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Study Protocol

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

1.0 Aims and Goals

The protocol is a randomized, dose-response pilot study of \pm 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in twelve subjects experiencing anxiety associated with a diagnosis of advanced-stage cancer with one year or less of life-expectancy. Subjects will be randomized into one of two groups that differ only in the dosage of MDMA administered; group assignment is double-blind.

This initial pilot study is intended to allow the researchers to evaluate the safety of the intervention for individuals with advanced-stage cancer as well as evaluate the instruments used for outcome measures and the timing of these measures. Because no previous well-controlled studies have assessed the efficacy of MDMA-assisted psychotherapy, this pilot study will also be used to refine the experimental intervention itself. We recognize that this study is under-powered for all but large effects and that trends seen in this study must be interpreted with caution. A preliminary treatment manual has been written to describe the use of MDMA-assisted psychotherapy in subjects with advanced-stage cancer with anxiety (Ruse et al. 2004).

If data collected from this study 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 results of both of these pilot studies are favorable, the data gathered 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.

MAPS is currently sponsoring an ongoing, FDA-approved pilot study of MDMA-assisted psychotherapy in subjects with posttraumatic stress disorder (PTSD), with this study still in the early stages (Mithoefer 2004). A preliminary treatment manual has been written to describe the use of MDMA-assisted psychotherapy in subjects with PTSD (Ruse et al. 2002), with this treatment sharing common elements with the treatment of subjects with anxiety related to advanced-stage cancer (Ruse et al. 2004). The Heffter Research Institute is sponsoring a study on the use of psilocybin-assisted psychotherapy in advanced-stage cancer patients. This study is currently underway at Harbor-UCLA Medical Center, under the direction of Dr. Charles S. Grob.

1.1 Specific Hypotheses

The proposed study is primarily intended for two purposes. The first is to explore whether MDMA-assisted psychotherapy can safely be administered to advanced cancer patients with a prognosis of less than 12 months who suffer from anxiety related to the advanced-stage cancer diagnosis. 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 STAI will serve as a primary outcome measure of anxiety. 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 2 for the timeline). The 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).

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.

2.0 Background and Significance

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 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; 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.

To date, several Phase I trials have been conducted in the United States, Spain, Switzerland, and the Netherlands; MDMA has been administered to over 112 participants in controlled studies conducted within the United States, and to over 133 more individuals in controlled studies conducted in Europe. When MDMA is used in therapeutic doses in a controlled setting, the risk/benefit ratio is favorable (Cami et al. 2000; Chang et al. 2000; de la Torre et al. 2000a; de la Torre et al. 2000b; Grob et al, In Preparation, data presented to FDA; Grob et al. 1996; Harris et al. 2002; Hernandez-Lopez et al. 2003; Lester et al. 2000a; b; 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). By and large, MDMA appears to have risks that are similar to those of other structurally-related sympathomimetic compounds

(Mas et al. 1999; Tancer and Johanson 2003), such as amphetamine (marketed in the United States as Adderall, Dexedrine, and others), that have been used clinically for many years.

Since the late 1970s, MDMA has been used by a growing number of individuals in non-medical settings. Illicit use of ecstasy (material sold as MDMA) is most commonly reported at dance events, such as “rave” parties and at nightclubs, but is not confined to these situations or subcultures. In the United States, prevalence of ecstasy use reported in 2002 was estimated to be 4.3% for persons aged 12 and up, and 15.1% for 18-25 year old adults (Office of Applied Studies, Substance Abuse and Mental Health Services Administration, 2003; tables online at

www.oas.samhsa.gov/nhsda/2k2nsduh/html/Sect1peTabs1to110A.htm#tab1.1a).

While a number of serious adverse events, including fatalities, have been reported after illicit use of ecstasy in uncontrolled conditions, such events are relatively rare when considering the prevalence of ecstasy use (Gore 1999; Baggott 2002; Henry and Rella 2001).

There has been no evidence of significant or lasting toxicity in Phase I studies of MDMA. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e.g., Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle neurocognitive changes may occur in a subset of repeated users of illicit MDMA and other drugs (e.g., Croft et al. 2000; Gouzoulis-Mayfrank et al. 2003; Gouzoulis-Mayfrank et al. 2000; Thomasius et al. 2003). In contrast, all available Phase I data indicate that it is unlikely that the MDMA exposures proposed in this protocol cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Tests of neurocognitive function have found that performance is not affected by participation in clinical trials with MDMA (Boone et al., unpublished data supplied to MAPS; see also Table 2.5 in Investigator’s Brochure; Ludewig et al. 2003; Vollenweider et al. 2001; Vollenweider et al. 2000). Vollenweider and colleagues (2000) presented positron emission tomography (PET) data at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine that found no change in estimated serotonin transporter binding sites four weeks after a dose close to 125 mg MDMA was given to MDMA-naïve volunteers. The same team of researchers failed to detect any differences in performance on a measure of executive function and memory in 15 drug-naïve volunteers given two doses of 1.5 to 1.7 mg/kg MDMA (Ludewig et al. 2003, data presented at the 58th Annual Conference of the Society for

Biological Psychiatry, San Francisco CA). Moreover, our own laboratory has investigated the question of neurocognitive deficits; we have already tested, in a pilot study, 23 “pure” illicit MDMA users versus 16 non-using matched controls. Initial results (Halpern et al. 2004, in press) found no significant differences between users versus non-users on any measure, but a post-hoc median split of users revealed some impaired performance on strategy application tests and on tests of perseverations in those individuals reporting 60 or more exposures to MDMA. No significant differences were found between non-users and those who reported more than 20 but less than 60 MDMA exposures. Our laboratory intends to expand this pilot study and has submitted a revised R01 application to do so with the National Institute on Drug Abuse (first round score: 211).

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to serve as a novel treatment for anxiety disorders associated with advanced-stage cancer, and that the modest risks of administering MDMA within a therapeutic context are outweighed by the possibility that this treatment may offer significant benefits.

2.1 Previous Clinical Experiences with MDMA

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 1997).

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 2000; Stevens 1999; Stevens 1997). Reduction in pain was often reported (Greer and Tolbert 1998;

Holland 2001; Stevens 2000; Stevens 1999; Stevens 1997). 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'Otalara 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 reported 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 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 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.

3.0 Methods

3.1 Overview

This randomized, dose-response pilot study is double-blinded for dose and uses a sub-threshold dose condition that functions as an active placebo control. The study will involve 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. All participants will be patients of the Medical Oncology department at the Lahey Clinic. Each participant will receive at McLean Hospital six one-hour sessions of non-drug psychotherapy, as well as two day-long experimental sessions using MDMA, scheduled 2-3 weeks apart, with overnight observation at McLean Hospital. Additional sessions may also be requested during the course of the study. 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. Following baseline measures and one introductory psychotherapy session, all participants will receive

MDMA on each of the two day-long experimental sessions (on Days 14 and 28).

A complete medical examination including an assessment of physical functioning ability will be performed at the Lahey Clinic's Medical Oncology Department ("Day - 1"), and at one week after the second MDMA session ("Day 36"). During experimental sessions ("Day 14" and "Day 28"), participants will be supervised at all times by a male and female co-therapist, both psychiatrists, and also by an internist who will be available throughout each experimental session to respond to any medical emergencies, and after the session a psychiatric resident will be available during the period of overnight observation.

