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A correlative analysis of mystical experiences and lasting symptom improvement from MDMA-assisted psychotherapy for treatment-resistant PTSD : a project based upon an investigation sponsored by Multidisciplinary Association for Psychedelic Studies (MAPS)

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Michiko Mitsunaga-Whitten
A Correlative Analysis of
Mystical Experiences and
Lasting Symptom
Improvement from MDMA-
Assisted Psychotherapy for
Treatment-Resistant PTSD

ABSTRACT

Before the Controlled Substance Act of 1985 categorized psychedelic substances as criminalized schedule I drugs, psychiatrists used 3,4-methylenedioxymethamphetamine (MDMA) as a catalyst to psychotherapy. Over two decades later, this project seeks to contribute to the renaissance of psychedelic research. Specifically, this study focuses on participants' experience of treatment in the recent FDA approved Phase 2 clinical study, "*A Randomized, Triple-Blind Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in conjunction with manualized psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-resistant PTSD.*" The current study presents results from correlation analyses of the Mystical Experience Questionnaire (MEQ30) with PTSD symptom improvement to determine whether outcomes are related to mystical experiences.

Mystical experiences are often described by people under the influence of psychedelics; however, that experience with MDMA is not correlated with long-term positive symptom change as reported by participants during long-term follow-up (LTFU) interviews and Clinician-Administered PTSD Scale (CAPS) scores.

Keywords

3,4-Methylenedioxymethamphetamine, MDMA, posttraumatic stress disorder, PTSD, psychedelic drugs, ecstasy, mental health, psychedelic-assisted psychotherapy, MDMA-assisted psychotherapy, mystical experience, treatment resistance, pharmacotherapy.

**A CORRELATIVE ANALYSIS OF MYSTICAL EXPERIENCES AND LASTING
SYMPTOM IMPROVEMENT FROM MDMA-ASSISTED PSYCHOTHERAPY
FOR TREATMENT-RESISTANT PTSD**

A project based upon an investigation sponsored by the
Multidisciplinary Association for Psychedelic Studies (MAPS),
submitted in partial fulfillment of the requirements
for the degree of Master of Social Work.

Michiko Mitsunaga-Whitten

Smith College School for Social Work
Northampton, Massachusetts 01063

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CHAPTER I

Introduction

Traumatic events such as war, natural disaster, sexual abuse, oppression, childhood neglect, violence, and accidents, can cause a psychiatric condition called posttraumatic stress disorder (PTSD). According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM V-TR), the four primary symptom categories for PTSD include arousal and reactivity, avoidance of triggers, negative thoughts and feelings, and intrusive thoughts and nightmares (APA, 2013). Currently, the mental health field is facing a staggering suicide increase, an overdose epidemic, and has largely failed the majority of people who need mental health services the most, those experiencing PTSD. However, as some stigma against the use of psychoactive drugs in the United States changes, a new era of research is emerging that utilizes hallucinogenic or psychedelic drugs such as lysergic acid diethylamide (LSD), psilocybin, ayahuasca, and \pm 3,4-methylenedioxymethamphetamine (MDMA) to treat pervasive mental health disorders like PTSD. Conversely, interrupted by the Nixon Administration's Controlled Substance Act of 1970 (CSA), researchers in this important field have faced substantial obstacles in learning more about psychedelic-assisted psychotherapy and its potential to reduce human suffering.

The Controlled Substance Act attempted to regulate drug importation, use, possession, and distribution in America by sorting substances into "schedules" and by implementing the Drug Enforcement Agency (DEA). The law established what President Nixon called, "the War on Drugs," in an attempt to make America completely drug-free. However, despite the billions of dollars that went into fighting what Reagan later deemed, "public enemy number one," and incarcerating unprecedented numbers of people of color for minor drug offenses, and filling

prisons with twice as many people than capacity, drug use and drug-related crime have not decreased at all. Not only did the law fail to achieve what it set out to do, but it also put the United States deeply in debt and substantially contributed to systemic racism. Recent news has emerged showing that Nixon's endorsement of anti-drug sentiment was entirely political and racially motivated. Nixon's domestic political chief John Ehrlichman said, "We knew we couldn't make it illegal to be either against the war or blacks, but by getting the public to associate the hippies with marijuana and blacks with heroin and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did (LoBianco, 2016, p. 1)."

Researcher, William Richards (2015) explains that the CSA included psychedelic substances in "the highly restricted Category I." This category includes drugs with absolutely no accepted use, including medical, in the U.S and are also considered to have high abuse potential (2015). This inclusion of psychedelic drugs such as LSD, psilocybin, and MDMA into this category was unjustified when we knew then, thanks to research in the 1960s (Leary, 1964), and know even more now, that evidence strongly indicates that these drugs can be safely administered for substantial medically positive results, are nontoxic, and are nonaddictive. Nixon's policy alone completely shut down psychedelic research for twenty-two years (2015).

It is also worth noting that one of the most dangerous and readily available drugs, alcohol, is physically addictive, causes physiological damage, and rarely allows spiritual growth or personal insights and knowledge. Psychedelics, or entactogens (meaning "touching within"), could be considered completely opposite, filled with potential for relieving anxiety, depression,

addiction, or simply a more integrated, vital life (Schuster, 2013). Pharmacologist, David Nichols (1986) coined the term “entactogen,” in describing MDMA’s therapeutic quality:

The idea of a therapy using one of these drugs, which is a totally new class of drugs or psychotherapeutic adjuncts,...is using a drug which specifically allows for the opening of certain kinds of communication. Above all, a good entactogen, especially MDMA...appears in most cases to eliminate the very deep fear of remembering trauma, of bringing up things which are tremendously painful and very frightening and full of rage and grief. And in some way we have no way of understanding, MDMA makes it possible for a patient to stop being afraid of the things coming back to the conscious mind. They are able to elicit very buried memories of difficult and painful things which need to be unburied.

There is not sufficient evidence to support the popular notion that the risks of adverse effects are too high to utilize psychedelic-enhanced psychotherapy and treatment. There has been research that shows that people with latent psychosis or genetic predispositions towards psychosis should not explore psychotropic medication. However, researcher Rick Strassman (1984) shows that the adverse effects and side effects are otherwise “subtle or nonsignificant.” Brain damage is minimal, especially compared with alcohol or addictive substances (1984). Moreover, if there are any negative affect or feelings experienced while on the drug, they tend to be short lived and are nonpermanent in nature (1984).

