differentiates “state anxiety” (i.e. anxiety dependent on a specific situation or stressor) from “trait anxiety” (long-standing anxious affect or disorder) and is considered the definitive instrument for measuring anxiety in adults (Spielberger et al. 1970). Extensive normative group

- data exists and the STAI has been administered to advanced-stage cancer patients with anxiety, as well. The STAI has 40 questions with 4 possible answers each. A score of 40 or greater is associated with clinically significant symptoms of anxiety. This will be the primary outcome variable for cancer related anxiety.
13. Structured Clinical Interview for the DSM-IV: SCID-IV (First et al, 1994). The SCID is a semi-structured interview that permits accurate diagnosis of lifetime and current psychiatric disorders using DSM-IV criteria
 14. Symptom Checklist 90-Revised: This is a standardized instrument used to measure subjective, feeling states (Derogatis 1994). Reliability, validity, and utility have been demonstrated across close to 1000 studies and normative data values have been published. The SCL-90-R has subscales along 9 primary symptom dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and 3 global indices (global severity index, positive symptom distress index, and positive symptom total). The SCL-90-R has 90 questions with a 5-point rating scale.
 15. Visual Analog Pain Scale: This is a simple and efficient tool that consists of a drawn 10-cm line labeled at one end “no pain” and at the other end with “worst pain possible.” Scoring is accomplished by having the participant mark the line to indicate pain intensity, and the line is then measured to the mark on a 0- to 10-point scale. Extensive prior research indicates that the VAPS is reliable and valid as both a sensitive measure of pain and as a measure of change in pain (Ohnhaus and Adler 1975).

As noted in “Subjects” above, the oncologist investigator will administer the STAI during the pre-screening examination, and the participant must have a STAI score of 40 or higher to be considered for study participation.

All outcome measures except for the Daily Diary and the VAPS will be administered during the baseline (introductory) session at the start of the study. Participants will be instructed on how to complete the Daily Diary and VAPS. As described in “Methods” above, participants will complete outcome measures on six separate occasions across the course of the study. In all cases, outcome measures will be completed prior to psychotherapy.

Measures made during the experimental sessions are primarily made for safety monitoring and are described below in “Monitoring for Toxicity.” These measures consist of assessing blood pressure, pulse and body temperature periodically throughout the experimental session. The investigators will also measure ambient temperature during each experimental session.

Monitoring for Toxicity

There is now a considerable body of information indicating that the likelihood of significant toxicity is very low from the doses of MDMA proposed in this study. To date, MDMA has been administered to over 230 people in controlled and uncontrolled trials in

clinical settings. Phase I studies conducted in the United States and Europe have failed to demonstrate toxicity (Boone et al. unpublished; Cami et al. 2000; Chang et al. 2000; de la Torre 2000a; de la Torre 2000b; Gamma et al. 2000; Frei et al. 2001; Grob et al. unpublished; Grob et al. 1996; Hernandez-Lopez et al. 2003; Lester et al. 2000; Lamers et al. 2004; Liechti and Vollenweider 2000a; Liechti and Vollenweider 2000b; Liechti et al. 2001a; Liechti et al. 2001b; Mas et al. 1999; Navarro et al. 2001; Pacifici et al. 2004; Pacifici et al. 2002; Pacifici et al. 2001; Pacifici et al. 2000; Pichini et al. 2003; Pichini et al. 2002; Pizarro et al. 2003; Pizarro et al. 2002; Segura et al. 2001; Tancer and Johanson 2003; Tancer and Johanson 2001; Vollenweider et al. 1998; Vollenweider et al. 1999). Single doses of up to 2.5 mg/kg were employed in one of the studies conducted in the US (Grob et al. unpublished), with eight subjects receiving single doses equal to or exceeding 125 mg MDMA, and two subjects receiving single doses over 187.5 mg during one session (data cited on p. 52 of IND #63,384). In another Phase I study in the US (Tancer and Johanson 2001), over twenty subjects were administered doses larger than 125 mg. The same team of researchers administered 2 mg/kg to subjects in a subsequent study (Tancer and Johanson 2003), including 9 single doses above 125 mg (Tancer 2003, personal communication to L Jerome, January 17, 2003).

Likewise, psychiatrists in the US and Europe reported using MDMA in a large number of patients before the drug was placed into Schedule I. When describing their experiences as therapists in books (Adamson 1985; Widmer 1998), book chapters (Metzner and Adamson 2001), articles in peer-reviewed (Greer and Tolbert 1998; 1986) and non-reviewed journals (Gasser 1994), these therapists did not report any severe adverse effects occurring during or after MDMA-assisted psychotherapy sessions.

Although serious untoward reactions are unlikely, the researchers will closely monitor participants during experimental sessions. Throughout all the sessions, participants will be attended to by Drs. Halpern and Naidoo, whose credentials are detailed above and in their attached CVs. Dr. Siegel (McLean Hospital's Chief of Internal Medicine) will remain available for contact over emergency radio and will be on-call and on grounds and available via the medical emergency response system set up for McLean throughout the hours of each experimental session. In addition, internal medicine will provide additional clinical supervision with site visits throughout the first two experiment sessions in addition to being available through radio coverage. Dr. Siegel will be directly available for consultation and for any emergency calls and will be able to come directly to the treatment site within a few minutes. Dr. Siegel will review medical status with Drs. Halpern and Naidoo at the conclusion of each experimental session.

The experimental sessions will be conducted at an appropriate research facility of or made available to the Biological Psychiatry Laboratory at McLean Hospital, which is less than 4 miles from the Mt. Auburn Hospital emergency room. The facilities will be equipped with a "crash cart" containing the emergency drugs and equipment necessary to respond to any complications. Diphenhydramine, injectable epinephrine, and other standard emergency drugs and equipment will be available in the treatment room if needed for countering an allergic reaction or another medical emergency. Available emergency medications include antihypertensive agents (such as nitroprusside and

labetolol), pressor agents, anxiolytics, and intravenous fluids. In addition to these medications, the crash cart contains a defibrillator (with telemetry capability), an oxygen tank, a 12-lead electrocardiogram (ECG) device, a suction device, a pulse oximeter, an IVAC pump, and intubation equipment (including laryngoscope, and endotracheal tubes). Contingency plans for responding to adverse events are based on a comprehensive review of case reports of toxicity in illicit users reported in the Investigator's Brochure, and in a number of reviews (Cole and Sumnall 2003; Baggott 2002; Henry and Rella 2001), and represent a very cautious approach to the remote possibility of a serious complication. With these personnel and equipment, the researchers should be able to stabilize a patient on the research unit and then transport them by ambulance if medical hospital admission were required.

Written notice of the occurrence of a life-threatening adverse event will be given to the Lahey Clinic Medical Center and McLean Hospital IRBs within 24 hours and will be given to the FDA within 72 hours. Written notice of the occurrence of any serious but not life-threatening events will be given within 15 days.

After the conclusion of the experimental session, a psychiatric resident will be hired for overnight availability and coverage. Participants or their support people, if present, will be able to contact the psychiatry resident (as well as the principal investigator) during their overnight period of observation if necessary.

The investigators will monitor the following variables in order to detect possible adverse events during or after MDMA-assisted therapy.

Hypertension

The investigators will monitor for the occurrence of hypertension and related complications through frequent measures of blood pressure. Blood pressure and pulse will be measured at the outset of each treatment session, once every 15 minutes for 4 hours, and then every 30 minutes for 2 more hours if the established thresholds for normal blood pressure and pulse have not been exceeded.

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 values stabilize and the participant remains asymptomatic, or show signs of trending downward.

Dr. Halpern will monitor the participant for signs and symptoms of a hypertensive crisis during the experimental session, with requested assistance from Dr. Siegel if and when applicable. The participant will be transferred to the Mt. Auburn Hospital if there is any indication that the participant is experiencing a severe cardiovascular event. Reasons for moving a participant to the Mt. Auburn Hospital would include, but not be limited to, severe headache in the setting of hypertension, angina or neurological deficits regardless of blood pressure. A crash cart will be immediately available at the McLean Hospital research facilities and will contain nitroprusside in addition to the usual resuscitation drugs and equipment. This will allow treatment to be instituted without transferring the

patient if that should become necessary. The physician/therapist may, at any time, make a clinical judgment to transfer the patient to Mt. Auburn Hospital for closer monitoring and additional treatment.

Angina or Myocardial Infarction

The investigators will observe the participant and note any complaints of chest pain. If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will undergo a STAT ECG, 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 patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI (J Am Coll Cardiol 34:890, 1999).

Stroke

The investigators will attend to any signs or symptoms of neurological deficit or confusion that is more extensive than might be expected from MDMA or from psychological distress. If any participant has neurological 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 Mt. Auburn 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).

Psychological Distress and Extreme Anxiety

Both psychotherapist investigators will observe the participant for any indications of extreme anxiety or panic throughout the experimental session. They will offer support to the participant when requested and will make all efforts to assist the participant in confronting deep emotions while noting any signs of intense fear or rage, or signs of psychosis. If, after eight hours, the participant is still extremely distressed or extremely anxious, the investigators will remain with the participant until anxiety has returned to manageable levels or until the investigators conclude that the participant is in danger of harming him or herself or others. In the event that a participant appears to be in danger of harming the self or others, the investigators may hospitalize the participant until he or she returns to stable condition.

In the event of a participant's experiencing severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or persisting insomnia following an MDMA

session, the investigators 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 or directly to McLean Hospital. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

Hyperthermia

Body temperature will be measured at the outset and then every thirty minutes for 6 hours with an automatic temperature sensor and telemetry device worn on the skin. The physician may also call for more frequent measurements in the event of clinically significant changes. Ambient temperature will be measured and recorded hourly for six hours, starting immediately after drug administration. Elevation in body temperature that exceeds 1 degree Centigrade is unlikely to occur, and elevation great enough to be considered hyperthermia is not expected to occur.

Dehydration

As described above, water or electrolyte containing fluids will be available during each experimental session, and participants may request fluids at any time, within the restrictions described below. Dehydration within the context of a controlled laboratory setting and in the absence of rigorous exercise is not expected to occur.