Data will be analyzed by mixed analysis of variance (ANOVA), with experimental intervention condition (Experimental Intervention Dose MDMA versus Sub-Threshold Dose MDMA) serving as a between-group factor and time of measurement, or experimental session (first or second) serving as within-subjects factors. It is predicted that participants receiving the Experimental Intervention doses will exhibit lower scores on measure of anxiety, higher scores on quality of life, and performance, and reduced indicators of physical pain and medication use than the participants receiving the Sub-Threshold doses. Statistical significance will be set at 0.05. Separate time-course analyses will be performed for systolic blood pressure, diastolic blood pressure, heart rate, and body temperature assessed during each experimental session. Of these measures, it is expected that statistically significant changes will only be detected in heart rate and blood pressure. These changes are expected to last several hours when Experimental Intervention Dose MDMA-assisted psychotherapy is compared to Sub-Threshold Dose MDMA-psychotherapy.

3.2 Subjects

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 of 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. Participants will be unpaid individuals, male or female, age 18 or older, who have been diagnosed by an oncologist (Dr. Shuster and/or colleagues) at the Lahey Clinic Medical Center with advanced-stage cancer who have or are reasonably predicted to have less than 12 months of life remaining. Advanced-stage cancer is

defined specifically for each cancer, but generally refers to a condition where the cancer is considered incurable or inoperable. Subjects 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. We will only include patients who are not taking or have safely withdrawn from other psychotropic prescription medications (example, SSRI or MAOI antidepressants) that might present an unreasonable risk of drug-drug interaction or that might confound any findings of therapeutic benefit.

3.2.1 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. Are at least 18 years of age.
4. 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).
5. 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.
6. 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.
7. 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.
 8. 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).
 9. 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 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.

3.2.2 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. Diagnosed with significant peripheral vascular disease, hepatic disease, renal insufficiency, or preexisting or past evidence of hyponatremia.
7. 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.
8. Weighing less than 45 kg.
9. Reporting a history of use of "ecstasy" (illicit drug preparations purported to contain MDMA) at any time within the previous 3 months.
10. Reasonably judged to present a serious suicide risk or who are likely to require psychiatric hospitalization during the course of the study.
11. Requiring ongoing concomitant therapy with a psychotropic drug other than PRN as needed anxiolytic medications and pain control medications.
12. Is unable to fully understand the potential risks and benefits of the study and give informed consent.
13. Is enrolled as a participant in any other medical research protocol.

3.2.3 Recruitment and Informed Consent

Potential participants will be identified through the oncology practice at the Lahey Clinic Medical Center. Prospective participants who meet the inclusion and exclusion criteria and express an interest in participating will be contacted by the principal investigator by telephone. In addition to answering any questions about the study during this phone conversation, Dr. Halpern will again discuss and review the study procedures (including risks, potential benefits, and alternatives) with the participants before participants give written informed consent at the first scheduled meeting ("Baseline Evaluation" – "Day 0") at McLean Hospital. Participants will be encouraged to ask questions and consider their alternatives. The prospective participant's comprehension of material in the informed consent will be assessed through a 17-item quiz administered after the prospective participant has read the consent form. The investigators will address any misunderstandings identified through incorrect quiz responses, and will use the quiz as a guide for further discussion of the study if necessary.

3.2.4 Oncology Assessment and Initial screening

Candidates for study participation will first be referred to the investigators through the Lahey Clinic's Medical Oncology Department. 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"), 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 to determine suitability for study participation. This "pre-study screening" exam ("Day -1") will be performed by co-investigator oncologist Dr. Shuster at the Lahey Clinic. Screening will last for up to one to two hours 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, ECG, metabolic profile, assessment of serum electrolytes, thyroid hormone levels and levels of TSH, HIV serology, and urine pregnancy test for females of childbearing potential. Dr. Shuster will perform the medical examination. 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 5-minute Spielberger State-Trait Anxiety Inventory (STAI). If a score of 40 or higher is recorded, and other eligibility criteria are met, an informed consent form will then be provided to the patient for review at home. Patients will then be contacted by Dr. Halpern to discuss the study procedure, answer questions and arrange for an initial visit ("Day 0") 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 ("Baseline Evaluation"; "Day 0") 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.

3.2.5 Screening Process

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") 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 (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 ≥ 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 2 for schedule and Table 3 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.

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.

We will attempt to recruit both men and women into this study. Similarly, it is anticipated that the racial/ethnic composition will be close to that of the regional population. We will attempt to reach individuals of different ethnic or racial backgrounds in our recruitment efforts.

3.3 Study Procedures

Interview and test procedures will generally be conducted in an appropriate research facility of or made available to the Biological Psychiatry Laboratory at McLean Hospital. The facilities will have overnight accommodations as well as full access to the ancillary facilities of the hospital. Following pre-study evaluation, individuals who meet the study criteria (as confirmed by review of this data by the principal investigator, co-investigator oncologist, and co-investigator internist) and who agree to participate will be scheduled for an introductory psychotherapy session ("Day 7") to be administered within 7-14 days prior to their first MDMA session ("Day 14"). Participants will be randomized to either the Sub-Threshold Dose Group (N = 4) or the Experimental Intervention Dose Group (N = 8) (see Table 1 below), and group assignment will be maintained

throughout the study (this protocol does not have a crossover-design component).

Table 1. Dose Regimen

	Session 1		Session 2 ^a	
	Dose ^b 1	Dose 2 ^c	Dose 1	Dose 2 ^c
Sub-Threshold 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.

The safety monitoring measures that will be used during the experimental sessions will include automated blood pressure and pulse monitoring equipment and a thermometer for reading body temperature. Blood pressure and pulse will be measured at the outset of each experimental 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 the values fall below these levels. Body temperature will be measured at the outset and then hourly for 6 hours. The physicians may also call for more frequent measurements in the event of clinically significant changes. After the occurrence of an adverse event, such as extremely elevated blood pressure or an extreme panic reaction, the investigators may arrive at a clinical judgment not to administer either the supplemental dose of MDMA within an experimental session, or a second experimental session. Monitoring participants throughout the study should effectively detect and respond to any cardiovascular or thermoregulatory problems during the study, especially with the co-investigator internist or appropriate designate immediately available for the first five hours of each experimental session by remaining in a room adjacent to the treatment room.

On experimental session days ("Day 14" and "Day 28"), 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. Doses of MDMA in the Sub-Threshold group will range from 25 mg (initial dose in both sessions) to 37.5 mg total per session. These doses are predicted to be slightly psychoactive (Grob et al. 1996; Harris et al. 2002) and are predicted to serve as an active placebo-control test condition. The Experimental Intervention doses of MDMA range from 83.3 mg (initial dose for Session 1) to 187.5 mg (total dose in Session 2).

The above-mentioned Phase 1 studies of MDMA with healthy normals, as well as anecdotal reports in cancer patients pre-dating the scheduling of MDMA, suggest that 83.3 mg of MDMA is a dose that will not achieve the full psychotherapeutic effects reported after 125 mg. Therefore, the experimental treatment paradigm is to explore the optimal strategy for administration of MDMA in this dosage range, with Experimental Session 1 administering 125 mg split into two doses, and with Experimental Session 2 administering 125 mg in the first dose and then supplementing this dose with 62.5 mg as a second dose. This will allow researchers to examine dose-dependent differences in safety and efficacy both across sessions and between groups, with active placebo serving as control.