So far, the statistical significance of psychedelic research has been astounding. Now that research on psychedelic drugs faces fewer obstacles, the current study seeks to add to its renaissance, discover more about therapeutic qualities of psychedelics, and promote safety around use. The following research summaries and assessments suggest the necessity to support further research of psychedelic psychotherapy. The current study focuses specifically on the participants’ experience of treatment in the recent Phase 2 clinical trials investigating MDMA-assisted psychotherapy for treatment-resistant PTSD and explores the correlation between participants’ mystical experiences on the drug and long-term treatment outcomes.

Study participants included seventeen subjects selected from the Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored Phase 2 investigation, *A Randomized, Triple-Blind Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in conjunction with manualized psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-resistant Posttraumatic Stress Disorder (PTSD)*. The present study is comprised of a subset of seventeen of the twenty-four participants who gave consent to be interviewed during their one-year follow-up procedure post-treatment and to have their interview used in a subsequent qualitative analysis. This study used a qualitative study design, interpretive phenomenological analysis (IPA), in order to blend the participants' vital personal experiences with acquired statistical data to gain further understanding on the therapeutic usages of MDMA on treatment-resistant PTSD, and long-term treatment outcomes. This study was based on the assumption that hallucinogenic or psychedelic drugs such as lysergic acid diethylamide (LSD), psilocybin, ayahuasca, and \pm 3,4-methylenedioxymethamphetamine (MDMA) are effective measures to treat pervasive mental health disorders.

MAPS is a U.S.-based non-profit research and educational organization supporting research of the therapeutic potential of MDMA. MAPS is sponsoring clinical trials to test medical uses of MDMA-assisted psychotherapy for patients with chronic disorders like PTSD, social anxiety related to autism, pain and anxiety related to terminal illnesses and further research into its potential for therapeutic applications.

The primary limitation to this study was the lack of control group for the follow-up interviews. It would be ethically problematic under the National Social Work Code of Ethics and American law to conduct a placebo control group over such a long period of time. Other limitations also reflect the preliminary nature of this study. The sample was small (n=17) and

homogenous, reflecting a largely Caucasian demographic (n=15). Factors that might impact the effects of MDMA were not explored, such as genetic history, religious or spiritual affiliation, or attachment style. Finally, though the basic dimensions of the MEQ30 were utilized, shortening the initial 100-item questionnaire (SOCQ-100) may have impacted our capacity to obtain more nuanced information about psychoactive effects, particularly when comparing the difference in dosage.

Chapter Two, which follows, provides a historical overview of MDMA and further demonstrates that psychedelic treatment has data-driven potential for medical usage and low to moderate risk for addiction. This chapter also defines PTSD and provides current available treatment options and efficacies.

CHAPTER II

Literature Review

This chapter informs the physiological and biological effects of MDMA on humans in order to make the connection between the drug's effects and how it constitutes change for people struggling with PTSD. This includes a review of existing studies surrounding MDMA-assisted psychotherapy to offer context for this research. A brief review of studies surrounding psychedelic-enhanced therapies using other drugs follow in order to highlight the specific usefulness of MDMA as compared to other hallucinogens.

History

Methylenedioxymethamphetamine was first synthesized and patented by the pharmaceutical company Merck in 1912 (Freudenmann, 2006). There is no current patent today on MDMA. Chemist Alexander Shulgin and his colleagues (1991) rediscovered MDMA in the late 1970s and found that human emotions could be positively influenced by the entactogen without experiencing adverse physiological or cognitive functioning. Shulgin (1991) also found, similar to more current research, that MDMA increased feelings of closeness with other people, feelings of wellbeing, and insightfulness. In 1985, MDMA was added to the category of Schedule I controlled substances (CSA). Methodological limitations for studying this particular drug, therefore, became difficult to overcome and research slowed to a standstill. Even today, MDMA continues to be considered a Schedule I drug with no medical usage and high risk for addiction, according to the CSA. MAPS (2013) explains the neurological effects of MDMA in the 7th Edition of the Investigator's Brochure:

MDMA is a ring-substituted phenethylamine that produces anxiolytic and prosocial effects through release of the monoaminergic neurotransmitters with the greatest effect on serotonin, followed by norepinephrine and dopamine. MDMA has been shown to acutely decrease activity in the left amygdala and increase

blood flow to the prefrontal cortex in the brain. MDMA has also been found to increase serum levels of the neurohormones oxytocin and arginine vasopressin in humans, which are likely to be involved in increased trust and attenuated reactivity to threatening cues. The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, while enhancing communication and capacity for introspection. These factors taken together can provide the opportunity for a corrective emotional experience in the context of psychotherapy. Many of the therapeutic effects of MDMA-assisted psychotherapy are evident within a short period of treatment, often after the initial session. Increased feelings of interpersonal closeness, changes in social perception and reduced anxiety may make MDMA a suitable pharmacological adjunct to enhance psychotherapy for anxiety disorders such as PTSD and possibly social anxiety more generally.

The following literature review demonstrates that MDMA has data-driven potential for medical usage and low to moderate risk for addiction. MDMA can provide a much-needed option in the treatment of PTSD and other conditions associated with anxiety.

Posttraumatic Stress Disorder (PTSD)

DSM-IV-TR diagnostic criteria. The American Psychiatric Association (APA) asserts in the text-revised, fifth edition of their Diagnostic and Statistical Manual of Mental Disorders (DSM V-TR) that PTSD begins with the exposure to an extreme traumatic stressor (APA, 2013). PTSD is an anxiety disorder with two main debilitating groups of symptoms. Primary PTSD symptoms consist of re-experiencing, hyper-arousal, and avoidance symptoms; the second group includes impaired functioning, poor coping skills, psychiatric and medical comorbidity, suffering, drug abuse, and suicide risk (Cohen, Marmar, Ren, Bertenthal, & Seal, 2009; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kozarić-Kovačić, 2008; Mithoefer et al., 2010). In spite of PTSD being a major world-wide health problem, psychotherapeutic and pharmacological treatments for this chronic illness have shown to be only partially effective for most people (Carr, 2011). While there is immense empirical literature on trauma, its treatment remains elusive.

Even 3,000 years ago, Homer (Fitzgerald, 1990) showed us that PTSD from combat trauma can impact the health of a veteran's psyche in the gruesome final chapter of *the Odyssey*, *Slaughter in Hall*. Despite the popular notion that the soldier, Odysseus achieves his goal when he arrives home in Ithaca, he is unable to integrate into society again, kills everyone in his home, and departs for another journey. Homer offers us a metaphor for the difficulties of fostering a healthy psychic life following a traumatic event (Shay, 2002). PTSD is still as pervasive and unrelenting because existing treatments are not reliable or lasting for the majority of people suffering from this disease. Even therapies with the most empirical support, like Cognitive-Behavioral Therapy (CBT), tend to show drop-out rates of up to 54% and nonresponse rates of up to 50% (Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). These forms of CBT currently have the most evidence for efficacy (Carr, 2011). While there is also evidence that pharmacotherapy and psychotherapy utilized in conjunction to treat PTSD leads to increased success rates, there are currently no manualized or legal therapies that offer such a reliable model (Hetrick, S., Purcell, R., Garner, B., & Parslow, R., 2010; Mithoefer et al., 2012).