Hyponatremia

Participants will be given electrolyte-containing 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 patient will be transported to the Mt. Auburn Hospital, where further intervention can be provided.

Liver Toxicity

Liver enzymes will be measured as part of the initial screening visit. Volunteers with preexisting abnormalities will be excluded from the study. Liver enzymes will be measured 4 days after the second MDMA session. Any participant who shows abnormalities on any of the liver enzyme determinations will receive further evaluation and follow-up by a gastroenterologist.

Neuropsychological Toxicity

Psychological and neurological status will be clinically monitored by the therapists during the MDMA sessions and during therapy sessions at frequent intervals thereafter.

If, on clinical examination during that period, a participant is found to have cognitive deficits that persist for more than two weeks, this participant will not be given a second MDMA session. Any participant who develops mania or psychosis will not be given a second MDMA session and will receive appropriate psychiatric treatment.

Reproductive and Developmental Toxicity

As discussed in the Investigator's Brochure, 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).

Pregnant women will be excluded from participation in the proposed study and urine pregnancy tests will be performed before each drug administration. Women of child-bearing potential enrolled in the study must practice a reliable method of birth control, and they must have a negative pregnancy screen before undergoing each experimental session. A positive pregnancy screen will be cause for removal from the study.

Abuse Potential

MDMA is classified as a Schedule I compound with a high potential for abuse, primarily because of its use in settings such as "rave" dance parties. A survey of a representative sample of young people living in the Munich, Germany area found that about 6% of the sample reporting ecstasy use showed signs of ecstasy abuse or dependence (Lieb et al. 2002; Von Sydow et al. 2002). A sample of largely drug-naïve participants who received MDMA in a controlled setting indicated that they would not seek out ecstasy again (Liechti et al. 2000; Liechti et al. 2001).

Individuals diagnosed with substance abuse or dependence disorders within sixty days of screening will not be admitted to the study. Prospective participants and participants will be encouraged to discuss their concerns about the abuse potential of MDMA with the investigators, and with their therapist or physician when applicable.

Diversion will not be an issue in the proposed study because MDMA will only be administered under supervision of the investigating psychiatrists. No take-home doses will be permitted. As discussed elsewhere, MDMA will be stored and handled in compliance with Federal and local regulations for Schedule I compounds.

Chemistry, Manufacturing and Control Information

The drug product is \pm (3,4)-methylenedioxyamphetamine HCl. As described in the Introductory Statement, MDMA is also referred to as N,-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules.

Complete details on the chemistry, manufacturing and control of the MDMA HCl to be used are described in Drug Master file # 6293. As described in that file, MDMA was prepared for human consumption by David Nichols, Ph.D., Dept. of Medicinal Chemistry and Pharmacology, Purdue University. The identity and purity of this MDMA was reconfirmed using HPLC in 1997 as described in DMF # 6293 and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor in relation to the study of MDMA-assisted psychotherapy in people with posttraumatic stress disorder, the analysis found it to be more than 99.7% pure. There was no evidence of deterioration at that time, 17 years following original synthesis in 1985.

MDMA is a Schedule I drug and will be handled in accordance with all federal, state, hospital, and university regulations.

Records pertaining to the use of Schedule I compounds will be maintained in accordance with relevant Federal and State Regulations. These records will be kept separate from other records and will be maintained in the Pharmacy at the McLean Hospital in an appropriately secured file cabinet. These records will include:

- Schedule I DEA Registration
 - Schedule I Massachusetts Department of Public Health, Division of Food and Drugs Registration
 - Unexecuted DEA 222 forms
 - Invoices and executed DEA 222 forms
 - Disposition records (control sheets)
 - Audit reports
 - Annual inventory reports
 - DEA form 41 (in the event that any contaminated, expired, or unwanted MDMA requires destruction by the DEA authorized Controlled Substance Investigator)
 - Disposition records (control sheets)
- The control forms, each with a unique identifying number, will be obtained from and tracked by the Pharmacy at McLean Hospital.

As described in “Drugs and Dosage” above, MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose used to ensure that all capsules have similar weights. The lowest dose contained in one capsule will be 12.5 mg, which is the supplemental dose offered to participants in the low dose condition, and the highest dose contained in one capsule will be 125 mg, which is the initial dose offered to participants in the Experimental Intervention condition on the second experimental session. Capsules will be prepared in such a way as to prevent

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investigators and participants from distinguishing contents of a Low Dose capsule from capsules containing Experimental Intervention doses.

Lactose will be used as the inactive compound used in admixture with MDMA to ensure that all doses will be of the same weight.

MAPS claims categorical exclusion from the requirement to submit an environmental assessment (21 CFR 25.15[a]). MAPS claims categorical exclusion (under 21 CFR 25.31[e]) for the study under this IND. To its knowledge, no extraordinary circumstances exist.

Pharmacology And Toxicology

Primary Pharmacodynamics

Mechanisms of Action

MDMA interacts with plasma monoamine transporters and storage vesicles to increase extracellular levels of 5-HT, dopamine, and norepinephrine (Cozzi et al. 1999; Fitzgerald and Reid 1990; Gudelsky and Nash 1996; Hiramatsu and Cho 1990; Kankaanpaa et al. 1998; Nash and Brodtkin 1991; Rudnick and Wall 1992; Schuldiner et al. 1993). Direct MDMA stimulation of postsynaptic 5-HT_{2A} receptors and α -2 adrenoceptors also contributes to MDMA's effects. For example, dopamine release is also indirectly increased by MDMA stimulation of 5-HT_{2A} receptors on GABAergic striatonigral neurons (Gudelsky and Nash 1996; Koch and Galloway 1997; Palfreyman et al. 1993; Schmidt et al. 1992; Yamamoto et al. 1995).

Although the specific mechanisms of MDMA's therapeutic effects are not fully understood, several observations and hypotheses can be made. Increased extracellular levels of dopamine and norepinephrine are known to be important to the reinforcing effects of psychostimulants (Ritz and Kuhar 1993; Rothman et al. 2001; Wise and Bozarth 1985). These neurotransmitters likely play a similar role with MDMA, producing feelings of excitement, euphoria, and well-being. When the D₂ receptor antagonist haloperidol was combined with MDMA, human volunteers reported less positive mood and greater anxiety (Liechti and Vollenweider 2000a), findings in keeping with these hypotheses. Central dopamine and norepinephrine are also thought to regulate readiness for action and arousal, with dopamine possibly mediating behavioral readiness, and locus coeruleus norepinephrine mediating conscious registration of external stimuli (Clark et al. 1987; Robbins and Everitt 2000). Increasing these neurotransmitters may therefore place the individual in a state of alertness that is ideal for recalling or even re-experiencing state-dependent memories of stressful events. This potentially aversive state may be modified by MDMA effects on both the serotonergic system and postsynaptic α -2 adrenoceptors.

MDMA effects on the serotonergic system are likely important for its therapeutic effects. MDMA induces 5-HT release and is a 5-HT₂ agonist. Serotonergic dysfunction is associated with anxiety, aggression, and depression. Increasing 5-HT release is thought to have opposite effects. For example, stimulation of 5-HT_{1A} and 5-HT_{1B} receptors decreases anxiety and aggression in rodent behavioral studies (Brunner and Hen 1997; Graeff et al. 1996) and likely contributes to reduced defensiveness and increased self-confidence reported after MDMA. 5-HT_{1A} receptors in the hippocampus have also been specifically hypothesized to enable disengaging from previously learned associations if they lead to adverse outcomes (Guimaraes et al. 1993). MDMA also has moderate 5-HT_{2A} activity (Nash et al. 1994), which leads to modest alterations in perception of meaning (Liechti et al. 2000b), possibly facilitating new ways of thinking. Case reports suggest increasing extracellular 5-HT levels may facilitate recovery of remote memories (Robertson 1997), a phenomenon that has been reported by psychotherapists administering MDMA to patients (Downing 1985). Studies in humans suggest that serotonergic activity plays an important role in generating the subjective effects of MDMA, since co-administration of a serotonin uptake inhibitor reduces most subjective effects (Liechti et al. 2000a; Tancer and Johanson 2004). Thus, MDMA effects on the serotonergic system may

decrease anxiety and aggression and create a state of mind that is conducive to psychotherapy.

Direct MDMA stimulation of postsynaptic α -2 adrenoceptors may modify this state by altering the balance of α -1 and α -2 stimulation, allowing the individual to remain emotionally calm despite noradrenergic activation. MDMA is an α -2 agonist (Lavelle et al. 1999). Like other α -2 agonists, such as guanfacine and clonidine (Arnsten 1998), MDMA produces feelings of calmness and relaxation (Cami et al. 2000). It is worth noting that open label trials suggest that clonidine may be helpful for treating symptoms of PTSD (Harmon and Riggs 1996; Kinzie and Leung 1989), indicating that α -adrenergic action may possess anxiolytic effects in humans.

Drug Activity Related to Proposed Action

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive psychotherapy. In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection (Greer and Tolbert 1998; Grinspoon and Bakalar 1986). Placebo-controlled clinical trials have confirmed 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; Hernandez-Lopez et al. 2002; Liechti et al. 2000a; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Tancer and Johanson 2001; Tancer and Johanson 2003; Vollenweider et al. 1998). These effects make it likely that MDMA would be useful in psychotherapeutic treatment of many different complaints.

Therapists conducting MDMA-assisted psychotherapy sometimes administered a smaller dose of MDMA approximately two to three hours after the first administration to prolong the session (Greer and Tolbert 1986; Stolaroff 1988). The supplemental dose of MDMA was usually smaller than the initial dose, and use of the supplemental dose was tolerated. Controlled, double-blind studies of repeated dosing with MDMA have used two equally large doses, either spaced four hours apart (Pacifci et al. 2001) or one day apart (Farre et al. 2004; Pacifci et al. 2001). To date, only immunological findings have been reported for the study with the schedule of repeated doses that most closely resembles the proposed study (Pacifci et al. 2001).