Data collection and experimental sessions will be completed according to the timeline contained in Table 2 and the test measures are listed in Table 3. One day after each experimental session, a non-drug psychotherapy session will occur at McLean Hospital ("Day 15" and "Day 29"). Also at McLean Hospital, additional non-drug psychotherapy sessions will be conducted and data will be collected between the two experimental sessions (on Day 21) and one week after the second experimental session ("Day 35"). A follow-up medical examination including physical and other measures of physical functionality will also follow one week from the second experimental session (on Day 36). This follow-up medical examination will be performed at the Lahey Clinic Medical Center by co-investigator oncologist Dr. Shuster. A final

data-collection session ("Day 84") will take place at McLean Hospital two months after the second experimental session and the participant will also have a final psychotherapy review hour with the co-therapists.

3.3.1 Timeline

The timeline for participation in the study is outlined below in Table 2. Visits are to be scheduled within the week that the below numbered days fall within.

Table 2. 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.

3.3.2 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-Revised	SCL-90-R	General current mental health and quality of life	12-15 minutes		X	Both
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).

3.4 Baseline Assessment

A battery of psychological and diagnostic assessments will be performed during the two weeks prior to the first experimental session in order to provide baseline measures of symptomatology, mood state, and global functioning ("Day -1" and "Day 0"). All study measures described above will be administered during baseline assessments. The baseline assessment should last from 1.5 to a little over 2 hours.

3.5 Non-Experimental Psychotherapy Sessions

Following the initial screening and data collection at baseline, all participants will receive one sixty-minute introductory psychotherapy session with the co-therapist investigators (Drs. Halpern and Naidoo) ("Day 7"). There will then be two individual experimental sessions conducted 2-3 weeks apart, each lasting approximately six to eight hours depending upon the participant's response ("Day 14" and "Day 28"). One sixty-minute non-drug psychotherapy session will be conducted in the time intervening between the two experimental sessions ("Day 21"). Outcome measures will be completed at McLean Hospital on the same day as the scheduled psychotherapy sessions, with completion of outcome measures taking approximately ninety minutes. Participants will also see the investigators in a sixty-minute follow up session a day after each experimental session ("Day 15" and "Day 29"). Outcome measures will not be completed on the day after the experimental sessions. Participants will meet with the investigators in one more psychotherapy session conducted after the second experimental session but before the study has been completed ("Day 35"). If a participant requests an additional psychotherapy session and the co-therapists agree, then additional sessions may be scheduled as well, with these sessions also lasting sixty minutes. If any additional psychotherapy sessions are conducted, participants will complete outcome measures before that session as well. The final research follow-up session will take place two months from the second experimental session ("Day 84"). 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.

3.6 Experimental Sessions

3.6.1 Drugs and Dosing

MDMA will be supplied by David Nichols, Ph.D., Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University. This MDMA is of confirmed identity and purity and has been used in all

Phase I and II clinical trials of MDMA conducted in the United States. Analytic data has been filed with the FDA in MAPS' MDMA Drug Master File # 6293.

Participants will receive MDMA on two experimental sessions spaced 2-3 weeks apart ("Day 14" and "Day 28"). 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 Sub-Threshold 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. The two doses of MDMA chosen for the Sub-Threshold 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 serving as an active placebo. Even 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 in some previous research studies without any adverse events (Grob et al., unpublished; Tancer and Johanson 2003). With participants carefully monitored for any indicators of adverse events, this dose should still prove tolerable and will produce the full array of subjective and physiological effects.

Group assignment will be randomized using a table of random numbers. 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.

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 above). 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 Acute 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.

3.6.2 Measures During Experimental Session

Participants will complete outcome measures on the day of the experimental study, but prior to the start of the experimental session. Measures made during the experimental sessions are primarily made for safety monitoring and are described below in "3.8 Monitoring for Toxicity." In addition, 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 all 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, the participant's immediate personal supports, and the participant's outside therapist.

3.6.3 Psychotherapeutic Procedures 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; see accompanying Treatment Manual). 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 "3.8 Monitoring for Toxicity." Food will be available during the latter part of the session. Foods provided will include crackers or bread, fruit and vegetables, and soups.

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. 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.

3.7 Post-Session Monitoring and Data Collection

Psychotherapy follow-up sessions ("Day 15" and "Day 29") will be conducted in the morning on the day after the experimental sessions at McLean Hospital. Seven days after each experimental session (on Day 21 and Day 35), outcome measures will be obtained and then a psychotherapy session will also occur. A final research follow-up ("Day 84") will be conducted two months after the second experimental session. Outcome measures will also be administered during the final meeting, and the participant will have a final opportunity to review participation in the study with Drs. Halpern and Naidoo. Participants may contact the investigators at any time throughout the study. 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. The investigators will schedule one or more additional hour-long psychotherapy sessions if requested by the participant and the investigators deem it necessary.

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. 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. Daily diaries will also be reviewed at these meetings. Outcome measures will be completed at McLean Hospital prior to each psychotherapy session (except for those conducted the day after the experimental session days – "Day 15" and "Day 29"). Participants will complete outcome measures on days when any additional sessions are scheduled.

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"). 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.

3.7.1 Therapy Follow-Up

One day after each experimental session ("Day 15" and "Day 29"), participants will meet with the therapist co-investigators, Dr. Halpern and Dr. Naidoo, for an hour-long non-drug psychotherapy follow-up session. During these follow-up sessions, participants will be encouraged to describe their experiences of the MDMA-assisted sessions and to freely express any thoughts, feelings, questions or concerns they have. Participants will also be asked to indicate whether they believe they received Sub-Threshold or Experimental Intervention doses of MDMA during the day-prior's experimental session. Participants will not complete any outcome measures, other than continuing to keep their Daily Diary, on this next day following the experimental session. After completion of these day-after psychotherapy sessions, the participant will be discharged to home and will be driven from McLean Hospital either by pre-arrangement with a designated support person to the participant or by a study-provided taxi. The participant will again be instructed to not drive a motor vehicle or operate heavy machinery during this day. 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. 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).

Follow-up sessions ("Day 21" and "Day 35") at McLean Hospital will be scheduled for participants one week after each experimental session. These research follow-up sessions will occur at an appropriate research facility of or made available to the Biological Psychiatry Laboratory. After participants complete the outcome measures (approximately 90 minutes), hour-long non-drug psychotherapy with Drs. Halpern and Naidoo will immediately follow. During these psychotherapy sessions, participants will be encouraged to continue to review their symptoms and problems related to their management of anxiety and how the prior week's experimental treatment session may have affected their

anxiety. Participants will be encouraged to describe their experiences of the MDMA-assisted session(s), including their experience of reviewing their videotapes, and to freely express any thoughts, feelings, questions, or concerns they have. If this is the first follow-up session ("Day 21"), participants will be scheduled for their second experimental treatment session ("Day 28"). If this is the second follow-up session ("Day 35"), participants will be scheduled for the final follow-up session ("Day 84"). The repeat medical examination ("Day 36") to be conducted by co-investigator oncologist Dr Shuster at the Lahey Clinic will also have been scheduled for one week after the second experimental session ("Day 28").