What is in fact known, however, is that talking about the trauma in a safe environment and emotionally stable state is healing both physiologically and psychologically. Elizabeth Maynard Schaefer (2008) explains how not talking about a trauma can lead to more debilitating symptoms and illnesses:

Psychological researchers have long known that traumas or significant emotional crises are stressful to the mind and body. This effect is so dramatic that traumatized people have higher rates of depression and other ailments and are even more likely to die of cancer and heart disease than that general population. What is it about these traumas that leads to such health problems? In the 1980s, researcher James W. Pennebaker (now at the University of Texas at Austin) and his team found a clue. They studied people who had experienced a life-changing trauma in childhood such as the death of a family member, the divorce of parents, physical abuse, or a sexual trauma. They discovered that people who had such an experience but kept it secret were at much higher risk for both major and minor

illnesses than those who spoke about it. Their different levels of health were easy to discern: the secret-keepers went to the doctor 40% more often.

PTSD appears to be so difficult to overcome because trauma can be incredibly hard to talk about. Symptoms of dissociation, hyper-vigilance, and re-experiencing all promote avoidance and therefore a roadblock to healing. As the following literature shows, MDMA has the potential to help people feel able to safely confront and hence work through their trauma.

Existing treatments for PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies for treatment of PTSD. Psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in treating some symptoms of PTSD (Ursano, 2004). Because of the enduring effect of PTSD, many people undergo more than one treatment to reduce or resolve PTSD symptoms (Hamner, Robert, & Frueh, 2004). A recent meta-analysis concluded that all accepted, evidence-based psychotherapies, including those listed above, are similarly effective for PTSD and have an average effect size of 0.25 (Benish, Imel, & Wampold, 2008). While a wide variety of treatments exist for PTSD, most have shown limited efficacy. The majority of accepted treatments benefit just a portion of the population or bring relief to a limited number of symptoms while bringing about difficult side effects that further lower quality of life (Foa et al., 2009; Kar, 2011; Mitheofer et al. 2010; Stein, 2009).

MDMA

Over two decades after the illegalization and criminalization of MDMA, Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., & Doblin, R. (2010) completed the first clinical trial evaluating MDMA as a therapeutic adjunct. Twenty subjects with treatment-resistant PTSD were randomly assigned to concomitant active MDMA (n=12) or inactive

placebo (n=8). The study utilized the Clinician Administered PTSD Scale (CAPS) as the outcome measure administered at baseline, 4 days after each experimental session, and 2 months after the second session. The rate of clinical change from baseline was significantly higher in the active dose group (83%) compared to the placebo group (25%). There were no serious adverse events related to MDMA, adverse neurocognitive effects, nor significant blood pressure increases. Mithoefer et al. (2010) shows initial efficacy and safety using MDMA-assisted psychotherapy.

Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., & Doblin, R. (2012) later completed a follow-up study to investigate the lasting effects of the aforementioned 2010 study. Using the Clinician-Administered PTSD Scale (CAPS), Impact of Events Scale-Revised, the Neuroticism Extroversion Openness Personality Inventory-Revised, and a long-term follow-up questionnaire (LTFU), the researchers found that on average subjects maintained statistically and clinically significant improvements in symptom relief and reported no harm from participating in the study. CAPS scores that were taken directly after treatment showed no significant difference from the long-term scores taken on average 3.5 years after treatment. This pioneering study gave the first evidence of enduring, clinically meaningful benefit of MDMA-assisted psychotherapy for treatment-resistant PTSD. The LTFU also showed that no participant developed a problem with any illicit substance after their MDMA-assisted psychotherapy, which supports the hypothesis that MDMA can be administered in a regulated, clinical setting without creating a dependence or addiction.

The Mystical Experience Questionnaire (MEQ30) measures unity, noetic quality, sacredness, positive mood, transcendence of time/space, and ineffability (Maclean, Johnson, Leoutsakos, & Griffiths, 2012). Participants in the current study completed the 100-item States

of Consciousness Questionnaire (SOCQ-100) after each MDMA-assisted psychotherapy session. The MEQ30 is comprised of 30 questions selected from the SOCQ-100. The research from Maclean, Johnson, Leoutsakos, & Griffiths (2012) shows that the MEQ30 is a reliable and valid measure that correlates with other mysticism scales, such as the Hood Mysticism Scale (Hood, 1977). This data may be biased towards positive experiences with psychedelics because the participants self-selected into the study. Nonetheless, the data here support that the MEQ30 is a useful tool in future scientific study of psychedelic experiences. This project will utilize data from the MEQ30 in order to understand the correlation of mystical experiences with long term MDMA-assisted treatment outcomes. This project will also utilize the outcome measure, Clinician-Administered PTSD Scale (CAPS) in order to assess the long-term effects of MDMA of PTSD. Blake, et. al, (1995) asserts that of all the structured diagnostic interviews available to assess PTSD, CAPS appears to be the most reliable and valid in measuring the frequency and intensity of each symptom.

Following the first investigations of the effects of MDMA on PTSD, researchers in Switzerland tested the safety and efficacy of this treatment and found similarly hopeful results. Oehen, Traber, Widmer, & Schnyder (2012) designed a randomized, double-blind, active-placebo controlled trial enrolled 12 patients for treatment with either low-dose (25 mg, plus 12.5 mg supplemental dose) or full-dose MDMA (125 mg, plus 62.5 mg supplemental dose). MDMA was administered during three experimental sessions and supplemented with weekly psychotherapy sessions. The Clinician-Administered PTSD Scale (CAPS) and the Posttraumatic Diagnostic Scale (PDS) were used as outcome measures. Patients were assessed at baseline, three weeks after the second and third MDMA session (end of treatment), and at the 2-month and 1-year follow-ups. This study supported the hypothesis that MDMA-assisted psychotherapy can

be safely administered in a clinical setting. No drug-related serious adverse events occurred and there were no statistically significant reductions in CAPS scores ($p = 0.066$). However, there was clinically and statistically significant self-reported (PDS) improvement ($p = 0.014$). Illuminating the long-term effects of MDMA-assisted psychotherapy, CAPS scores improved further at the 1-year follow-up. Additionally, researchers found that three MDMA sessions were more effective than two ($p = 0.016$).