Past reports of psychotherapeutic use of MDMA in people with terminal illnesses suggested that MDMA in combination with psychotherapy might assist in reduction of cancer diagnosis anxiety in people with advanced stage cancer. Therapists made use of the reduced anxiety in relation to emotionally upsetting thoughts or memories, the greater accessibility of deeply emotional material and the increased acceptance of self and others in helping people deal with anxiety and impending death (Holland 2001; Greer and Tolbert 1998; Stevens 1997; Stevens 1999; Stevens 2000). Narrative accounts of MDMA-assisted psychotherapy also point to increased analgesia, strengthened communication with loved ones, and less guilt or distress on noting deteriorating health.

People with advanced stage cancer may face a reduction in quality of life arising from anxiety and distress stemming from the diagnosis, lack of control over life events and increasing need to rely on others. Anxiety may be amenable to treatment with conventional anxiolytics, and people may decide to avoid anxiolytics because of their side effects. MDMA-assisted psychotherapy

offers another means of reducing anxiety and increasing quality of life to people with advanced stage cancer by administering MDMA in a setting that enhances and augments subjective effects assumed to be therapeutic, such as increased recall of deeply emotional material and reduced anxiety. These effects are probably mediated partially or wholly through release and inhibition of serotonin, norepinephrine and dopamine uptake, and through direct or indirect action on monoamine neurotransmitters. It is also possible that changes in neurohormone release, such as increased release of arginine vasopressin (Forsling et al. 2001) may be involved in producing some of these therapeutic effects.

Secondary Pharmacodynamics

The psychotherapeutic effects of MDMA are accompanied by dose-dependent physiological effects including vasoconstriction and increased heart rate and blood pressure (Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Tancer and Johanson 2001, and see pp 44-48 of IND #63,384). Physiological effects of MDMA reach their maximum within 1 and 2 hrs after oral MDMA administration and have largely subsided within 6 hrs of drug administration (Gamma et al. 2000; Mas et al. 1999; Tancer and Johanson 2003; Vollenweider et al. 1998, see also Baggott et al. 2001). Data on maximum changes in heart rate and blood pressure collected from human studies published or in preparation in mid-2001 are summarized in Table 3.1 in the Investigators' Brochure. Data from more recent reports (e.g. Farre et al. 2004; Hernandez-Lopez et al. 2002; Lamers et al. 2003; Tancer and Johanson 2003) are similar to data collected in previous reports. Pre-treatment a serotonin uptake inhibitor attenuated or prevented elevations in blood pressure and heart rate (Liechti and Vollenweider 2000), and the 5HT_{2A} receptor antagonist ketanserin reduced elevated diastolic pressure (Liechti et al. 2000a), while the D₂ antagonist haloperidol failed to attenuate any of the cardiovascular effects of MDMA (Liechti et al. 2000b). These findings suggest that cardiovascular effects are at least partially due to serotonergic activity. When given in controlled settings, MDMA produced only slight increases in body temperature (Harris et al. 2002; Lester et al. 2000; Liechti et al. 2000b; Tancer and Johanson 2003), with the increase undetected in a number of studies (Farre et al. 2004; de la Torre et al. 2000; Liechti et al. 2000a).

On the basis of data from human studies of physiological effects, an initial dose of 25 mg is expected to have a minimal impact on blood pressure, heart rate, or body temperature, and effects are also expected to be minimal after a total dose of 37.5 mg MDMA, though findings from at least one study suggest that this dose might produce detectable increases in tension and relaxation (Harris et al. 2002). Both the initial dose of 83.3 mg and 125 mg, which will serve as the total dose during the first session and the initial dose on the second session, are similar or identical to the dose used in the study of MDMA-assisted therapy in people with PTSD (IND #63,384). These doses are expected to produce significant increases in blood pressure and heart rate, but are not expected to produce sustained increases in heart rate or blood pressure above 170/100 mm Hg. There is no data from controlled studies on the effects of 187.5 mg MDMA, the total dose for the second experimental session. It is expected that elevation in blood pressure and heart rate may be greater than the elevation seen after 125 mg, but with the increase in blood pressure and heart rate not greatly exceeding the elevation reported after 2.5 mg/kg MDMA. The physiological effects of a second dose of MDMA that is half the original dose and given two and a half hours after the first dose are not yet known. Administering a second dose of 100 mg

MDMA a day after an initial 100 mg dose increased systolic blood pressure, diastolic blood pressure and heart rate to levels greater than seen after the initial dose, but not significantly greater.

MDMA dose-dependently and acutely increases cortisol, prolactin, and adrenocorticotrophic hormone concentrations (Farre et al. 2004; Grob et al. 1996; Grob et al. Unpublished; Harris et al. 2002; Mas et al. 1999; Pacifici et al. 2004; Tancer and Johanson 2003), while growth hormone is unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peak at about 2 hours after MDMA administration. A second dose of 100 mg MDMA given four hours after an initial dose of 100 mg produced a second increase in cortisol during an interval when cortisol levels were declining (Pacifici et al. 2001), and a dose of 100 mg MDMA given 24 hours after an initial dose stimulated a greater release of cortisol, but not prolactin (Farre et al. 2004). In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was a trend for increased levels of the hormone dehydroepiandrosterone (DHEA) after 0.5 mg/kg MDMA, and a significant increase after 1.5 mg/kg MDMA (Harris et al. 2002), with DHEA levels peaking 2 to 3 h post-drug. Harris and colleagues failed to detect any changes in luteinizing hormone (LH), estradiol, progesterone or follicle stimulating hormone (FSH) in women participants. 40 mg MDMA acutely increased circulating levels of antidiuretic hormone (arginine vasopressin) in eight male volunteers (Forsling et al. 2001; Henry et al. 1998). Antidiuretic hormone reached maximum levels between 1 to 2 hours after MDMA administration. Increased retention of fluid is unlikely to be of any consequences in a clinical setting. Nonetheless, precautions will be taken to avoid dilutional hyponatremia, including providing electrolyte-containing beverages and restrictions on fluid consumption.

Studies conducted in Spain suggest that MDMA acutely affects the immune system (Pacifici et al. 1999; Pacifici et al. 2000; Pacifici et al. 2001; Pacifici et al. 2002; Pacifici et al. 2004). These acute changes in immunologic function include reduced CD4 T-cell count, increased NK cell count, and decreased phytohaemoagglutinin A-induced lymphocyte proliferation. MDMA decreased levels of the immune system stimulating and proinflammatory cytokine interleukin 2 (IL-2) and increased levels of the immunosuppressive and anti-inflammatory cytokine interleukin 10 (IL-10) (Pacifici et al. 2004; Pacifici et al. 2001). Generally, MDMA appears to decrease the concentration of Th1 cytokines and increase the amount of Th2 cytokines measured in blood. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose (Pacifici et al. 2001; Pacifici et al. 2002), and a second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose (Pacifici et al. 2002). Given this data, it is possible that administering a smaller supplemental dose 2.5 h after the first dose will slightly enhance the immunological effects set in motion by the first dose. These acute changes are unlikely to be of consequence in healthy individuals and are of a similar magnitude to changes produced by other pharmacological agents. For example, the CD4 T-cell count decrease was similar in magnitude to that produced by 0.8 g/kg oral ethanol (the equivalent of 4-5 drinks) in the same report (Pacifici et al. 2001). The mechanism of this MDMA-induced immunomodulation is unclear but may involve MDMA-induced glucocorticoid release or sympathomimetic activity, and activity at alpha adrenergic receptors (Connor et al. 2004). Serotonin release probably plays a role in these changes, since paroxetine pretreatment attenuates and in some cases completely eliminated the immunological

effects of MDMA (Pacifici et al. 2004) while only partially reducing elevated cortisol levels after MDMA. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 1998; Connor et al. 2000a; Connor et al. 2000b; Connor et al. 2004). This immunomodulation is an acute effect of MDMA and is not likely to persist for more than 48 hours after MDMA administration.

Safety Pharmacology

Neurological Effects

In clinical studies, doses of MDMA similar to that currently proposed (125 mg) have led to acute neurological changes such as impaired gait, tremor, or nystagmus in a minority of volunteers. The incidence of these effects in clinical MDMA studies is summarized in Tables 2.2 to 2.4 in the Investigators' Brochure. Studies published subsequent to the Investigator's Brochure found similar effects, as reviewed in the first and second updates to the Investigator's Brochure. These effects resolve within several hours. Lasting neurological effects have not been noted.

MDMA appears to produce modest acute changes in neurocognitive performance during peak drug effects. The acute effects of MDMA, generally at doses of either 125 mg or 1.7 mg/kg, have been assessed using the digit symbol substitution task (Cami et al. 2000), a simple reaction time task (Cami et al. 2000; Hernandez-Lopez et al. 2002), a continuous performance attention task (Gamma et al. 2000), the Stroop task (Vollenweider et al. 1998), and a prepulse inhibition measure of sensorimotor gating (Liechti et al. 2001b; Vollenweider et al. 1999b). Of these tasks, only the digit symbol substitution task and the prepulse inhibition task have detected MDMA-induced performance alterations. A study employing the slightly lower dose of 75 mg assessed skills potentially used in driving motor vehicles (Lamers et al. 2003), including visual tracking, divided attention, Object Estimation Under Divided Attention (OMEDA), the Tower of London, and verbal fluency (word generation). Seventy-five mg MDMA did not affect performance on most of the tasks listed above except for the estimation of time needed for a temporarily hidden object to move from one place to another.