Participants will need approximately 1.5 hours to complete outcome measures during the final follow-up session ("Day 84") scheduled two months after the second experimental session ("Day 28"). After the participants have completed all outcome measures, they will have a final meeting with the co-therapist investigators. This session will take place at an appropriate research facility of or made available to the Biological Psychiatry Laboratory at McLean Hospital.

If the participant requests an additional psychotherapy session and the co-therapists agree, then additional sessions occurring prior to the final follow-up may be scheduled as well, with these sessions also lasting sixty minutes. If any additional psychotherapy sessions are conducted, participants will complete outcome measures before that session as well. All such sessions will be held at McLean Hospital.

3.8 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; 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 doses equal to or exceeding 125 mg MDMA. In another Phase 1 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. These therapists did not report any severe adverse effects occurring during or after MDMA-assisted psychotherapy sessions (Adamson 1985; Greer and Tolbert 1986; Gasser 1994; Metzner and Adamson 2001; Widmer 1998).

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. Dr. Halpern has been board certified in general psychiatry, has completed a multi-year research fellowship at McLean Hospital's Alcohol and Drug Abuse Research Center (ADARC), and is Associate Director of Substance Abuse Research at the Biological Psychiatry Laboratory. Dr. Naidoo is a board-eligible psychiatrist who has completed a Fellowship in Psychosocial Oncology at the Dana Farber Cancer Institute. She is currently Acting Medical Director of the Erich Lindemann Mental Health Center. In addition, Dr. Siegel (McLean Hospital's Director of Internal Medicine) or another physician Board Certified in Internal Medicine credentialed for practice at McLean Hospital and qualified for the management of medical emergencies will remain in a room adjacent to the location of the experimental session for five hours after administration of the initial dose of MDMA. Dr. Siegel or the appropriate designate will also remain on-site at McLean Hospital throughout the remaining hours of the experimental session and will review medical status with Drs. Halpern and Naidoo at the conclusion of each experimental session.

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 the values fall

below these levels. Body temperature will be measured at the outset and then hourly for 6 hours. The physician may also call for more frequent measurements in the event of clinically significant changes.

The 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 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). 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 within 72-hours to the FDA. 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 resident (as well as the principal investigator) during their overnight period of observation if necessary.

4.0 Costs to Participants

There will be no costs to the study participants. The sponsor will cover all costs of study participation. Charges for treatment of the participant's condition that are unrelated to the research study or any of its procedures will continue to be billed to the health insurance provider of the participant or to the participant him or herself.

5.0 Treatment and Compensation of Study-Related Injury

Treatment of a study-related emergency would first be billed to a participant's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a participant's health insurance. Most study-related emergencies can be treated by the investigators as described within "3.8 Monitoring for Toxicity" and within "11.0 Appendix." If the investigator cannot treat a study-related emergency, there are contingency plans for the transport of participants to Mt. Auburn Hospital.

6.0 Risks to Participants

6.1 Risks and Discomforts Associated with Drawing Blood

Blood specimens will be obtained from the subjects during the screening ("Day -1") evaluation. Temporary discomfort may arise as a result of sampling blood. Blood samples will be used to assist in the investigator's determination of whether or not the participant can safely take part in the study. A risk-benefit analysis suggests that the temporary discomfort from providing blood samples is outweighed by the need to ensure that participants are healthy enough to meet all inclusion criteria at screening.

6.2 Risks and Discomforts Associated with Screening Procedure

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

Psychological data will be obtained through interviews and SCID testing. Because these interviews require individuals to discuss their condition, interviews may prove upsetting for some. Because psychiatric interviews and discussion of symptoms of anxiety are used

during screening, they cannot be avoided. The investigators, however, will seek as much as possible to reduce anxiety and distress during these interviews.

6.3 Risks and Discomforts Associated with Non-Experimental and Experimental Psychotherapy

During non-drug and experimental sessions, participants will be asked to think about and discuss their thoughts and emotions relating to their medical condition. They may experience intense emotional responses to speaking about this material. Psychotherapy is conducted as part of the research study, including the experimental intervention (MDMA-assisted psychotherapy), and individuals undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

6.4 Risks and Discomforts Associated with the Experimental Intervention

In doses similar to those proposed for this study, MDMA produces sympathomimetic effects similar to the effects of a moderate dose of methamphetamine or other stimulants (Cami et al. 2000; Grob et al. unpublished; Grob et al. 1996; Harris et al. 2002; Lester et al. 2000; Liechti et al. 2001a; Mas et al. 1999; Tancer and Johanson 2003; Tancer and Johanson 2001; Vollenweider et al. 1998). The amount of MDMA used in this study is not likely to produce changes in blood pressure or heart rate greater than 40% of resting values. These changes should last no more than six hours, with peak effects occurring 1 to 3 hours after drug administration (Liechti et al. 2001a; Tancer and Johanson 2003). These changes have been well-tolerated by volunteers in previous studies and should not pose large risks to participants enrolled in this study, who will be carefully screened for cardiovascular and related problems. In less than 5% of volunteers, increases in blood pressure were higher. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of participants and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity.

MDMA also may produce mild alterations in perception and altered perception of time (Cami et al. 2000; Hernandez-Lopez et al. 2003; Vollenweider et al. 1998). Women may be more sensitive to these effects of MDMA (Liechti et al. 2001a). Some participants receiving

MDMA report experiencing periods of increased anxiety (Harris et al. 2002; Liechti et al. 2001a; Tancer and Johanson 2003; Tancer and Johanson 2001; Vollenweider et al. 1998). Psychological distress could arise at any time after the onset of the effects of MDMA, from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress is liable to occur in 40% to 70% of subjects, and may last for as little as 15 minutes or for as long as 5 hours or longer. In previous Phase I studies, these symptoms have been modest, self-limiting, and responded well to reassurance from investigators. Anxiety may be greater in participants already experiencing anxiety. In the proposed study, participants 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 as part of the psychotherapy to be conducted during the experimental treatment sessions (see the treatment manual; Ruse et al 2004). Hence 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. If significant anxiety persists more than two hours after the expected end of the experimental session, contingency plans (described in the below appendix) include the continued presence of the investigators, support and assistance provided by an individual close to the participant, and the possibility of administering anxiolytic agents as a rescue medication as a last resort. Hospitalization will be considered in cases of extreme psychological distress in individuals who are judged to be a danger to themselves or others.

Side effects of MDMA are modest and generally have not been associated with serious discomfort among volunteers in previous studies (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001a; Tancer and Johanson 2001; Vollenweider et al. 1998). Decreased appetite, jaw clenching, dry mouth, difficulty concentrating, and impaired gait or balance are commonly reported during peak MDMA effects, while fatigue may be felt up to several days afterward. Less commonly, mild anxiety and depressed mood are reported one to three days after MDMA administration (Harris et al. 2002; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Liechti and Vollenweider 2000b; Vollenweider et al. 1998). Some of these

effects are very likely to occur, but proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects, so that they will not be unduly troubled by them.