In 2008, some of the leading researchers in this field produced another study to show how MDMA-assisted psychotherapy can help women with chronic post-traumatic stress disorder. Bouso, Doblin, Farre, Alcazar, and Gomes-Jarabo (2008) tested different doses of MDMA with women diagnosed with chronic PTSD stemming from sexual assault in a fully approved, controlled study about safely administering MDMA. The study was meant to have 29 participants, but because of political reasons, it was shut down before more than six participants could complete the trial. The study deemed MDMA safe for the six subjects. No participant experienced an increase in symptoms on any of the psychopathological scales that were used and all participants were entirely safe physiologically as well.

Since there is evidence that certain psychedelic drugs are safe physiologically, neurologically, and psychologically, it is helpful to develop an understanding of their specific therapeutic uses. Bedi, Phan, Angstadt, and de Wit (2009) studied the effects of MDMA on sociability with regards to social threat and social reward. The researchers compared fMRI responses in participants' brains to angry facial expressions, frightened facial expressions, and happy expressions on placebo and on 1.5mg/kg of MDMA. They found that MDMA attenuated amygdala responses in reaction to the threatening or angry face and heightened ventral striatum responses in reaction to the happy face. In other words, subjects using the MDMA were less

threatened by the angry face and happier in response to the happy face than those taking the placebo. Interestingly, there was no difference in reaction to the fearful face in both control groups. This study is important in understanding potential therapeutic uses as well as risks. In chronic abuse situations, it is a useful protective strategy for victims to have a highly reactive amygdala. However, if a person is no longer in danger, but suffering from PTSD, this study shows that MDMA decreases perceptions of social threat, which could therefore assist in relieving anxiety and stress.

In essence, because there are robust data that show psychedelics can be safe for humans, the article by Dumont, Sweep, Van der Steen, Hermsen, Donders, and Touw et. al. (2009) that seeks to explain why they may be useful therapeutically is the logical next step of exploration. According to the article abstract, the researchers used a double blind, randomized, crossover, and placebo-controlled study in 15 healthy volunteers in order to assess blood oxytocin and MDMA concentrations as well as subjective prosocial effects and behavior. The study found that MDMA increases oxytocin levels which, based on what we know about oxytocin, might be correlated with the prosocial effects of the drug. The subjective accounts from the participants about their prosocial feelings correlated with the amount of MDMA and oxytocin in their blood. Of course, there is confounding bias in this study since the design cannot determine if the rise of oxytocin caused the prosocial feelings. The study would have gained validity if a more objective measure to study the prosocial effects was used. Instead of simply asking patients, the study suggests utilizing measurable social games so that the participants not only perceive themselves as friendlier, but also actually objectively act more socially.

There have also been useful studies solely involving self-reports of experiences under the influence of MDMA. In 1997, Davidson & Parrott interviewed twenty recreational drug users,

asking them to describe the psychological and physiological effects they experienced under MDMA. The subjects comprised 11 males and 9 females, 18-31 years old, who took MDMA anywhere from 1-10 times. Each subject completed a modified Profile of Mood States Questionnaire (POMS), an Ecstasy Effect Questionnaire, and a structured interview that included questions about their past MDMA-use. Each participant reported increased feelings of elation, agreeableness, energy, and mental confusion while they were on the drug. The subjects also generally reported a faster heart rate, feeling hot, increased sweating and dehydration, dilated pupils, and tight jaw. There was also a consensus that coming off of MDMA led to feelings of lethargy, moodiness, insomnia, depression, irritability, and paranoia, which Davidson & Parrott (1997) attribute to a possible reason why risk for addiction with MDMA is so low. Bad MDMA trips were reported by 25% of the sample, following a variety of unpleasant experiences. An increased tolerance was not apparent, although the regular users all described their first MDMA experience as 'the most intense,' later trips were affected by knowledge and expectancy, rather than any diminution in drug response.

Liechti, M., Gamma, A., Vollenweider, F., (2001) conducted a study on gender differences in subjective effects of MDMA. Their work analyzed data from three different controlled studies on the physiological and psychological effects of MDMA in a total of 74 healthy volunteers (54 male, 20 female). The research concluded that psychoactive effects of MDMA tend to be more intense in female subjects than male subjects. Women had higher scores for MDMA-induced perceptual changes, thought disturbances, a fear of loss of body control. Moreover, the administered dose correlated positively with the intensity of perceptual changes in women. Acute adverse effects were also more frequent in female subjects than male subjects. However, the male subjects showed higher increases in blood pressure than woman. Equal doses

of MDMA per kilogram of body weight was used to control for weight differences in males and females. With this control, women showed stronger responses and increases in susceptibility compared to men. It is important that researchers are aware that gender is related to susceptibility differences when assigning appropriate dosages for future studies and therapies.

Other Psychedelics

We know that psilocybin mushrooms, ayahuasca, peyote, and other psychedelic plants have been ingested by humans for thousands of years for religious or spiritual purposes. However, we lack knowledge about the long-term effects of hallucinogens (Griffiths, Richards, Johnson, McCann, & Jesse, 2008). The experiential differences of MDMA and other psychedelic substances are important to explore in order to best utilize their capacities for particular mental health problems. Griffiths, Richards, Johnson, McCann, and Jesse (2008) did a double-blind study on the psychological effects of a high dose of psilocybin and enacted a follow-up study 14 months later in order to learn more about long-term effects. Of the 36 participants who had never experienced any kind of hallucinogenic drug prior to the study, 67% rated that their psilocybin-occasioned experience was one of the five most personally meaningful and spiritually significant experiences of their entire lives (2008). This study suggests that even 14 months later, mystical experiences with psychedelic, also referred to as entheogenic, drugs can produce positive changes in attitudes, mood, altruism, behavior and life satisfaction. This study used the Panhke-Richards Mystical Experience Questionnaire (MEQ30) in order to quantify mystical experience. The reliability and validity of this questionnaire were explored by Thomas et al. (2013).

Thomas et al. (2013) found in a study on problematic substance use and stress that after four days of group counseling and two ayahuasca-assisted therapy sessions, “improvements were demonstrated for scales assessing hopefulness, empowerment, mindfulness, and quality of life

meaning and outlook (Thomas, Lucas, Capler, Tupper, & Martin, 2013, p. 1).” The findings show that alcohol, cocaine, and tobacco use significantly declined and remained lower in a six month follow-up. This study not only shows that ayahuasca can benefit people suffering from particular addictions, but also shows that the mental and behavioral health issues coinciding with the addiction subside. However, the study was limited in that it had no matched control groups and lost touch with a few participants for the six-month follow-up.