Participation in clinical MDMA studies has not been associated with chronic alterations in neurocognitive performance. Data collected by Grob and associates (described in "Previous Human Experience" below) and by Vollenweider and colleagues (Ludewig et al. 2003; Vollenweider et al. 2000, see also pp. 189-190 for IND #63,384) indicate that performance on tests of neurocognitive function is not altered after receiving one or two doses of MDMA in a clinical setting. In contrast, studies of illicit ecstasy users have suggested that repeated MDMA use may be associated with lowered neurocognitive performance, specifically in the areas of memory and executive function (planning and decision making). While a majority of studies have detected these differences (see the Investigator's Brochure and subsequent updates (Baggott et al. 2001; Baggott and Jerome 2003; Jerome 2004 for a detailed discussion), not all studies have detected lower cognitive performance in ecstasy users. A number of studies employing more appropriately matched controls (Halpern et al. 2004; Thomasius et al. 2003) have tended

to find fewer differences in cognitive function, with Halpern and colleagues failing to find impaired verbal memory even in ecstasy users reporting use on 50 or more occasions, indicating that differences detected in earlier studies were at least partially due to use of other drugs, or factors associated with polysubstance use. Subtle but detectable impairments in cognitive function may also appear in people reporting heavy use of ecstasy (Back-Madruga et al. 2004; Bolla et al. 1998; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004). In a retrospective study finding impairment in very high dose recreational users of ecstasy, there was no effect seen among those who had taken up to an estimated 440 mg of “ecstasy” per month for a year or longer and had used it a minimum of 25 times (unpublished table from published study, Bolla et al. 1998). A recent study employing samples of ecstasy users and non-ecstasy users well-matched for moderate use of other substances detected impaired information processing and executive function in people who reported taking ecstasy on 50 or more occasions, but not in people who reported taking ecstasy on fewer than 50 occasions (Halpern et al. 2004). Another study detected impaired memory in ecstasy users who had consumed at least 80 ecstasy tablets over a lifetime, but failed to detect memory impairment in ecstasy users who had taken fewer than 80 tablets (Gouzoulis-Mayfrank et al. 2003).

An examination of the literature relating to ecstasy use and signs and symptoms of anxiety, depression, and other psychiatric symptoms found inconclusive support for increased psychopathology or psychological difficulties in ecstasy users. A number of recent investigations failed to support claims that ecstasy use is uniquely associated with increases in psychological problems. Increased rates of psychiatric symptoms or psychological difficulties in ecstasy users appear to be more strongly associated with polysubstance use or with pre-existing conditions associated with drug use (see for example Dafters et al. 2004; Daumann et al. 2004; Daumann et al. 2001; Lieb et al. 2002; Thomasius et al. 2003). Given the tenuous link between repeated ecstasy use and psychiatric symptoms, it is not expected that two doses of MDMA will have any effects upon subsequent psychological well-being.

Clinical studies have investigated the effects of MDMA on cerebral blood flow. MDMA acutely alters regional cerebral blood flow (rCBF) and may decrease rCBF for several weeks after drug exposure. Gamma et al. (2000a) used [$H_2^{15}O$]-Positron Emission Tomography (PET) to measure rCBF at 75 min after 1.7 mg/kg MDMA in 16 volunteers. They detected increases in prefrontal, inferior temporal, and cerebellar cortex rCBF. Decreased rCBF was detected in limbic, paralimbic, central frontal, and temporal areas. These acute effects of MDMA on rCBF may be followed by decreases in rCBF (Chang et al. 2000), as found in a study where SPECT was performed upon eight volunteers 10 to 21 days after receiving the second of two doses of MDMA administered in a clinical setting. These decreases appeared to be time-limited. Two additional volunteers assessed at 41 and 80 days after last MDMA exposure did not show decreases. Similarly, Gamma et al. did not detect differences in cerebral blood flow between ecstasy users and nonusers during a vigilance task (Gamma et al. 2001). Finally, in the study of acute changes in rCBF (Gamma et al. 2000), the eight volunteers who received 1.7 mg/kg MDMA in their first session did not have altered cerebral blood flow in their second session, which was

conducted at least two weeks later (Vollenweider 2001, letter of support, pp. 189-190, Mithoefer and Wagner 2001; IND #63,384).

Cardiovascular Effects

The acute cardiovascular effects of MDMA were investigated by Lester et al. (2000). 8 volunteers were administered placebo, 0.5 mg/kg, and 1.5 mg/kg (approximately 105 mg) MDMA in a three session placebo-controlled, double blind study. Two-dimensional Doppler echocardiograms were performed one hour after MDMA administration. MDMA was well tolerated and produced hemodynamic effects similar in magnitude to the α -agonist dobutamine, 40 ug/kg per minute intravenously. As discussed above, the dose-dependent effects of up to 2.5 mg/kg (approximately 175 mg) MDMA on heart rate and blood pressure have been characterized by five different research groups, including three in the United States.

In vitro studies of human heart cells demonstrate that MDMA activates 5-HT_{2B} receptors, which stimulate heart valve cell growth (Setola et al. 2003). 5-HT_{2B} receptor agonism is associated with increased incidence of heart valve disease associated with the serotonin releaser fenfluramine (Rothman and Baumann 2002). However, only fenfluramine and its metabolite dexfenfluramine produced statistically significant increases in heart valve cell growth. It is also important to note that valvular heart disease is associated with daily use of fenfluramine, whereas MDMA will not be administered on a daily basis in this study.

Abuse Liability

MDMA is classified as a Schedule I compound with a high potential for abuse, primarily because of its use in settings such as “rave” dance parties. It should be noted that instead of experiencing euphoria, individuals undergoing MDMA-assisted psychotherapy are likely to experience deeply emotional thoughts, feelings, and memories, including thoughts associated with grief, rage, and fear. As a result, it seems unlikely that people undergoing this emotionally challenging psychotherapy 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 with MDMA have been motivated to seek out and use MDMA in non-medical settings. Liechti et al. (2001) reviewed the effects of MDMA in 54 male and 20 female volunteers who had participated in clinical studies and stated “none of the participants expressed any interest in taking MDMA as a recreational drug” after participation in an MDMA study.

In the currently proposed study, diversion is not an issue because MDMA will only be administered under supervision of a research psychiatrist and no take-home doses will be permitted. As discussed elsewhere, MDMA will be stored and handled in compliance with Federal and local regulations for Schedule I compounds. The issue of abuse liability

is discussed in more detail in this application under “Additional Information.”

Pharmacokinetics/Toxicokinetics

Summary of Pharmacokinetic Parameters

Table 4. MDMA Pharmacokinetics

MDMA Dose	N	Cmax <i>μg/l</i>	Tmax <i>H</i>	AUC ₀₋₂₄ <i>μg*h/l</i>	AUC/dose <i>μg*h/(l*mg)</i>	Reference
50	2	19.8 and 82.8	2 and 3	100.1 and 813.9	2 and 16.3	de la Torre et al. 2000a
75	8	130.9 ± 38.6	1.8 ± 0.38	1331.5 ± 646.03	17.8 ± 8.6	Mas et al. 1999
75	12	178 (no SD)	3	Not reported	NA	Lamers et al. 2003
100	8	222.5 ± 26.06	2.3 ± 1.1	2431.38 ± 766.52	24.31 ± 7.7	de la Torre et al. 2000b
100	9	180 ± 33	2 ± 0.26	1452 ± 771	14.52 ± 7.7	Farre et al. 2004
100	7	208.7 ± 17.1	16 ± 0.4	Not reported	NA	Pizarro et al. 2004
125	8	236.4 ± 57.97	2.4 ± 0.98	2623.7 ± 572.9	21 ± 4.6	Mas et al. 1999
150	2	441.9 and 486.9	1.5 and 2	5132.8 and 5232	34.2 and 34.9	de la Torre et al. 2000a

MDMA Dose	N	k _a <i>/h</i>	k _e <i>/h</i>	T _{1/2} <i>H</i>	MDA T _{1/2a} <i>H</i>	Reference
50	2	Na	na	2.7 and 5.1	Na	de la Torre et al. 2000b
75	8	2.3835 ± 2.1362	0.1171 ± 0.0818	7.86 ± 3.58	0.42 ± 0.2	Mas et al. 1999
100	8	2.7 ± 1.53	0.081 ± 0.018	8.96 ± 2.27	1.31 ± 0.55	De la Torre et al. 2000b
100	7	na	0.07 ± 0.03	11.8 ± 4.4	na	Pizarro et al. 2004
125	8	2.1253 ± 1.1001	0.0923 ± 0.0428	8.73 ± 3.29	0.41 ± 0.22	Mas et al. 1999
150	2	Na	na	6.9 and 7.2	Na	De la Torre et al. 2000a

The pharmacokinetics of MDMA, summarized above in Table 4, have been primarily characterized by a group of Spanish researchers, with the exception of one publication from a team of researchers in the Netherlands that was not primarily concerned with pharmacokinetics. Additional pharmacokinetic parameters for MDMA and metabolites are given in the papers cited in Table 4. For example, after 125 mg MDMA, total clearance for MDMA was 51.1 ± 14.1 per hr, while renal clearance was 13.0 ± 5.4 per hr (de la Torre et al. 2000a). The findings of the Spanish researchers are consistent with other investigations using limited doses (Fallon et al. 1999; Hensley and Cody 1999) or illicit users (Crifasi and Long 1996; Moore et al. 1996; Ramcharan et al. 1998).

As can be seen in Table 4, MDMA kinetics are dose dependent within the range of commonly administered doses (de la Torre et al. 2000b). These dose-dependent kinetics appear to be due to dose-dependent metabolism rather than changes in absorption or excretion. Mas et al. (1999) reported that 75 mg and 125 mg doses of MDMA had similar absorption constants and absorption half-lives. On the other hand, non-renal clearance for 125 mg MDMA was approximately half that of 75 mg MDMA. The dose-dependent metabolism of MDMA is at least partially due to inhibition of CYP2D6, as discussed below. It has also been established that the fraction of MDMA bound to dog plasma proteins is approximately 0.4 and is concentration-independent over a wide range of concentrations (Garrett et al. 1991). Therefore, changes in plasma partitioning are not likely to be significant.

Farre and colleagues reported the pharmacokinetics of a second dose of 100 mg MDMA given 24 hours after an initial 100 mg dose in nine men (Farre et al. 2004). C_{\max} was $232 \pm 39 \mu\text{g/L}$, $\text{AUC}_{(24-48)}$ was $2564 \pm 762 \mu\text{g} \cdot \text{h/L}$, $T_{\max(24-48)}$ was $25.5 \pm 0.33 \text{ h}$, and AUC/dose was $25.64 \pm 7.6 \mu\text{g} \cdot \text{h}/1 \cdot \text{mg}$. Maximal MDMA concentration after the second dose was similar to maximal concentration after the slightly higher dose of 125 mg (see Table 4 above), and probably results from non-linear pharmacokinetics. Based on these findings, metabolism of an initial dose will also be affected by a supplemental dose. However, since the size and timing of this dose are different from the dosing regimen employed by Farre and colleagues, it is not clear whether the supplemental dose will produce slightly higher maximal values than expected after the supplemental dose only or the combined dose, or whether it will instead lengthen T_{\max} .