MDMA may produce modest changes in immune functioning, lasting up to two days after drug administration. A research team in Spain has studied the immunological effects appearing after the administration of one or two doses of 100 mg MDMA (Pacifici et al. 2004; Pacifici et al. 2002; Pacifici et al. 2001; Pacifici et al. 2000). They reported a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-Gamma and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 cytokines and increase the amount of Th2 cytokines measured in blood. A second dose of 100 mg given four hours after an initial dose of 100 mg enhanced the immunological effects produced by the first dose (Pacifici et al. 2001) without increasing the duration of these effects. The mechanism of this MDMA-induced immunomodulation is unclear, but may involve MDMA-induced glucocorticoid release or sympathomimetic activity. Serotonin release may play a direct or an indirect role in producing immunological changes, since paroxetine pretreatment in humans attenuated or eliminated most of the changes described above (Pacifici et al. 2004). Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine (Pacifici et al. 2000; Pacifici et al. 2001). Because of their limited duration, these changes are not likely to have clinical significance beyond a possibly increased risk of the common cold or similar illness for several days. Previous Phase I studies have not reported any indication of increased risk of illness occurring after MDMA administration.

MDMA may cause modest changes in cerebral blood flow lasting several weeks after drug exposure. These changes have been hypothesized to be the result of short-term down-regulation of serotonergic receptors controlling cerebral vasodilatation (Reneman et al. 2002a; Reneman et al. 2000). MDMA induced decreased regional and global cerebral blood flow (CBF) 10 to 21 days after administration (Chang et al. 2000), as reported in a study of 10 ecstasy users given two separate ascending doses of MDMA at a two-week interval, with comparisons made at baseline and after the administration of both

doses. Doses per administration in this study ranged from approximately 17 mg (0.25 mg/kg) to approximately 175 mg (2.5 mg/kg). The authors did not find differences in regional or global CBF when 21 MDMA-experienced volunteers (with a reported 211 ± 340 exposures) were compared to 21 non-users (data are presented in the same paper), suggesting that effects on CBF do not last indefinitely. There are no known consequences of these changes and neurocognitive performance was not altered in these volunteers.

Serious MDMA toxicity is rare even in uncontrolled settings, considering the millions of users taking ecstasy of unknown identity, potency, and purity (Baggott, 2002; Gore 1999; Henry and Rella 2001). Many users routinely consume estimated MDMA doses higher than those proposed in the current protocol without any apparent toxicity. Under unsupervised and non-medical conditions, the most common serious adverse event involves hyperthermia, which often appears to be influenced by prolonged physical exertion (dancing) and other unsafe conditions of use, such as high ambient room temperature. In addition to hyperthermic syndromes, other rare adverse events include dysphoric responses, hyponatremia, and hepatotoxicity, though none of these have occurred in clinical research contexts with the administration of pure MDMA. In the proposed clinical study, volunteers will be carefully monitored for signs and symptoms of these unlikely events and temperature and liquid intake will be controlled. Contingency plans for responding to these unlikely events are described in the appendix.

MDMA may interact with pain management medication. Currently, there are no systematic published studies of the effects of co-administration of MDMA and pain management medication, such as opiates. However, there are several anecdotal accounts that indicate that MDMA can be safely administered along with opiates used in pain management (Anonymous 1999; Doblin, 2004, personal communication; Stevens 2004, personal communication). A study in rodents comparing analgesia after MDMA with morphine-induced analgesia did not see any changes in MDMA effects on analgesia when given with the opioid antagonist naloxone (Crisp et al. 1989), suggesting that the two drugs affect pain independently. MDMA should not interfere with the effects of opioid-based pain control medication. The investigators will monitor vital signs and respond accordingly to any clinically significant changes. Weighing the risks of combining pain control medication and MDMA with the risks of abstaining from pain control medication, which will increase suffering and may in some

cases produce symptoms of opiate withdrawal, we conclude that it is preferable to allow continued medication for pain control.

Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth, but the validity of these findings are in dispute (McElhattan et al. 1999). Studies in mice and rats have detected changes in serotonin neurons and some behavioral changes when repeated doses of MDMA were given at certain times during pregnancy or infancy (Broening et al. 2001; Williams et al. 2003; Won et al. 2002), suggesting that exposure to MDMA during pregnancy could pose a developmental risk. However, doses used in these studies were higher than those used by humans. Women who are able to bear children will be required to use effective contraception during the study (barrier-type contraceptives, oral contraceptives, or long-acting injection or implanted contraceptives), with pregnancy tests performed before administration of MDMA on each of the two experimental session days. Pregnant women will be excluded from participation.

MDMA is classified as a Schedule I compound, largely on the basis of its growing popularity at nightclubs and parties in the early to mid-1980s. There is no evidence suggesting that the abuse potential of MDMA will negatively affect participants exposed to MDMA when given along with psychotherapy. The abuse potential of MDMA is almost certainly lower than the abuse potential of some of the medications used to reduce anxiety or pain, such as opiates or benzodiazepines (Lieb et al. 2002; Von Sydow et al. 2002).

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

In the currently proposed study, diversion is not an issue because MDMA will only be administered under supervision of a psychiatrist and no take-home doses will be permitted. MDMA will be handled in accordance with all DEA and Massachusetts Department of Public Health regulations pertaining to the handling and dispensing of Schedule I substances within research studies.

6.4.1 Potential Neurotoxicity Associated with Ecstasy Use

Extensive studies in animals indicate that high or repeated dose MDMA exposure can damage serotonergic axons originating in the dorsal raphe nucleus of the brainstem, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site density (See Baggott and Mendelson 2001; Green et al. 1995; O'Callaghan and Miller 1994; Chapters 4 and 5 in the Investigator's Brochure, aChapter 3 in the 2002 Update to the Investigator's Brochure, and Chapter 3 in the 2003 update to the Investigator's Brochure). Although some regrowth occurs, seemingly permanent redistribution of axons was noted in a study with squirrel monkeys (Hatzidimitriou et al. 1999). Similar changes can be induced by methamphetamine and some other psychostimulants (Miller and O'Callaghan 1996; Molliver et al. 1990; O'Callaghan and Miller 1994; Sabol et al. 1995; Seiden and Kleven 1989; Seiden and Sabol 1996). There is controversy over the extent to which analogous changes occur in humans. Imaging studies comparing ecstasy users with non-users have found evidence of lower binding to serotonin transporter re-uptake (SERT) sites (Buchert et al. 2003; McCann et al. 1998; Obrocki et al. 2000; Reneman et al. 2001a; Reneman et al. 2001b; Reneman et al. 2002c; Semple et al. 1999). Because these studies use novel experimental techniques to compare self-identified drug users and non-users and because the degree of reduction in SERT vary widely across studies (e.g. Buchert et al. 2003 versus McCann et al. 1998), it is not always clear what is being measured or how apparent differences relate to MDMA exposure (Kish 2002). More importantly, there has been no evidence of these changes occurring in volunteers enrolled in clinical trials of MDMA. Vollenweider and colleagues measured serotonin transporter density using positron emission tomography (PET) with the same radioligand (radioactively labeled drug) employed in one of the previous studies [¹¹C]McN5652 (McCann et al. 1998) before and after a clinical administration of approximately 105-120 mg (1.5-1.7 mg/kg) MDMA (Vollenweider et al. 2001; Vollenweider et al. 2000). Comparisons were made in a pilot study with six MDMA-naïve healthy volunteers, and later in a second study with additional volunteers (n = 8), so that the two investigations examined a total of 14 subjects. Vollenweider and colleagues failed to find any lasting differences in scans made before and after MDMA administration. These findings indicate that it is unlikely that MDMA will produce significant serotonergic toxicity at the dosage that will be used in the proposed study.