Beyond qualitative reporting of the effectiveness of psychedelic psychotherapy, there has been important research on the effects on the brain. Neuroscientists, Robin Carhart-Harris, Kaelen, and Nutt (2014) led a study that observed the brain while on LSD. Through the first modern neuroimaging of LSD, the researchers found significant correlative activity. Carhart-Harris et al. (2014) found that the brain on LSD has “increased visual cortex CBF, RSFC, and decreased alpha power, predicting the magnitude of visual hallucinations; and decreased DMN integrity, correlating with profound changes in consciousness, typified by ego-dissolution (Carhart-Harris, Kaelen, & Nutt, 2014, p. 4856).” Essentially, this study shows, via neuroimages, *how* hallucinogens profoundly affect brain function and, therefore, consciousness. Ego-dissolution, an integral feeling contributing the loss of a sense of self, is usually involved in mystical experiences. This study sheds light on what occurs in the brain during consumption of a psychedelic which aligns with qualitative reports of ego-dissolution and mystical experiences.

Scott Hill’s (2013) book, *Confrontation with the Unconscious: Jungian Depth Psychology and Psychedelic Experience*, connects the latest scientific data with clinical practice. Hill (2013) integrates Carl Jung’s theoretical orientation of archetypes, the collective unconscious, and mysticism with psychedelic psychotherapy. The mythological and symbolic similarities of Jung’s writing of the unconscious and images or feelings reported on

hallucinogens deems further research on this comparison for legitimacy. One limitation Hill (2013) presents is that Jung (1966) himself was relatively opposed to hallucinogenic-enhanced paths to unconscious material. With reason, Jung wrote about the risks involved in ignoring the natural defenses humans put in place in order to restrict access to the depths of our psyches that psychedelics bring us. Jung (1966) believed in the transformative power of confrontation with the darkest aspects of ourselves, but also believed getting there too fast could be destructive. Therefore, the way in which practitioners help their clients prepare for and then integrate their experiences on hallucinogens seems particularly important.

A study by Maclean, Johnson, and Griffiths (2011) showed that personality change in adults is possible following a high-dose psilocybin session. The researchers tested five domains of personality -- neuroticism, extroversion, openness, agreeableness, and conscientiousness -- to find that openness was statistically significantly increased and stayed increased over one year after the trial. This study shows that effects of high-dose psilocybin can be measurable and lasting using double-blind, controlled methods. They also explored the concept of mystical-experiences-- “feelings of unity and interconnectedness with all people and things, a sense of sacredness, feelings of peace and joy, a sense of transcending normal time and space, ineffability, and an intuitive belief that the experience is a source of objective truth about the nature of reality” (p. 2). This experience led participants to experience lasting and beneficial personality change. Maclean, Johnson, and Griffiths (2011) include helpful subjective reports as well, which show that 50-80% of participants felt lasting changes in values, personality, attitudes, and behavior.

Peter Gable, a psychology professor at the Claremont Graduate School, provides additional psychedelic literature. He describes his personal experience using psilocybin and his

conversations with both Skinner and Maslow around his experience. One of the most important anecdotes is Gable's claim that ingesting psilocybin mushrooms has helped him communicate with his terminally ill patients in the hospice where he worked. Skinner responded to Gable regarding psilocybin, "We may have been able to make the same change by manipulating standard environment variables; the drug now permits us to circumvent that manipulation" (p. 45). The original behaviorist may have been interested in helping people make changes when their environment or situation is unchangeable with the assistance of psychedelic-assisted therapy.

Finally, Gasser, Kirchner, and Passie (2015) published an important study on the safety and efficacy of LSD-assisted psychotherapy in patients with existential anxiety induced by a life-threatening disease. One year after completing LSD-assisted psychotherapy, 10 participants were tested for anxiety (STAI) and participated in a semi-structured interview. A Qualitative Content Analysis (QCA) was conducted on the interviews to elaborate about LSD effects and lasting psychological changes. Improvements measured by the STAI were sustained over the year showing that the changes are long lasting. Subjects consistently reported insightful, cathartic and interpersonal experiences, accompanied by a reduction in anxiety (77.8%) and a rise in quality of life (66.7%) in the QCA. These reported experiences helped restructure the participants' emotional trust, situational understanding, habits, and worldview. No lasting adverse reactions were reported by any of the participants. This study is particularly useful because it highlights the importance of collecting qualitative data in order to understand subjective reports of efficacy and sustainability.

The most compelling purpose in investigating psychedelic psychotherapy is to learn more about the efficacy of treatment and how it is being facilitated. If the opportunity exists to use new

treatments to relieve human suffering, then it must be explored. This is particularly true when current medication and treatment options are minimal and unreliable for a vast amount of people. While we now know that this type of therapy can be safe and effective, the existing literature reveals a knowledge gap in the understanding of long-term effects of psychedelic-assisted therapy.

Summary

Existing treatments for the destructive disease, PTSD, are not adequate in providing lasting help for a significant number of traumatized people. Based on what is known about the effects of MDMA on humans, there is reason to explore how this psychedelic can promote therapeutic action and lasting symptom improvements. The current study aims to address the lacuna in the existing literature by investigating the correlation between mystical experiences and long-term MDMA-assisted treatment outcomes on treatment-resistant PTSD. Ultimately, learning about what makes psychedelic psychotherapy therapeutic and meaningful may reveal roadblocks and direction for future safe and useful treatments. Current data are thin regarding what specific experiences or feelings within a psychedelic treatment cause therapeutic action. The current study specifically explores the correlation of MEQ30 scores with CAP scores and data from participants' LTFU interviews as outcome measures. Information on demographics may be informative about who this therapy is available to and for whom it works or does not work.

Chapter III

Methodology

Research Design

A wealth of both quantitative data and qualitative data on the therapeutic use of psychedelics is available. Historically, personal accounts of mystical experiences while under the influence of psychedelics show that these drugs can increase insightfulness, acceptance, and empathy. Lately, research has taken a more quantitative turn that shows that the personal descriptions align with the science. The current study blends vital personal experiences with the necessary statistical data in order to shed light on the therapeutic usages of MDMA on treatment-resistant PTSD, and long-term treatment outcomes. The methodological framework of the current study is Interpersonal Phenomenological Analysis (IPA) and includes detailed analysis of participants' personal accounts followed by a presentation and discussion of experiential themes in order to make meaning of the participants' experiences with MDMA-assisted therapy (Pietkiewicz, I. & Smith, J., 2012).