Absorption/Distribution/Metabolism/Excretion

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA which have been identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called alpha-methyldopamine), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999; Pizarro et al. 2002; Segura et al. 2001). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published (de la Torre et al. 2000; Pizarro et al. 2002; Pizarro et al. 2003; Pizarro et al. 2004). HMMA appears to be the main metabolite in humans (Pizarro et al. 2004). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

The oxidation of the methylenedioxy group can take place via enzymes such as cytochrome p450 (Hiramatsu et al. 1990; Kumagai et al. 1991; Lim and Foltz 1988; Tucker et al. 1994) or by a non-enzymatic process involving the hydroxyl radical (Lin et al. 1992). The enzymes catalyzing this reaction have been examined in the rabbit (Kumagai et al. 1991), rat (Gollamudi et al. 1989; Hiramatsu and Cho 1990; Hiramatsu et al. 1990; Hiratsuka et al. 1995) and human (de la Torre et al. 2000; Kraemer and Maurer 2002; Kreth et al. 2000; Lin et al. 1997; Maurer et al. 2000; Tucker et al. 1994; Wu et al. 1997). In human liver microsomes, Michaelis-Menten kinetics for formation of dihydroxylated metabolites are biphasic (Kreth et al. 2000). The low K_m component for demethylenation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher K_m also contribute to MDMA demethylenation, including CY1A2 and CYP3A4.

Although it was hypothesized that genetic variations in CYP2D6 activity might influence risk of MDMA toxicity, this is no longer a concern. Several *in vitro* studies have shown that MDMA is not just a substrate for CYP2D6 but also binds to it, forming an inhibitory complex (Brady et al. 1986; Delaforge et al. 1999; Heydari et al. 2004; Wu et al. 1997).

Compelling *in vivo* evidence of enzyme inhibition was provided by de la Torre et al. (de la Torre et al. 2000a) who showed that plasma levels and 24-hour urinary recovery of HMMA are dose-independent. This is likely the result of inhibition of CYP2D6-mediated DHMA formation. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant. In fact, there currently seems to be no evidence that the poor metabolizer genotype is by itself a major risk factor for acute MDMA toxicity. Kreth et al. (2000) reported that the poor metabolizer trait did not lead to significant alteration in maximal drug plasma concentrations in an individual participating in a clinical study of the MDMA analogue, MDE. At least one poor metabolizer has received MDMA as a participant in a study conducted by the Spanish team (Pacifci et al. 2002, see also Pacifci et al. 2004) without any adverse events occurring. The individual had 60% greater MDMA AUC after a first and a second dose, but the only other reported difference for this participant was a statistically significant increase in amount of NK cells. Issues involved in MDMA metabolism is addressed in a review by de la Torre and colleagues (De la Torre et al. 2004). Evidence from *in vitro* and *in vivo* studies and the cases described above provide further evidence that the role of CYP2D6 in MDMA metabolism is sufficiently limited that it is not a major risk factor for immunocompetent individuals participating in clinical research with MDMA.

Enzymes involved in the formation of MDA from MDMA in human liver microsomes have been investigated by two groups (Kreth et al. 2000; Maurer et al. 2000). Maurer et al. reported that formation of MDA was predominantly catalyzed by CYP1A2 (and to a lesser extent by CYP2D6), but did not present detailed results of their experiments. Kreth et al., in a publication focusing on MDE metabolism, reported high correlations between MDMA and MDE N-dealkylation and MDE N-dealkylation and human liver microsome CYP2B6 content. MDE N-dealkylation and CYP1A2 levels were also significantly correlated. This indicates that CYP2B6 and CYP1A2 participate in the formation of MDA. The role of CYP2B6 in human MDMA metabolism is consistent with rodent research (Gollamudi et al. 1989).

MDMA is a chiral compound and has been almost exclusively administered as a racemate. Studies in human volunteers (Fallon et al. 1999; Hensley and Cody 1999; Pizarro et al. 2003; Pizarro et al. 2004) and rodents (Cho et al. 1990; Fitzgerald et al. 1990; Matsushima et al. 1998) indicate that the disposition of MDMA is stereoselective, with the S-enantiomer having a shorter elimination half-life and greater excretion than the R-enantiomer. For example, Fallon et al. (1999) reported that the area under the curve (AUC) of plasma concentrations was two to four times higher for the R-enantiomer than the S-enantiomer after 40 mg, p.o., in human volunteers. Moore et al. (1996) found greater levels of R-(-)-MDMA in blood, liver, vitreous and bile samples from an individual who died shortly after illicit MDMA use. Stereoselective analysis of biosamples in both an MDMA overdose and a traffic fatality had similar findings (Ramcharan et al., 1998; Crifasi and Long, 1996). The stereoselective pharmacokinetics of MDMA are reflected in formation of MDA and DHMA enantiomers (Fallon et al. 1999; Pizarro et al. 2004; Pizarro et al. 2003). In the first 24 hours after MDMA administration, greater plasma and urine concentrations of S-(+)-MDA than its R-enantiomer occur (Fallon et al. 1999; Moore et al. 1996). By contrast, R/S ratios of

HMMA are more similar to those for MDA (greater amounts of R-(-)-HMMA than S-(+)-HMMA during the first 24 hours), or there is no difference between concentrations of the two enantiomers of HMMA (Pizarro et al. 2003; Pizarro et al. 2004).

Table 5. Urinary Recovery for MDMA and Metabolites (de la Torre et al. 2000a)

MDMA Dose mg (mol)	N	Urinary Recovery (mol)					Dose Excreted (%)
		MDMA	MDA	HMMA	HMA		
50 (259)	2	20.7 and 40.9	1.4 and 1.0	152.0 and 89.2	4.7 and 4.2	69.1 and 38.3	
75 (358)	8	71.2 ± 13.7	3.5 ± 0.9	128.3 ± 21.8	5.4 ± 0.4	53.7 ± 11.4	
100 (518)	2	232.6 and 74.7	1.4 and 5.6	59.8 and 124.0	2.9 and 6.8	57.3 and 40.7	
125 (647)	8	169.6 ± 69.5	6.4 ± 2.7	148.3 ± 102.8	6.2 ± 3.7	51.0 ± 16.2	
150 (776)	2	160.3 and 333.3	2.6 and 4.7	122.2 and 82.4	4.1 and 3.7	37.3 and 54.7	

The urinary excretion of MDMA and its metabolites was first characterized by de la Torre and colleagues, with data from that study presented in Table 5 above. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004; Segura et al. 2001; Pizarro et al. 2004; Pizarro et al. 2003). Urinary excretion of the MDMA metabolite HHMA reported after the administration of 100 mg MDMA to four men are 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

Toxicology

The toxicity of MDMA has been investigated in numerous animal and *in vitro* studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Finally, 28-day toxicity studies in canines and rodents have been performed and are included in the MDMA Drug Master File (DMF #6293). Thus, the toxicity of MDMA is well characterized.

Serious MDMA toxicity is rare in uncontrolled settings, considering the millions of users taking “ecstasy” of unknown identity, potency, and purity (Baggott 2002; Gore 1999; Henry and Rella 2001). Under these conditions, the most common serious adverse event involves hyperthermia, which often appears to be influenced by prolonged physical exertion (dancing) in an area with a high ambient temperature. Reports of toxicity in illicit ecstasy users are summarized in the Investigator’s Brochure (Baggott et al. 2001), and a brief review of more recent reports are covered in the latest update of the Investigator’s Brochure (Jerome 2004). In addition to hyperthermic syndromes, other rare adverse events include dysphoric responses, hepatotoxicity, and hyponatremia. In the proposed clinical study, volunteers will be carefully monitored for signs and symptoms of these unlikely events, as discussed in “Monitoring for Toxicity,” above. As described in “Previous Human Experience” below, exposure to MDMA in a controlled clinical setting has not been associated with toxicity. As well, improvement in quality of life occurring

after MDMA-assisted psychotherapy should be weighed out against any concerns of MDMA toxicity.

Published animal and *in vitro* studies have specifically investigated the possibility of hyperthermia, hepatotoxicity and neurotoxicity after MDMA exposure. These types of toxicity appear to be dose-dependent and all available evidence indicates that the risks in these areas are minimal in the currently proposed study. These areas of toxicity are discussed below. Neurotoxicity will be discussed in two sections; the first concerning serotonergic axon damage and the second concerning neuronal cell death. Finally, the issue of reproductive and developmental toxicity will be briefly mentioned.

Hyperthermia

As discussed above, MDMA administered in a controlled setting produces only a slight increase in body temperature. However, hyperthermia is one of the most commonly reported serious adverse events in ecstasy users. Peripheral vasoconstriction (Pedersen and Blessing 2002), non-shivering heat production and possible effects on heat-production related uncoupling proteins (Mills et al. 2003; Sprague et al. 2003), and activity at serotonin or norepinephrine receptors (Fantegrossi et al. 2003; Fantegrossi et al. 2004) all may play a role in generating hyperthermia. Hyperthermia may be dose dependent, as suggested by case series of people who took ecstasy in the same London area nightclub on the same evening (Greene et al. 2003). Studies in rats and mice suggest that crowded housing (Fantegrossi et al. 2003) and high ambient temperature (see for example Brown and Kiyatkin 2004; Green et al. 2004; Malberg et al. 1998) promotes a hyperthermic reaction to MDMA. It is expected that hyperthermia will be very unlikely in the proposed study setting, since the participant will be in a room maintained at a comfortable temperature and he or she will not experience crowding. The investigators will periodically measure body temperature with an automatic temperature sensor and telemetry device worn on the skin, and the investigators will also measure ambient temperature during the course of the study.

Hepatotoxicity

Because hepatotoxicity has been noted in ecstasy users, five *in vitro* and two *in vivo* studies have examined the hepatotoxicity of MDMA. These studies show that MDMA can impair liver cell viability, but 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.