Structural imaging of ecstasy users' brains has generally failed to find significant changes (Chang et al. 1999; Obergriesser et al. 2001; Reneman et al. 2002b; Reneman et al. 2001c; Reneman et al. 2000). Recently, researchers imaging brains of ecstasy user and polydrug user controls with structural magnetic resonance imaging with voxel based morphometry (VBM) detected reduced gray matter in selected brain areas in frontal, occipital and temporal cortex, and in the brainstem (Cowan et al. 2003). While provocative, drawing conclusions from these findings is difficult, due in part to the retrospective study design and the novelty of the imaging technique used. As well, the researchers found associations between use of a number of different drugs, including cannabis and hallucinogens, and reductions or changes in gray matter. One report detected elevated amounts of a substance associated with injured neurons (Reneman et al. 2001c), while another study failed to find such indicators, finding instead an increase in an indicator of stress and repair (Chang et al. 1999), and the third study failed to detect any signs of neuronal injury and did not assess the marker for stress and repair (Obergriesser et al. 2001). Findings from structural imaging studies remain inconclusive, and their significance at present remains unclear. However, these studies have only been conducted so far in ecstasy users, and so reflect the effects of repeated ecstasy use and use of other drugs, and not the effects of MDMA administered in controlled settings.

A report appearing in 2002 that claimed that MDMA damaged dopamine neurons in non-human primates (Ricaurte et al. 2002) was later retracted after it was discovered that the monkeys and baboons in the study had received methamphetamine, and not MDMA (Ricaurte et al. 2003). To date, no studies in humans have found reduced numbers of dopamine transporter sites in ecstasy users (Kish et al. 2000; Reneman et al. 2002c; Semple et al. 1999). Furthermore, the researchers responsible for the study of dopamine toxicity in non-human primates failed to replicate the findings reported in the retracted paper (Ricaurte 2004). Ricaurte did not detect dopamine neurotoxicity after three oral (intra-gastric) doses of up to 8.6 mg/kg MDMA to monkeys within a six-hour period (25.8 mg/kg total), or after three 4 mg/kg injections given within six hours (12 mg/kg total) (Ricaurte 2004), suggesting that even high doses of MDMA are unlikely to change dopamine function in primates.

If long-term serotonergic changes do occur in some humans, it is not known if these changes have clinically significant consequences. Studies of ecstasy users have suggested that repeated MDMA use may be associated with lowered neurocognitive performance, including

measures of verbal memory (Alting Von Geusau et al. 2004; Bhattachary and Powell 2001; Bolla et al. 1998; Curran et al. 2003; Dafters et al. 2003; Gouzoulis-Mayfrank et al. 2003; Gouzoulis-Mayfrank et al. 2000; Hanson and Luciana 2004; McCardle et al. 2004; McCann et al. 1999; Morgan 1999; Reneman et al. 2000; Rodgers 2000; Thomasius et al. 2003; Alting Von Geusau et al. 2004; Zakzanis and Young 2001a), visual memory (Fox et al. 2002; Wareing et al. 2004) and executive function (Gouzoulis-Mayfrank et al. 2000; Hanson and Luciana 2004; McCardle et al. 2004; Verkes 2000; Wareing et al. 2000; Zakzanis et al. 2001b). There is continuing controversy over whether these findings reflect pre-existing differences or the effects of other drug use (particularly cannabis) (Croft et al. 2000; Dafters et al. 2003; Simon et al. 2002) as well as or instead of the effects of repeated ecstasy use. The possible decreases are clinically insignificant, and do not appear to disrupt the lives of most ecstasy users examined in these studies. Moreover, our own laboratory's findings in an initial pilot study of neurocognitive performance of essentially "pure"/exclusive illicit MDMA users failed to replicate decreased performance on most measures, including tests of verbal memory (Halpern et al. 2004). Subtle deficits that were statistically significant were, however, observed by us on some measures of impulsivity and mental processing speed – but only in users reporting 60 or more separate exposures to illicit MDMA preparations.

As is also the case with imaging studies, conclusions drawn from examining regular ecstasy users may be inappropriately applied in estimating risks of one or two doses of MDMA in a controlled environment. A study failed to find decreased memory in ecstasy users reporting a lifetime dose of under 80 tablets (mean = 39.5 ± 18 tablets), with decreased memory function appearing only in ecstasy users reporting a lifetime dose of 80 or more tablets (Gouzoulis-Mayfrank et al. 2003). Another study comparing a sample of 22 regular ecstasy users with 28 archival controls only found lower scores on some tests of visual memory in individuals with a lifetime dose of over 50 tablets (Back-Madruga et al. 2004). A Phase I study comparing 14 ecstasy users (similar sample to that appearing in Back-Madruga et al. 2004) at baseline and again after two separate administrations of MDMA, at doses per administration ranging from 0.25 mg/kg (approximately 17 mg) to 2.5 mg/kg (approximately 175 mg) (combined dose of 0.75-4.75 mg/kg, or approximately 52.5-332.5 mg) in a controlled setting failed to find differences between performance on an extensive battery of neurocognitive tests given at baseline and after MDMA administration (Boone et al. Unpublished, also see Table 2.5 in Investigator's Brochure). Measures employed in

this study included assessments of verbal recall and executive function.

It would thus appear that while regular ecstasy use may be related to subtle decline in some areas of cognitive function, administration of MDMA at doses similar to those proposed for this study does not appear to produce differences in neurocognitive function. Lastly, findings from several recent publications suggest that use of cannabis and other drugs may play a role in reduced memory or executive function. Some recently published studies failed to find reduced memory function in ecstasy users when compared with cannabis user controls (Dafters et al. 2003; Simon et al. 2002). Other studies have found that when samples are well-matched for polydrug use, current ecstasy users perform similarly to polydrug user controls, and former ecstasy users, who reported more cannabis and amphetamine use, performed less well than non-drug user controls (Thomasius et al. 2003). Based on the above data, and additional data listed in the Investigators Brochure, it appears very unlikely that sessions with two doses with a cumulative dose ranging from 37.5 to 187.5 mg MDMA will have any lasting untoward effect on neurological functioning.