To provide this qualitative perspective, analysis focuses on participants' one-year follow-up LTFU interviews. These interviews were designed to investigate participants' experience with MDMA-assisted treatment, how they have felt it has or has not led to changes in symptomology in their life, suggestions for changes to benefit the study protocol, substance use changes, differences in interpersonal relationships, and a variety of other topics. The analyses of these qualitative interviews focus on interview transcripts and are considered with other quantitative data sources including pre and post-therapy CAPS scores, measuring symptom severity and MEQ30 scores, a measure of alterations in consciousness related to mystical experiences.

Additional insight about study effectiveness and protocol is expected, potentially leading to the development of a treatment that can reach a wider variety of people in need. Finally, these data serve as a foundation to discuss a theory for how the neurochemical actions of MDMA work in the context of therapeutic action for posttraumatic stress disorder.

Qualitative Methodology

Interpretative Phenomenological Analysis (IPA). Biggerstaff and Thompson (2008) refer to IPA as a qualitative methodology that “can offer as a research tool in understanding healthcare and illness from the patient or service user perspective” (p.2). IPA supplements other traditional qualitative methods in using an idiographic component to analysis in addition to the standard phenomenology and hermeneutic practices of other methods (Smith, Flowers & Larkin, 2013). This allows researchers to look beyond the simple “what” and “how” of participants’ experiences towards the meaning behind their experiences. Smith & Osborn (2003) explain that the purpose of using IPA is simply “to explore in detail how participants are making sense of their personal and social world” (pg. 53). The primary attribute for an IPA study is the meaning specific experiences, events, or self-states hold for participants (Smith & Osborn, 2003). Finally, IPA was chosen as the methodology for this study because it has been the primary methodology in similar qualitative investigations into MAPS sponsored studies. For example, the MAPS sponsored New York University study of psilocybin-assisted psychotherapy for end-of-life anxiety used IPA to explore the safety and efficacy of this psychedelic-assisted treatment. Using IPA in this qualitative analysis will help to further evaluate its usefulness in the field of psychedelic study.

Sample

Inclusion criteria. Subjects are men or women aged 18 or older with a confirmed diagnosis of chronic, treatment-resistant PTSD who have undergone psychotherapeutic or psychopharmacological treatment for PTSD of adequate dose/duration without achieving remission. All participants in these samples were in the severe category of symptoms as outlined by results on the CAPS as well as deemed treatment resistant by unsuccessful psychotherapy or pharmacological treatments (Mithoefer et al, 2010; Mithoefer et al, 2012). Mean baseline CAPS scores (84.7) indicated extreme chronic PTSD with an average duration of 17.8 years. Subjects who discontinued PTSD treatment due to inability to tolerate psychotherapy (e.g. due to persistent “over-engagement”) or psychopharmacology due to treatment-emergent side effects were not excluded. Subjects were not excluded for having more than one traumatic event. Subjects had a last month CAPS score equal to or greater than 50 and are in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA were eligible for study inclusion.

Exclusion criteria. Criterion which would have excluded participants from taking part in the Phase 2 trials mainly describe conditions that would put the participant or others in danger, or would drastically confound data from their participation. These criteria can be found in the original MAPS Investigators Brochure (2010) which excludes participants that:

1. Are pregnant or nursing, or are women of child bearing potential who are not practicing an effective means of birth control;
2. Have a history of, or a current primary psychotic disorder, bipolar affective disorder type 1 or, dissociative identity disorder;

3. Have evidence or history of coronary artery disease or cerebral or peripheral vascular disease, hepatic disease with abnormal liver enzymes, or any other medical disorder judged by the investigator to significantly increase the risk of MDMA administration;
4. Have hypertension using the standard criteria of the American Heart Association (values of 140/90 or higher assessed on three separate occasions [72]), unless their hypertension has been successfully treated and is currently well-controlled on antihypertensive medicines. In this case subjects with well-controlled hypertension were enrolled if they passed additional screening to rule out underlying cardiovascular disease;
5. Have liver disease with the exception of asymptomatic subjects with Hepatitis C who have undergone additional evaluation. Subjects with Hepatitis C were enrolled if they received appropriate screening;
6. Have history of hyponatremia or hyperthermia;
7. Weigh less than 48 kg;
8. Would present a serious suicide risk, as determined through psychiatric interview, responses to C-SSRS and through the clinical judgment of the investigator, or who, in the judgment of the investigator, are likely to require hospitalization during the course of the study;
9. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist;
10. Have used “Ecstasy” (material represented as containing MDMA) more than five times within the last 10 years or at least once within 6 months of the MDMA session;
11. Require ongoing concomitant therapy with a psychotropic drug;
12. Meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days;

13. Are not able to give adequate informed consent;
14. Have any current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the protocol.

Sample characteristics. The sample of the current study includes 17 subjects. 15 participants identified as White/Caucasian and 2 identified as Native American. 12 participants identified as male and 5 as female. At baseline, participants ranged in age from 24 years to 56 years (6 were 20-30 years old, 5 were 31-40 years old, 4 were 41-50 years old, and 2 were 51-60 years old).

Recruitment procedures. Participants were recruited via letters of referral sent to psychiatrists and psychotherapists, contact with veterans' organizations, written advertisements, announcements placed on appropriate internet sites and the sponsor website, and word of mouth. Candidates could also be individuals who had previously contacted the investigators expressing interest in taking part in the initial study of MDMA-assisted psychotherapy for PTSD after that study had closed enrollment.

One of the investigators or their assistant interviewed prospective participants by telephone to learn if they met basic eligibility criteria. If the prospective participant was interested in taking part in the study, the investigators provided her or him with consent materials for review and consideration through postal mail or electronically. If, after review, a potential participant remained interested in taking part in the study, then he or she met with the investigators to complete the consent process. Participants completed a quiz to assess their understanding of the consent forms. Investigators reviewed the quiz responses with the prospective participant to ensure that he or she correctly understood study procedures, risks and benefits.

Data Collection

Data was comprised from secondary data from MAPS (2016) study, *“A Randomized, Triple-Blind Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in conjunction with manualized psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-resistant Posttraumatic Stress Disorder (PTSD)”* in the form of transcriptions of qualitative interviews one year following the treatment, long-term follow-up questionnaires, MEQ30 scores taken between the end of each MDMA-assisted psychotherapy session and before they left the treatment facility the next day, and CAPS scores from before and after treatment.

Measures

The CAPS is the primary outcome measure that determines PTSD symptom severity. The CAPS yields a global symptom severity score, as well as a categorical ranking as to whether or not a subject meets DSM-IV-R criteria (American Psychiatric Association, 2000) for PTSD diagnosis (Weathers et al., 2001; Blake et al., 1995). The current study utilized pre and post-treatment CAPS scores in order to compare PTSD symptom severity before and after treatment.