In one study, MDMA caused increases in ALT, AST, and LDH activities in rat hepatocytes (Beitia et al. 2000). These increases were statistically significant with high concentrations of MDMA (1 mM for six hours) or lower concentrations for prolonged exposures (0.1 mM for 24 hours). Further evidence of MDMA-induced toxicity to hepatocytes came from moderate decreases in ATP (after three, but not one, hour incubation with 0.1 mM MDMA). A second *in vitro* study examined the possible pro-fibrogenic effects of MDMA on the liver by measuring expression of procollagen mRNA

in a cell line of hepatic stellate cells (Varela-Rey et al. 1999). These cells produce the collagen characteristics of a fibrotic liver. Expression of $\alpha 1(I)$ procollagen mRNA was significantly increased by 0.5, but not 0.1, mM MDMA for 24 hr. This effect required sustained exposures, as 1 mM MDMA for 8 h did not increase mRNA expression. A third *in vitro* study using mouse hepatocytes showed that MDMA increases lipid peroxidation and loss of cell viability produced by hyperthermic conditions (Carvalho et al. 2001). 1.6 mM MDMA slightly but significantly decreased cell viability, yet it did not affect lipid peroxidation over 60 to 180 min under normothermic (37° C) conditions. When temperature was raised to 41° C, the hepatotoxicity of MDMA was dramatically increased. At this temperature, 1.6 mM MDMA approximately doubled lipid peroxidation after 180 min and decreased cell viability after as little as 60 minutes. A lower concentration, 0.8 mM MDMA, also decreased cell viability after 180 min at 41° C but not at 37° C. The fourth study incubated rat liver cells with 0.5 to 5 mM MDMA for 8 or 24 hours and assayed for apoptosis with cell staining, Western blot for apoptosis-related factors, and bax assays (Montiel-Duarte et al. 2002). Higher concentrations increased signs of apoptosis, but at doses that are about eleven times those usually seen in humans. The fifth study examined the effects of 3 hours of incubation with 0.8 to 1.6 mM MDMA metabolites MDA and alpha-MeDA on liver cells (Carvalho et al. 2003) and found that alpha-MeDA but not MDA increased signs of liver peroxidation at the higher concentrations.

In vivo studies in mice indicate that ambient temperature and oxidative stress may be involved in liver toxicity. Carvalho and colleagues assayed liver sections from mice given a single i.p. injection of 5, 10 or 20 mg/kg MDMA in either a 20 °C or a 30 °C environment for antioxidant enzyme levels, signs of lipid peroxidation, and cell histology (Carvalho et al. 2002). The researchers found that increases in MDMA dose and ambient temperature during MDMA administration affected degree of apparent oxidative stress and detectable liver abnormalities. In the second study, repeated injections of 10 mg/kg, but not 5 mg/kg, of the MDMA enantiomer S-(+)-MDMA (4 s.c. every 2 h), produced some hepatic necrosis (Johnson et al. 2002), with more pronounced effects in mice fed a vitamin E deficient diet than in mice receiving sufficient amounts of vitamin E.

Hepatotoxicity has not yet been reported to occur in any of the clinical studies where MDMA was administered to research subjects, and the drug exposures that can damage liver cells would not occur in the currently proposed clinical study. The lowest concentration that impaired cell functioning in these studies (0.1 mM or ~19.3 mg/l MDMA) affected indices of cell viability after 24, but not 6, hours in the study by Beitia et al (2000). This same concentration had no significant pro-fibrogenic effect after 24 hr in the study by Varela-Rey et al (1999). This lowest toxic concentration is approximately 82 times higher than the expected peak MDMA plasma level ($236.4 \pm 57.97 \mu\text{g/l}$ MDMA) after 125 mg, the proposed dose in this study. Liver exposure to drugs is often higher than plasma levels. In an autopsy of a deceased ecstasy user, liver MDMA concentration was 7.2 times higher than femoral blood MDMA concentration (Rohrig and Prouty 1992). Thus, the peak liver exposure to MDMA in a clinical setting should be approximately one-eleventh the concentration shown to impair cell viability in these studies. This peak concentration would only be briefly sustained. Therefore it is unlikely

that MDMA exposures in clinical studies will approach those demonstrated in these studies to impair rat liver cell viability or induce procollagen mRNA. Higher ambient temperatures appear to amplify the degree and likelihood of hepatotoxicity, and since study participants will receive MDMA in a comfortable room and the investigators will monitor ambient temperature during the course of the study, it seems especially unlikely that MDMA will induce hepatotoxicity. Nonetheless, people with significant liver disease will be excluded from the study, and participants will be monitored for hepatotoxicity with liver panels performed before MDMA administration and at the time of medical examination follow-up (“Day 36” – see Table 1 above).

Neurotoxicity

Extensive studies in animals indicate that high or repeated dose MDMA exposure can oxidatively damage serotonergic axons originating in the dorsal raphe nucleus of the brainstem. This is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter. Although some regrowth occurs, seemingly permanent redistribution of axons was noted in a study with squirrel monkeys (Hatzidimitriou et al. 1999). These serotonergic changes have not been associated with lasting behavioral impairment in the vast majority of animal studies, despite dramatic serotonin depletions. The great volume of research addressing MDMA neurotoxicity is discussed in more detail in the Investigator’s Brochure and subsequent updates of the Investigator’s Brochure (Baggott et al. 2001; Baggott and Jerome 2003; Jerome 2004).

A study published in 2004 comparing MDMA administration (3 7.5 mg/kg doses given i.p.) with the serotonin neurotoxin 5,7-DHT in rats found that DHT, but not MDMA, reduced serotonin transporter and brain serotonin while increasing levels of glial fibrillary acidic protein (GFAP), a marker of neuronal injury (Wang et al. 2004). MDMA lowered brain serotonin without altering levels of serotonin transporter or GFAP, suggesting a dissociation between brain serotonin levels and other presumed markers of neurotoxicity, and an investigation of neurons from the substantia nigra of mice given four 5 mg/kg doses every 2 hours found signs of oxidative stress, such as increased signs of DNA fragmentation and ubiquitin-positive whorls, but no signs of cell death (Fornai et al. 2003). However, in contrast, raphe neurons taken three weeks after rats received twice-daily s.c. doses of MDMA on four consecutive days were much less able to transport radioactively labeled praline, used as a measure of axonal neurotoxicity (Callahan et al. 2001). Examining and considering these and other research findings continues to demonstrate the contentious nature of findings relating to MDMA neurotoxicity.

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 in previous clinical MDMA studies. 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. 1999a; Vollenweider et al. 2001), 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). Finally, studies in rhesus monkeys suggest that use of interspecies scaling to arrive at dosing in previous studies produced inappropriately high doses of MDMA.

Vollenweider and colleagues recently measured serotonin transporter density using positron emission tomography (PET) with [¹¹C]McN5652 before and after a single clinical MDMA exposure (Vollenweider et al. 2000, data presented at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine). Vollenweider and colleagues were unable to detect any lasting effect of 1.5 or 1.7 mg/kg MDMA in a pilot study with six MDMA-naive healthy volunteers and in a second study with additional volunteers (n = 8). This ligand and measurement technique had been previously reported by another group to be sensitive to apparent serotonin transporter changes in illicit ecstasy users with at least 70 drug exposures (McCann et al. 1998). This measurement technique was validated in a study using a baboon exposed to a neurotoxic MDMA regimen (Scheffel et al. 1998), and this validation study found that PET tended to overestimate serotonin transporter changes in most cases. A more recent study in humans that employed this ligand also found reduced levels of serotonin transporter in current ecstasy users, but did not report as large a reduction in serotonin transporter as did the original study (Buchert et al. 2003; Buchert et al. 2004). Given the small sample size in the study by Vollenweider et al., it is possible that a modest change in SERT density could have gone undetected. However, very little variance in ligand binding was found in baseline measures of ligand binding.

Imaging studies in repeated ecstasy users have consistently found lower serotonin transporter levels, but these findings are also qualified by degree of exposure and period of abstinence. One study using the same ligand used by McCann and colleagues (Buchert et al. 2003; Buchert et al. 2004) and one study using a different ligand (Reneman et al. 2001) both found that serotonin transporter levels returned to normal in people who abstained from ecstasy for a year to a year and a half. Both studies also found greater reductions in serotonin transporter, greater numbers of affected areas, in women. Reneman and colleagues (2001) also compared people reporting at least 50 exposures with people who reported fewer than 50 exposures, and they found that moderate ecstasy users (those reporting use on fewer than 50 occasions) did not have significant reductions in serotonin transporter sites. These findings suggest that effects on serotonin transporter may be at least partly dependent on degree of use and time since last exposure.

Because of findings in humans and non-human animals, the possibility of neurotoxicity will be discussed with all volunteers, even though strong evidence from studies in humans and non-human animals suggests that the risk of neurotoxicity posed by participating in this study is low.

Interspecies pharmacokinetic comparisons support the safety of 125 mg MDMA in humans. 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 AUC are approximately 30% of the rat AUC. Similarly, human C_{max} are approximately 10% of rat C_{max}.

We note that this comparison is limited by several considerations. First, it is not known whether rats and humans have different vulnerability to the same MDMA exposure. Second, it is not known whether metabolites of MDMA contribute to neurotoxicity. If they do, then the margin of safety for 125 mg MDMA should be even wider because formation of metabolites is more extensive in rodents than in humans. Third, rats and humans may differ in the brain concentration of drug produced by a given blood concentration. In rats, MDMA concentrations in the brain are 7 to 10 times higher than in plasma (Chu et al. 1996). In a human fatality, postmortem MDMA concentrations were about 6 times higher in the brain than in the plasma (Rohrig and Prouty 1992), although postmortem drug redistribution may have occurred. If these data are reliable, rats may have similar peak brain levels to humans when plasma levels are the same. Fourth, neurotoxicity in rodents appears to be increased by hyperthermia in many studies. Finally, the threshold for neurotoxicity is not well established in rats. The threshold for neurotoxicity in Sprague-Dawley rats appears to be above 10 mg/kg (Battaglia et al. 1988) and below 20 mg/kg (Commins et al. 1987). Therefore, a conservative comparison indicates that human MDMA exposure (measured as plasma AUC) after 125 mg is likely between 30% and 60% of the exposure required for neurotoxicity in rats. Because of non-linear pharmacokinetics and possible differences in rat versus human MDMA disposition, at least one researcher has concluded that using interspecies scaling is not recommended for calculating equivalent doses in neurotoxicity studies (De la Torre and Farre 2004). We think that the margin of safety is probably wider due to the presence of hyperthermia and increased formation of toxic metabolites in animal studies but not in clinical MDMA trials.