Researchers have detected decreased psychological well-being (either as depressed mood, dysphoria, increased aggression, or increased impulsivity) in illicit MDMA users (Bond et al. 2003; Daumann et al. 2004; Daumann et al. 2001; Gamma et al. 2000; Gerra et al. 2001; Gerra et al. 2000; Hanson and Luciana 2004; MacInnes et al. 2001; McCardle et al. 2004; Morgan et al. 2002; Parrott et al. 2002; Thomasius et al. 2003). These changes include elevated scores on measures of depression (Hanson and Luciana 2004; MacInnes et al. 2001; McCardle et al. 2004) and on self-reported psychological symptoms (Daumann et al. 2004; Morgan et al. 2002; Thomasius et al. 2003). However, other studies have failed to detect decreased psychological well-being in ecstasy users (Curran et al. 2003; Simon et al. 2002), and a number of researchers who found decreased psychological well-being in ecstasy users also found that decreased psychological well-being was equally or more strongly related to cannabis use (Dafters et al. 2003; Daumann et al. 2004; Daumann et al. 2001) or polydrug use (Bond et al. 2003; de Win et al. 2004; Thomasius et al. 2003). Furthermore, a prospective examination of a representative sample of Munich residents aged 14 to 24 suggests that psychiatric problems are more likely to precede onset of ecstasy use than to follow it (Lieb et al. 2002). An examination of the literature and a consideration of the methodological flaws inherent in retrospective studies suggests that while an association between

exposure to MDMA and changes in psychological health or personality cannot be ruled out, this association, if it exists, is weak and influenced by other factors. Given the findings reported in studies of ecstasy users, estimated risk of decline in psychological well-being after the administration of two doses of MDMA in the course of this study is likely to be extremely low.

Estimating the risk of reductions in memory, cognitive function or psychological well-being associated with 187.5 mg MDMA is more difficult, as only one study employing doses in this range has also studied cognition (Boone et al., unpublished), and no one has yet assessed psychological well-being after larger doses of MDMA. It is notable that at least two studies did not detect reduced memory in ecstasy users reporting average doses per use equal to or above 187.5 mg (Curran et al. 2003; Thomasius et al. 2003), assuming an average of 60 to 80 mg per tablet, as estimated in recent analyses of ecstasy pill contents (Baggott et al. 2000; Cole et al. 2003). Likewise, one of these studies failed to detect notable differences in psychological well-being, and the other only found differences in one measure of depressed mood in the same samples (Curran et al. 2003; Thomasius et al. 2003). These findings suggest that risks to cognitive or psychological function associated with doses of 187.5 mg MDMA or higher are minimal.

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials (McCann et al. 2001). Relying on a commonly used calculation for estimating pharmacological effects across species and data from studies in rats and monkeys, the researchers claim that humans should be even more sensitive to the effects of MDMA than smaller animals with higher metabolisms. However, their use of interspecies scaling may be inappropriate in this case. Interspecies scaling models may not be suited for estimating effects of extensively metabolized drugs, and there is some evidence that calculations using less than three different species are not as accurate as those using three or more species (Mahmood and Balian 1996). A recent study in rhesus monkeys challenges the use of interspecies scaling with respect to MDMA (Bowyer et al. 2003), finding instead that plasma levels of S-(+)-MDMA after 10 mg/kg to be ten times levels seen in human clinical trials. Vollenweider et al. (2001) compared 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 is

approximately 30% of the rat AUC. Similarly, human C_{max} are approximately 10% of rat C_{max}. The same research team that has used interspecies scaling to calculate a neurotoxic dose in humans has found no signs of neurotoxicity when 2.5 mg/kg was administered once every two weeks to squirrel monkeys over a period of four months, at a total of eight doses (Vollenweider et al. 1999b, citing personal communication from Ricaurte to the Swiss Federal Ethical Committee). Another recent study in rhesus monkeys failed to detect signs of serotonin or dopamine toxicity in animals that had self-administered MDMA over an 18-month period (Fantegrossi et al. 2004), with monkeys self-administering, on average, 2 to 4 mg/kg MDMA, though sometimes up to 15 mg/kg was administered during a session. When comparing monkeys that had self-administered MDMA with monkeys that had not had the opportunity to self-administer MDMA, Fantegrossi and colleagues failed to detect any changes in markers of axonal health, no changes in brain dopamine levels, and insignificantly lower brain serotonin levels. Taken together, these findings suggest that the dose of 125 mg MDMA is very unlikely to produce serotonergic neurotoxicity in humans.

We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies.

Similar conclusions have been drawn by the FDA, which has permitted three Phase I and one Phase II clinical trials by other research groups in the United States.

Nevertheless, the risks of neurotoxicity arising from MDMA administration will be discussed with all potential participants prior to and during the informed consent process.

7.0 Alternative treatments and procedures

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

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

There are a number of recognized treatments for anxiety associated with a medical condition. Treatment often includes both psychotherapy and medication. Most commonly recommended psychotherapeutic treatment includes anxiety management (stress inoculation training), cognitive therapy, exposure therapy, and psychodynamic psychotherapy. Medications that may ameliorate symptoms of anxiety include SSRI antidepressants, nefazodone, venlafaxine, tricyclic antidepressants, benzodiazepines, buspirone, zolpidem, and mood stabilizers.

8.0 Confidentiality of Records

Every effort will be made to strictly safeguard the confidentiality of all participants. Despite this, privacy cannot be guaranteed. Data collected from each participant will be identified only by the participant's initials on the source document and by a randomly generated numeric code on all secondary documents and databases. All measures, records, and videotapes will be kept in a locked file drawer in a locked office of the Biological Psychiatry Laboratory. Access to measures will be limited to regulatory agencies and researchers assessing the participant for changes in symptoms and individuals analyzing data. Researchers with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number. If necessary, identifying information may be erased or otherwise removed from videotaped material. Storage and access to all records will remain fully adherent with HIPAA regulations. Participants will sign forms for the release of information to any of the individuals who will need to obtain this information. Interested parties might include the prescribing physician or psychiatrist.

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

9.0 Risk-Benefits Analysis

While there are a number of available means for the treatment of anxiety related to diagnosis with serious life-threatening illnesses such

as advanced-stage cancer, the search for a wider array of potential treatments is crucial. Not all individuals with anxiety due to a medical condition that is associated with an expectation of less than 12 months of remaining life will respond to currently available treatments. MDMA-assisted psychotherapy may prove to be yet another treatment option for individuals experiencing anxiety as they face their own near-term mortality. If MDMA is found to be safe and efficacious in this population, then a potentially greater number of individuals will be able to increase their quality of life through the reduction or alleviation of these symptoms. If this pilot study demonstrates improvement in anxiety symptoms, then future research may assist in the development of MDMA as a novel treatment that supports a better quality of life than otherwise would be possible for those individuals facing their own death from advanced-stage cancer.

Even currently available methods of reducing anxiety in people with advanced-stage cancer, such as use of benzodiazepines, have drawbacks such as over-sedation. MDMA-assisted psychotherapy may increase quality of life by reducing need for daily anxiolytic or pain control medication in this population. MDMA-assisted psychotherapy may also improve other aspects of quality of life not addressed by currently available treatments, such as reducing fear in the face of impending death and greater interpersonal connection with loved ones or friends.

There is good evidence that administering MDMA in a clinical setting poses a low risk to subjects. Previous studies examining the effects of MDMA in humans found that it has been well-tolerated, and no lasting toxicity has been reported in clinical trials with MDMA (Cami et al. 2000; Grob et al. unpublished; Grob et al. 1996; Harris et al. 2002; Lamers et al. 2004; Lester et al. 2000; Liechti et al. 2000a; Liechti et al. 2000b; Liechti et al. 2001; Liechti et al. 2000; Mas et al. 1999; Pacifici et al. 2004; Pacifici et al. 2002; Pacifici et al. 2001; Pacifici et al. 2000; Tancer and Johanson 2003; Tancer and Johanson. 2001; Vollenweider et al. 1998). There is no evidence for long-term changes in serotonin function or neurocognitive function after a small number of MDMA administrations conducted during a clinical trial (Boone et al., unpublished; Ludewig et al. 2003, Vollenweider et al. 2001; Vollenweider et al. 2000). Case reports of therapeutic work carried out before the scheduling of MDMA indicate that MDMA can be safely administered (Adamson 1985; Gasser 1994; Greer and Tolbert 1986; Grinspoon and Bakalar 1986). In conclusion, MDMA has been safely administered in numerous Phase I and II studies around the world (including in the United States) and in therapeutic settings.