The LTFU questionnaire is designed to capture the perceived benefit or harm of MDMA-assisted psychotherapy and changes in any areas not addressed by standard outcome measures, such as changes in relationships or creativity. The questionnaire measures the degree (with an ordinal scale of 1-Slight to 5-Large) and persistence (scale of 1-Small to 5-All) of the perceived benefits and/or harms of MDMA-assisted psychotherapy for PTSD (Mithoefer, 2012).

Additionally, the questionnaire includes items addressing participant beliefs concerning the potential benefit of receiving an additional MDMA-assisted psychotherapy session, any psychiatric treatment after the study (whether psychotherapy or psychiatric medications), and their use of “ecstasy” (material represented as containing MDMA) and/or any other illicit

psychoactive substances after study participation, plus any perceived changes in cognition after study participation. The participants were invited to write comments relating to their participation in the study. The full questionnaire is available online (MAPS, 2009) as supplemental material.

In conjunction with the questionnaire, subjects completed a dynamic, verbally-performed and video-recorded, semi-structured LFTU interview one year following treatment. Therapists of the Phase 2 clinical trials, Michael and Annie Mithoefer facilitated the interviews. A Long-Term Follow-Up Qualitative Interview Guide was created by the research team of the current study in accordance with the practices of IPA to lead the interviewers to gain pertinent data for analysis throughout the interview (Smith, 2004). This interview guide includes subjects such as participant perceptions on benefit of study participation, harm of study participation, helpfulness of an additional MDMA-assisted session, and perception of therapy prior to and after the study. This interview guide also aims to gain any information on psychiatric medication use before and after the study, any use of MDMA/ecstasy before or after the study, non-prescription substance use before and after the study, information on any significantly stressful events since study completion, subject requests, and other pertinent information.

Participants completed the SOCQ100, a 100-item questionnaire measuring the dimensions of classic mystical experience: unity, noetic quality, sacredness, positive mood, transcendence of time/space, and ineffability directly after each MDMA-assisted psychotherapy session. Maclean, Leoustakos, Johnson, & Griffiths (2012) researched the efficacy of the SOCQ100 and found that 30 items alone effectively measure mystical experience. The current study utilized the 30 items from the SOCQ100 that constitute the MEQ30. The MEQ30 is a self-report measure that has been used to study the effects of hallucinogens in laboratory studies

(Maclean, Leoustakos, Johnson, & Griffiths, 2012). Each item was rated on a 5-point scale (0=none, not at all; 1=so slight cannot decide; 2=slight; 3=moderate; 4=strong [equivalent in degree to any previous strong experience]; and 5=extreme [more than ever before in my life and stronger than 4]).

Participation

Risks of participation. While serious MDMA toxicity is rare even in uncontrolled or recreational settings, there were some risks involved in participating in this study. Although no participant reported adverse effects in the current study, some associated rare negative physiological effects can be hyperthermic syndromes, dysphoria, panic or psychotic response, hepatotoxicity, and hyponatremia (Downing, 1986). The majority of hospital visits related to MDMA or ecstasy use occur because of anxiety or panic attacks. Anxiety or distress during the MDMA session could last anywhere from 15 minutes to 5 hours, according to Phase 1 MDMA-assisted psychotherapy research (MAPS, 2013). Moreover, psychological distress could arise following an MDMA session as a result of participants having difficulty integrating their experience after the effects of MDMA have subsided. Fatigue, feeling anxious or weak, or experiencing low mood are occasionally reported up to three days after MDMA administration (1986). Participants were also expected to experience significant, but transient increases in heart rate and blood pressure. In the current study, participants were informed that experimental sessions have the intention of confronting and working through traumatic experiences. Therefore, psychological distress, anxiety, or other unpleasant psychological reactions were generally expected and considered important aspects of the therapeutic process (MAPS, 2016).

Benefits of participation. Participants who chose to engage in the current study were people who attempted at least one other type of treatment to relieve their symptoms of PTSD. Because no other treatment proved efficacious or lasting improvement for these participants, they had few alternative options for getting help and showed potential to benefit from this new treatment. Subjects have categorized their benefit of the treatment in the long-term follow-up questionnaire as, “benefit has lasted and continued to grow” (n=9), “virtually all benefit has lasted” (n=3), or “most, but not all of the benefit has lasted” (n=3). Participants more specifically labeled their benefit types as, “increased general wellbeing” (n=14), “increased ability to feel emotions” (n=13), “less avoidance of people or places” (n=11), “improved sleep” (n=11), “improved relationships with spouse, partner, or family members” (n=12), “improved relationships in general” (n=11), “enhanced spiritual life” (n=10), “increased self-awareness or understanding” (n=14), “increased creativity” (n=7), “increased empathy for others” (n=11), “more involved in the community or world” (n=10), “fewer nightmares, flashbacks, or intrusive memories” (n=12), “reduced anxiety” (n=12), “less excessive vigilance” (n=11), “improved work performance” (n=9), “improved mood” (n=10), and “other psychological benefit” (n=8).

Informed consent procedure. The informed consent form (ICF) was signed and dated by the participant and countersigned by the investigator. The investigator provided a copy of the signed ICF to the subject, and maintained the original in the investigator’s study file. See Informed Consent Form in Appendix A.

Written consent to take part in the study session included giving the investigators permission to view the participant's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation included past medical history,

psychiatric interview, physical examination, and clinical laboratory tests. Participants could withdraw consent for their participation in the protocol at any time without prejudice.

Confidentially and anonymity. Every effort was made to strictly safeguard the confidentiality of participants in their role as research participants. MAPS removed identifying information from data and restricted access only to researchers directly involved in assessing the participants, preventing the dissemination of confidential data. The informed consent and a subject contact information sheet were stored separately from other documents. All data was identified only by the participant's initials on the source document and four- digit subject number. If past medical records were required, participants signed forms for the release of information upon consent to permit screening for protocol enrollment. Copies of audio and video recordings intended for sharing with participants were marked only with the participant's subject number. Any materials mailed to participants were sent along with stamped return envelopes using the office address of the Clinical Investigator both as main and return address. All assessment records were kept in a locked file drawer or cabinet in a locked office, and access to measures were limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators directly involved in the protocol, with access to data were not provided with any information that would identify participants by name or by other means, such as social security number.

All psychotherapy sessions were video and audio recorded. These recordings were used for manual development and may potentially be used for training therapists to perform MDMA-assisted psychotherapy. Full names and addresses do not appear in these recordings.