In conclusion, the lack of apparent toxicity in previous clinical MDMA studies, evidence of unaltered serotonin transporter density after similar doses, and toxicokinetic comparisons suggest that the doses of MDMA used in this study are unlikely to produce measurable neurotoxicity or significant adverse functional consequences.

MDMA-Induced Neuronal Apoptosis (Programmed Cell Death)

Two *in vitro* studies have suggested that MDMA may trigger programmed neuronal cell death (apoptosis) under certain conditions. This phenomenon has not been verified *in vivo*. No cell death occurs in regions containing the cell bodies of serotonergic neurons after MDMA exposure (Fischer et al. 1995; Hatzidimitriou et al. 1999; O'Hearn et al. 1988). However, one study detected evidence of non-serotonergic cell body damage in the rat somatosensory cortex after 80 mg/kg MDMA (Commins et al. 1987). It is theoretically possible that this damage was due to apoptosis. MDMA-induced apoptosis appears to require high concentrations and exposure times. It is unlikely that 125 mg MDMA in the currently proposed clinical study will trigger programmed cell death in neurons. In the currently proposed study, the peak brain concentration of MDMA is

estimated to be approximately 6% of a concentration that produced no toxicity after 96 hr of exposure *in vitro*.

Forty-eight hours of incubation with MDMA dose-dependently decreased survival of cultured human placental serotonergic cells (Simantov and Tauber 1997). This decreased cell viability was accompanied by DNA fragmentation and cell cycle arrest (in the G2M phase). Forty-eight hour exposure to 0.4 mM MDMA decreased cell survival by $1.4 \pm 4\%$, while 1.2 mM MDMA decreased cell survival by $61 \pm 9\%$. In another study, the effects of MDMA on cultured rat neocortical neurons were studied at concentrations of 125 to 1000 μM MDMA and exposure times of 1, 24, and 96 hours (Stumm et al. 1999). Cell survival was decreased by $34.2 \pm 11.4\%$ at 96 hours after an average exposure of 500 μM MDMA, but not after 125 μM MDMA. Stumm et al. also noted DNA fragmentation and altered expression of the *bcl-x_{LS}* gene, which supports the interpretation that programmed cell death had occurred. The degree of cytotoxicity noted for MDMA in this study was comparable to the toxicity produced by other structurally related amphetamines.

A study that used fluoro-jade staining to examine brain sections from rats killed 3 days after receiving 10, 20 or 40 mg/kg MDMA found increased staining in most brain areas in rats given 40 mg/kg MDMA, and in some brain areas in some rats given 20 mg/kg MDMA (Schmued et al. 2003). Increased signs of neuronal degeneration were strongly associated with hyperthermia, suggesting a role of dose and body temperature in producing these effects. However, as discussed earlier, another study examining substantia nigra in mice given a total dose of 20 mg/kg (four doses of 5 mg/kg) found signs of oxidative stress, but failed to find signs of frank cell death (Fornai et al. 2003).

It is unlikely that MDMA exposures in the currently proposed clinical study will approach those demonstrated to trigger programmed cell death in neurons. If MDMA levels in the brain are about 6 times higher than in plasma (Rohrig and Prouty 1992), then 125 mg MDMA should produce peak plasma levels of $236.4 \pm 57.97 \mu\text{g/l}$ MDMA (de la Torre et al. 2000b) and peak brain levels of $1.4 \pm 0.3 \text{ mg/L}$. This estimated peak level is significantly less than the lowest drug concentration used in either apoptosis study. While 0.4 mM MDMA or 77.3 mg/L had modest effects in the first study, 125 μM or 24.2 mg/L had no significant effect in the second study. Peak plasma levels after a supplemental dose of 62.5 mg follows 125 mg are liable to be somewhat higher, but they are not likely to approach levels in brain that produced cell death. Given these concentration differences and the long exposure times used in these studies, it does not seem likely that human oral doses of MDMA would be sufficient to induce programmed cell death in neurons. Additionally, body temperature is only slightly elevated in humans given MDMA in clinical settings, further reducing any possible effects due to hyperthermia.

Reproductive and Developmental Toxicity

As discussed in the Investigator's Brochure, 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 McEllhatton and colleagues are, in fact, the result of “ecstasy” consumption. Neonatal rats given repeated doses of MDMA show signs of lower brain serotonin and showed impairments in learning and memory, with the neonatal period in rats considered equivalent to the third trimester of pregnancy in humans. In one study, rats given the very high, repeated dose regimen of 20 mg/kg MDMA twice daily from Day 11 to Day 20 performed less well on a task assessing spatial learning and memory (Williams et al. 2003), and had lower brain serotonin and greater increases in the dopamine metabolite homovanillic acid (HVA) in frontal cortex, hippocampus and striatum (Koprach et al. 2003A). Maternal administration has produced contradictory results. Rats born to dams given twice-daily injections of 15 mg/kg for 7 consecutive days were less active in a novel environment (Koprach et al. 2000B), yet lower brain serotonin was not detected in rats born to dams given twice-daily injections of 20 mg/kg MDMA for four days (Kelly et al. 2002). Pregnant women will be excluded from participation in the proposed study and urine pregnancy tests will be performed before each drug administration.

Previous Human Experience

Clinical MDMA research using healthy volunteers has been conducted by at least six research groups, including three in the United States. Double-blind placebo-controlled MDMA studies have been published in peer-reviewed journals. To date, the most extensive studies have been carried out by Franz Vollenweider of the University of Zurich and his colleagues. They have administered up to two doses of 1.5 to 1.7 mg/kg MDMA to 74 subjects. These researchers have published studies of brain imaging, EEG, cardiovascular, neuroendocrine and subjective effects of MDMA (Frei et al. 2001; Gamma et al. 2000; Liechti et al. 2000a; Liechti et al. 2000b; Liechti et al. 2001a; Liechti et al. 2001b; Liechti and Vollenweider 2000a; Liechti and Vollenweider 2001b; Vollenweider et al. 1998; Vollenweider et al. 1999). The Zurich researchers have also published a review of the data that notes gender differences in MDMA effects (Liechti et al. 2000a), and they have presented data at conferences investigating the effects of up to two doses of 1.5 to 1.7 mg/kg MDMA on levels of serotonin transporter or cognitive function (Ludewig et al. 2003; Vollenweider et al. 2000). A team of researchers in Spain have measured the subjective, cardiovascular, and immunological effects of 50, 75, 100, 125 and 150 mg MDMA, alone and, in some studies, in combination with ethanol (Cami et al. 2000; Hernandez-Lopez et al. 2002; Mas et al. 1999; Pacifici et al. 1999; Pacifici et al. 2001; Pacifici et al. 2002; Pacifici et al. 2004). This same team of researchers has investigated the effects of repeated doses of 100 mg MDMA, with the second dose given four or 24 hours after the initial dose (Farre et al. 2004; Pacifici et al. 2002), and they have published countless pharmacokinetic and drug detection studies (e.g. de la Torre et al. 2000; Navarro et al. 2001; Pichini et al. 2002; Pichini et al. 2003; Pizarro et al. 2002; Pizarro et al. 2003; Segura et al. 2002). While it appears that the researchers reported data from the same sample in several studies, they have administered MDMA to 42 to 54 subjects. A team of researchers at Wayne State University in Detroit has assessed cardiovascular, subjective, and neuroendocrine effects of about 1.1, 1.6, and 2.1 mg/kg MDMA, as compared with the psychostimulant d-amphetamine and the serotonin releaser and serotonin receptor agonist mCPP in 22 men and women with prior use of ecstasy (Tancer and Johanson 2001). This team has also performed a similar study of 1 and 2 mg/kg MDMA in 12 men and women that also measured rewarding effects (Tancer and Johanson 2003). The Wayne State researchers have also presented data from studies of ambient temperature and 2 mg/kg MDMA in four subjects, and co-administration of fluoxetine with 1.5 mg/kg MDMA in eight subjects (Tancer and Johanson 2004; Tancer et al. 2003). Researchers at UCLA-Harbor Medical Center assessed cardiovascular, neuroendocrine and some subjective effects of ascending doses of MDMA that varied from 0.25 to 2.5 mg/kg MDMA in 18 men and women who had reported some ecstasy use (see IND #63,384, pp. 44-48 and pp. 52-70 for more details; Grob et al. 1996). A team of researchers in the Netherlands has studied the cardiovascular and subjective effects of 75 mg MDMA in 12 men and women reporting ecstasy use (Lamers et al. 2003; Samyn et al. 2002), focusing on acute effects of MDMA on skills related to driving. Researchers at the University of California-San Francisco have studied the cardiovascular, subjective and neuroendocrine effects of MDMA in eight men and women with past experience with ecstasy (Harris et al. 2002; Lester et al. 2000). Lastly, researchers in England studied the neuroendocrine effects and pharmacokinetics of 47.6

mg MDMA (equivalent to 40 mg freebase) in eight drug-naïve men, specifically examining changes in arginine vasopressin release (Fallon et al. 2000; Forsling et al. 2001; Henry et al. 1999). Up to 2.5 mg/kg MDMA was well tolerated in these clinical trials, and no serious adverse events were reported in any of the published or unpublished reports. More information on the acute effects of MDMA can be found in the Investigator's Brochure (Baggott et al. 2001) and the two successive revisions to the IB (Jerome and Baggott 2003; Jerome 2004).