Subjects receiving sub-threshold (25 mg MDMA followed by 12.5 mg MDMA) in the course of this pilot study are not expected to improve as much as those receiving higher doses. Use of a sub-threshold dose as an active placebo is recognized as a means of investigating the effects of an intervention, allowing for clearer evidence concerning safety and efficacy. Sub-threshold doses of MDMA produce feelings of tension and some mild physical discomforts (Grob et al. unpublished; Harris et al. 2002), but also mild feelings of relaxation (Harris et al. 2002). Otherwise, risks associated with these doses are unlikely to be greater than those associated with an inert placebo. All subjects in the study will receive 5 non-drug therapy sessions as well as experimental treatment sessions.

Previous accounts and an uncontrolled study indicate that an additional dose of MDMA that is approximately one half the size of the initial dose was used in therapy conducted prior to the scheduling of MDMA in the US (Greer and Tolbert 1986; Stolaroff 1988), and that this procedure was well-tolerated. There is less information concerning the risks associated with the addition of a second smaller dose of MDMA, but studies of the effects of repeated doses of MDMA in humans (Farre et al. 2004; Pacifici et al. 2001) suggest that one additional dose administered four hours later, and equal to the initial dose, slightly enhanced subjective and physiological effects without increasing most side effects. Prolonging the therapy session is expected to have a greater chance of improving symptoms of anxiety, since there will be more time to rely on the anxiolytic and insight-fostering effects of MDMA.

The possibility of developing a novel means of reducing or alleviating symptoms of anxiety associated with the diagnosis of advanced-stage cancer with a less than 12 month prognosis of remaining life outweighs the low risks of administering MDMA in a controlled laboratory setting. The advantages of a prolonged working period provided by an additional dose of MDMA are predicted to more than compensate for any slight increase in risk of acute or long-term adverse effects resulting from this slight increase in dosage.

An examination of the risks and benefits of the study, both with respect to risks and benefits faced by study participants and arising from conducting the study, indicate that the proposed study has an acceptable risk-benefit analysis.

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11.0 Appendix: Procedures for Treating Serious Adverse Events

Description of potential adverse events and procedures described to address these unlikely events are presented in order of relative likelihood. Contingency plans for responding to these events were all negotiated with and approved by the FDA in the context of a study of MDMA-assisted therapy in patients with posttraumatic stress disorder (PTSD), and has been adapted for this present study, as below.

Hypertension

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

Individuals with evidence of cardiovascular disorders, including hypertension, will be excluded from study participation. Blood pressure and pulse will be measured at the outset of each MDMA or placebo session, then once every 15 minutes for the first 4 hours, and then every 30 minutes for the next 2 hours. If at any time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110, measurements will then be taken every 5 minutes until the values fall below these levels. During this time, the physician-investigators will continually evaluate the participant for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular or neurologic emergency. If needed, additional care will also be provided by internist co-investigator Dr. Siegel or an appropriate designate, who is also immediately available to the co-therapist investigators by remaining in a room adjacent to the treatment room for the first 5 hours of each experimental session and who will remain on McLean Hospital grounds for the remainder of the

experimental session. The investigators will make a clinical judgment about whether additional monitoring or treatment is required. If a participant exhibits systolic > 220 or diastolic > 120 , he or she will be considered to be in hypertensive crisis, and will receive immediate treatment to lower blood pressure. Reasons for transport to the local emergency room would include, but are not limited to, severe headache in the setting of hypertension, or angina or neurologic deficits regardless of blood pressure. A crash cart is immediately available and will contain nitroprusside and other antihypertensives in addition to the usual resuscitation drugs and equipment. This will allow treatment to be instituted without transferring the participant if that should become necessary. The physician-investigators may, at any time, make a clinical judgment to transfer the participant to the emergency room in the nearest local hospital (Mt. Auburn Hospital) for further observation and care.

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

Psychological distress

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

The potential for destabilizing psychological distress will be minimized by excluding individuals who might be more vulnerable to it (such as individuals diagnosed with bipolar affective disorder or with psychotic disorders), by preparing individuals before the experimental session, by creating an atmosphere of trust during the experimental session, by close monitoring and by providing non-drug integrative psychotherapy sessions. In addition, participants are encouraged to find someone

who will stay with them and who will provide support during and after each experimental session.

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

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

If a participant is anxious, agitated, in danger of any self harm or is suicidal at the end of the MDMA treatment session, the investigators will remain with the participant for at least two more hours. During this time, the investigators will employ affect management techniques described in the MDMA treatment manual, will talk with the participant to help him or her gain cognitive perspective of their experiences. If this situation should occur at the end of one of the sixty-minute follow-up sessions at least one of the investigators will be available to stay with the participant for at least two additional hours.

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

- A. The psychiatry resident (who has been hired to stay overnight with the subject until the time of his or her appointment with the co-therapist investigators the next day) will be informed that the participant continues to experience psychological distress. If psychological distress is present during the next day's non-drug psychotherapy follow-up session, but this distress is not considered to meet criteria for inpatient psychiatric hospitalization, one or both of the co-therapist investigators will meet with the subject daily until the period of destabilization has passed. (Such a period of destabilization may result in withdrawing or suspending the participant from the study, and will be reported as an Adverse Event to the McLean Hospital and Lahey Clinic's IRBs and the FDA). At any time during this

process, Dr. Halpern may make the clinical judgment to proceed to option B.

- B. Hospitalization for stabilization: Individuals requiring hospitalization due to study participation will be suspended from the study until after recovery or stabilization, at which time the co-therapist investigators will carefully evaluate the participant's emotional status. If this response occurs during the first experimental session, the investigators may elect to forego the second administration and drop the subject from the study. This decision will be made after submission of a report to the IRBs and the FDA.

Participants may contact the investigators 24 hours a day throughout the course of the study. The investigators can schedule an additional psychotherapy session if requested to do so by the participant.

For those participants engaged in an ongoing therapeutic relationship, we will actively involve their outside therapists in the management of any psychiatric complications of treatment.

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

Angina or Myocardial infarction

If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will 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

If any participant has neurologic deficits, whether or not they are associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored as described above. He or she will be transported to the 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).

Hyponatremia

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

History of hyponatremia or detection of hyponatremia on initial physical examination will be cause for exclusion from the proposed study. Participants will be given electrolyte-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.

Hyperthermia

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

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

If, during the first MDMA session, a participant's temperature rises more than 1° C and does not rapidly come down after the above adjustments have been made in blankets, clothing, ambient temperature and ventilation, then that participant will not be given a second experimental session.

In order to avoid dehydration, participants will be encouraged to drink at least 750 - 1500 mL (and up to 3 L) of an electrolyte-containing fluid (such as Gatorade) during the session depending on their size, level of activity, and body temperature.