Clinically significant hypertension has occurred in approximately 5% of individuals enrolled in controlled studies of MDMA (Grob et al., Unpublished, see also pp. 45 in IND #63,384; Vollenweider et al. 1998), and significant hypertension has occurred in at least one participant in the study of MDMA-assisted therapy in people with PTSD (Mithoefer, 2004a, personal communication to R Doblin and L Jerome, Nov 4, 2004). However, hypertension subsided without clinical intervention in all cases. Plans for monitoring and treating hypertension are described in detail below in "Monitoring for Toxicity."

A study of the effects of two separate sessions of MDMA-assisted therapy in people with posttraumatic stress disorder (PTSD) is underway (Mithoefer 2004c). This study is described in IND #63,384 and uses two doses of 125 mg MDMA or placebo given three to five weeks apart. So far, five participants have completed the study without occurrence of any serious adverse events (Mithoefer, 2004b, personal communications to R Doblin Nov 12, 2004). Because the study is still operating and the blind has not been broken, it is not known how many of these subjects have received MDMA, but it can be assumed given the study design that between one and three individuals have received the experimental intervention. A team of researchers in Spain have administered 50 mg, 75 mg MDMA, or placebo to women with PTSD arising from a sexual assault. This study also reported no serious adverse events. However, this study has since been halted due to political concerns expressed by the local anti-drug authority (Bouso, 2003, communication to R Doblin and L Jerome, January 15, 2003). Since the study was halted without being discontinued, the blind was not broken and it is not known whether participants received the experimental intervention or placebo. MDMA has been tolerated by participants in both the ongoing and the halted study, assuming that one or more participant received MDMA.

There also exists an extensive history of using MDMA as an adjunct to psychotherapy prior to scheduling (Adamson 1985; Greer and Tolbert 1986; Greer and Tolbert 1998; Grinspoon and Bakalar 1986; Metzner and Adamson 2001; Stolaroff 1997; Widmer 1998). Narrative accounts and case reports of MDMA given in these circumstances indicated that MDMA was tolerated and that no serious adverse events occurred. Two uncontrolled studies of MDMA (Downing 1986; Greer and Tolbert 1986), including one performed in a psychotherapeutic context (Greer and Tolbert 1986) also found that study participants tolerated MDMA and reported no serious adverse events. Lastly, during a period lasting from 1988 to 1993, psychotherapists in Switzerland were permitted to administer MDMA to patients (Gasser 1994; Widmer 1998). These therapists reported

that MDMA-assisted psychotherapy was tolerated and did not report any serious adverse events occurring after MDMA administration.

In summary, researchers have measured the cardiovascular, physiological, neuroendocrine, neurofunctional (PET and EEG), psychiatric, and subjective effects of MDMA at doses ranging from 0.25 to 2.5 mg/kg, and researchers are currently studying the effects of 125 mg MDMA given as an adjunct to psychotherapy in people with posttraumatic stress disorder. MDMA has been generally well tolerated in these studies, and we are aware of no serious adverse events. Participants with and without previous experience with MDMA reported that the effects of MDMA were mostly pleasant and otherwise tolerable (Cami et al. 2000; Farre et al. 2004; Grob et al. 1996; Harris et al. 2002; Hernandez-Lopez et al. 2002; Liechti et al. 2001; Tancer and Johanson 2001; Tancer and Johanson 2003; Vollenweider, 1998). Occasionally, dysphoric responses to MDMA have occurred, but have always resolved within several hours, and transient changes in thought processes are reported (Harris et al. 1998; Vollenweider et al. 1998). Clinically significant hypertension has occurred in several volunteers; these cases are discussed above. To date, there is no indication that administration of MDMA in controlled settings has any adverse effects on cognitive function (Grob et al. Unpublished; Ludewig et al. 2003; Vollenweider et al. 2000). As shown in Table 2.5 of the Investigator's Brochure, Grob et al. did not detect any change in neurocognitive function in their volunteers. Similarly, Vollenweider and colleagues (Ludewig et al. 2003; Vollenweider 2001; IND #63,384 pp. 189-190; Vollenweider et al. 2000) report that retrospective analysis of their studies did not detect any lasting effect of MDMA on psychological and neuropsychological measures, cerebral blood flow ($H_2^{15}O$ -PET), and electrophysiological indices of information processing such as prepulse inhibition of the startle reflex (PPI) and brain wave activity (EEG/ERP). Most importantly, preliminary analysis using positron emission tomography (PET) and the radioligand McN-5256 revealed no significant changes in estimated serotonin transporter density four weeks after a single dose of MDMA (1.5–1.7 mg/kg) in MDMA-naive volunteers (Vollenweider et al. 2001). This data and the history of past use of MDMA in psychotherapy prior to scheduling indicate that MDMA can be safely administered to humans.

Additional Information

Most of the proposed study will take place at appropriate research facilities at McLean Hospital in Belmont, MA. McLean Hospital is a psychiatric facility and research hospital affiliated with Harvard Medical School. Pre-screening of prospective subjects and a medical examination performed one week after the second experimental session will be conducted by Dr. Shuster, the oncologist investigator, at the Department of Medical Oncology at the Lahey Clinic in Burlington, MA.

Staff at McLean Hospital will be capable of dealing with any medical or psychiatric emergencies that arrive during the course of either experimental sessions. As noted, Dr. Siegel will be present on grounds during each experimental session and will be reachable through on-call radio. There will be a crash cart available for treating hypertensive crises or other related events, and the investigators can call on staff to assist in treatment of medical emergencies. Diphenhydramine, injectable epinephrine, and other standard emergency drugs and equipment will be available in the treatment room if needed for countering an allergic reaction or other medical emergency. Available emergency medications include antihypertensive agents (such as nitroprusside and labetalol), pressor agents, anxiolytics, and intravenous fluids. In addition to these medications, the crash cart contains a defibrillator (with telemetry capability), an oxygen tank, a 12-lead electrocardiogram (ECG) device, a suction device, a pulse oximeter, an IVAC pump, and intubation equipment (including laryngoscope, and endotracheal tubes).

The hospital nearest McLean Hospital that has a medical emergency room and intensive care unit is Mt. Auburn Hospital, which is about four miles from McLean Hospital. It should take less than ten minutes to reach Mt. Auburn Hospital by ambulance.

Drug Dependence and Abuse Potential

As noted above in the Introductory Statement and in “Monitoring for Toxicity”, MDMA is classified as a Schedule I drug with a high potential for abuse. Studies in non-human animals and retrospective studies of humans confirm the presence of abuse potential. However, clinical trials of MDMA do not suggest that drug-naïve participants given MDMA in controlled settings are likely to seek out ecstasy in uncontrolled settings. Features of MDMA-assisted psychotherapy are expected to lessen the likelihood that participants will seek out or use ecstasy outside the confines of the study.

Recreational use of MDMA started possibly as early as the 1960s (see Shulgin 1991) and is known to have occurred during the late 1970s and early 1980s. Instances of abuse and dependence in users have been reported (Jansen 1995; Topp et al. 1999). While studies using non-representative samples, including samples of drug users, have reported diagnosing up to 30% of users with abuse or dependence (Topp et al. 2002; Cottler et al. 2001), a survey of a representative sample of young Munich residents found that about 6% of people reporting ecstasy use had signs of abuse or dependence on the drug. This suggests that some people who take ecstasy may develop substance abuse or dependence on the drug. It is important to note that people begin using ecstasy only after they have

begun using cannabis or other illicit substances (Pedersen and Skrondal 1999; see also age of onset in Daumann et al. 2004, for example). Measuring reward value by finding the point at which people would switch from receiving drug to either giving up or receiving money, Tancer and Johanson (2003) found that 2 mg/kg MDMA and 20 mg d-amphetamine had higher reward value than placebo, and that 1 mg/kg MDMA and 10 mg d-amphetamine did not significantly higher reward value than placebo. However, participants in this study were selected for past use of ecstasy and minimal use of other substances, so seems likely that study participants would assign high reward value to MDMA.

Studies in rodents (e.g. Cornish et al. 2003; Robledo et al. 2004; Schenk et al. 2002; Wakonigg et al. 2004) and non-human primates (Beardsley et al. 1987; Fantegrossi et al. 2002; Fantegrossi et al. 2004; Lamb and Griffith 1987) suggest that animals will self-administer MDMA. Conditioned place preference, referring to the tendency to spend more time in a chamber associated with an injection of the drug, was reported to occur in rats given MDMA (Bilsky et al. 1990; Cole and Sumnall 2003; Meyer et al. 2002). A study that examined the rapidity with which a drug-naïve rat descended a runway to obtain an injection of MDMA also found that animals descended the runway more rapidly when MDMA was available (Wakonigg et al. 2004). All of these findings suggest that MDMA possesses some reward value for rats, usually considered a sign of human abuse potential.

A number of studies have found that non-human primates self-administer MDMA, though to date, all studies have employed animals previously experienced with the self-administration of other substances, such as cocaine or methamphetamine. Rhesus monkeys self-administered an average of 2 to 4 mg/kg MDMA in one study (Fantegrossi et al. 2004) during twice-daily hour-long sessions occurring approximately three times a week. Less self-administration was seen at the end of an eighteen-month period, suggesting that when repeatedly self-administered, MDMA loses some reward incentive. However, overall findings in non-human primates support the presence of at least some abuse liability. Baboons that had previously self-administered cocaine also self-administered MDMA (Beardsley et al. 1987)

MDMA given within the context of psychotherapy will be associated with both pleasant and unpleasant emotional experiences. It is expected that some participants will be confronting thoughts, feelings, and memories that provoke negative emotions such as fear, anger, and grief. The investigators will encourage participants to explore these deeply emotional thoughts and experiences. While MDMA is expected to have an anxiolytic effect during these explorations, it is not expected that experimental sessions will be carefree events. As noted, even healthy participants taking part in research studies did not express a desire to use MDMA outside of laboratory settings when asked about future behavior (Liechti et al. 2001).

The abuse potential of MDMA is acknowledged but appears to be no greater than the abuse liability of conventional anxiolytics. The investigators will include only study participants who have not received a diagnosis of substance abuse or dependence on any

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substances save caffeine or nicotine in the sixty days prior to screening. Prospective participants and participants will be encouraged to voice concerns about abuse or dependence issues with the investigators.

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Appendix A

Investigator *Curriculum Vitae*

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