Any use of recordings for purposes other than research or training (e.g. a documentary film) may occur only with separate written informed consent of the participant obtained after study participation is complete.

Maintaining data in a secure environment ensured the prevention of the accidental or deliberate examination or removal of data by unauthorized persons. While it is possible that individuals may be identified on audiotape or video recording through means other than their names, restricting access to audio recordings or video recordings to researchers or trainees greatly reduced the risk of a breach of confidentiality.

Human Subjects Review Board. This study was reviewed and approved by the Copernicus Group, the Institutional Review Board of record, and received exemption from Smith College School for Social Work based upon the Copernicus Group's approval. See Human Subjects Review Board approval letter in Appendix B.

Voluntary nature of participation. Participants volunteered for the sessions with the intention of confronting and working through traumatic experiences. Consent forms were provided by the primary investigators describing the participants' complete voluntary involvement and choice to end participation at any point in the study.

Data Analysis

A computer-assisted qualitative data analysis software package, ATLAS.ti, was utilized to assist in data analysis of the interview transcripts. Both individually and with committee members, interviews were coded for content, emerging themes were identified, and data was organized into thematic constructs utilizing a content analysis approach. A Pearson correlation analysis was run in order to determine linear dependence of mystical experience scores and long-term symptom change.

CHAPTER IV

Findings

The current study was an interpretive phenomenological analysis (IPA) that used a qualitative method design and a non-random purposive sampling method. The purpose of this study was to investigate if mystical experience constitutes therapeutic change in MDMA-assisted psychotherapy. By long-term follow-up (at least 12 months following the final MDMA session) the overall remission rate was 66.2%, with an average drop of 47.7 points on the CAPS or mean percentage improvement of 43.24%. The potential for MDMA-assisted psychotherapy to benefit participants with treatment-resistant PTSD is clear by these measures. However, the current study shows that mystical experience is not necessarily the therapeutic change agent for participants in the Phase 2 clinical trials.

This chapter contains summaries of the quantitative data, including CAPS scores and mean mystical experience scores, as well as qualitative data from long-term follow up interviews completed 12 months after treatment. Some observations and inferences can be made for further exploration and are described in the discussion chapter.

Quantitative Data

Table 1 shows that Pearson correlations between mean MEQ30 scores and long-term positive symptom change codes (Sx+(LT)) are not statistically significant ($r=0.171$, $p=0.512$). from their 12-month (long-term) symptom change codes. This suggests that MEQ30 scores of assisted psychotherapy and long-term positive symptom change codes (Sx+(LT)) as reported in LTFU interviews were not significantly different, and did not reach statistical significance.

Table 1: Correlations between mean MEQ30 scores and Sx+(LT) codes as reported in LTFU Interviews

		Sx+(LT)	Mean MEQ30 Scores
Sx+(LT)	Pearson Correlation	1	0.171
	Sig. (2-tailed)		0.512
	N	17	17
Mean MEQ30 Scores	Pearson Correlation	0.171	1
	Sig. (2-tailed)	0.512	
	N	17	17

The following figure shows individual experimental data of participants' MEQ30 scores in relation to the number of instances Sx+(LT) was mentioned during LTFU interviews. There was no correlation between MEQ30 and Sx+(LT) codes ($r=0.171$, $p=0.512$).

Figure 1: Sx+(LT) as reported in LTFU interviews as a function of mystical experience during the active-dose MDMA session (n=17).

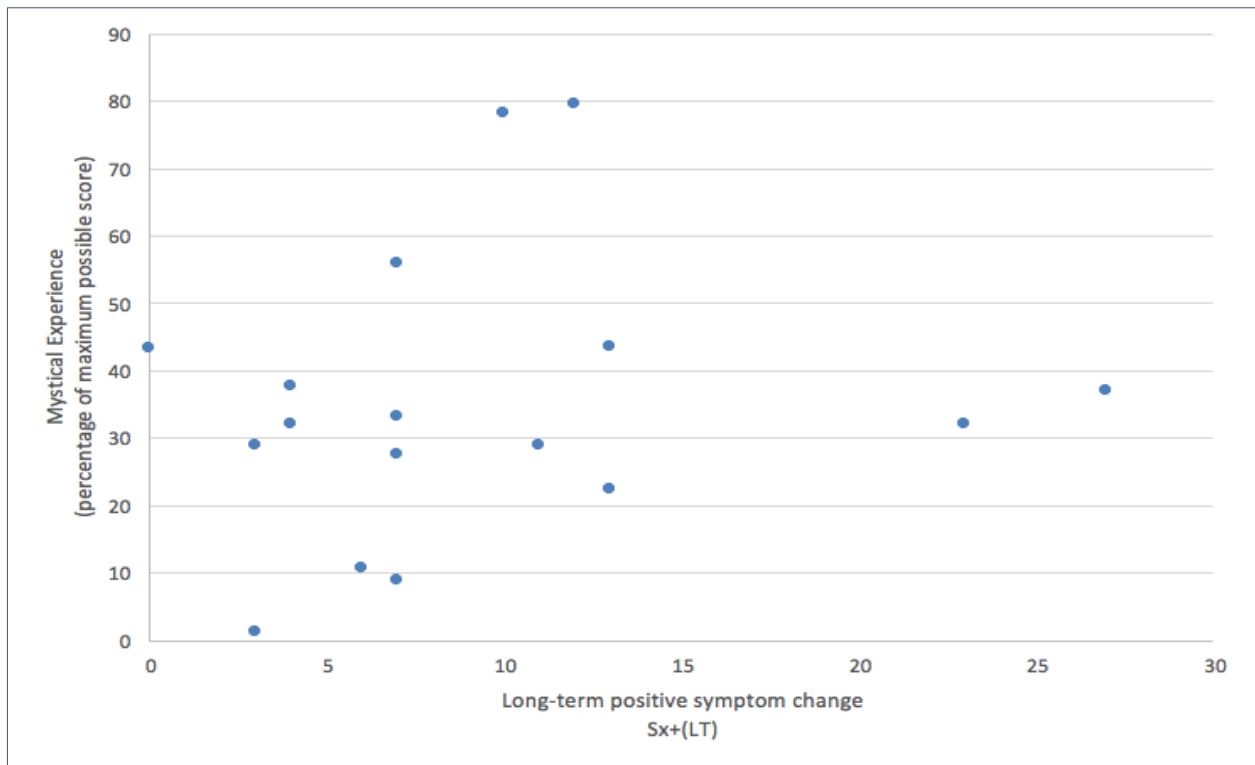


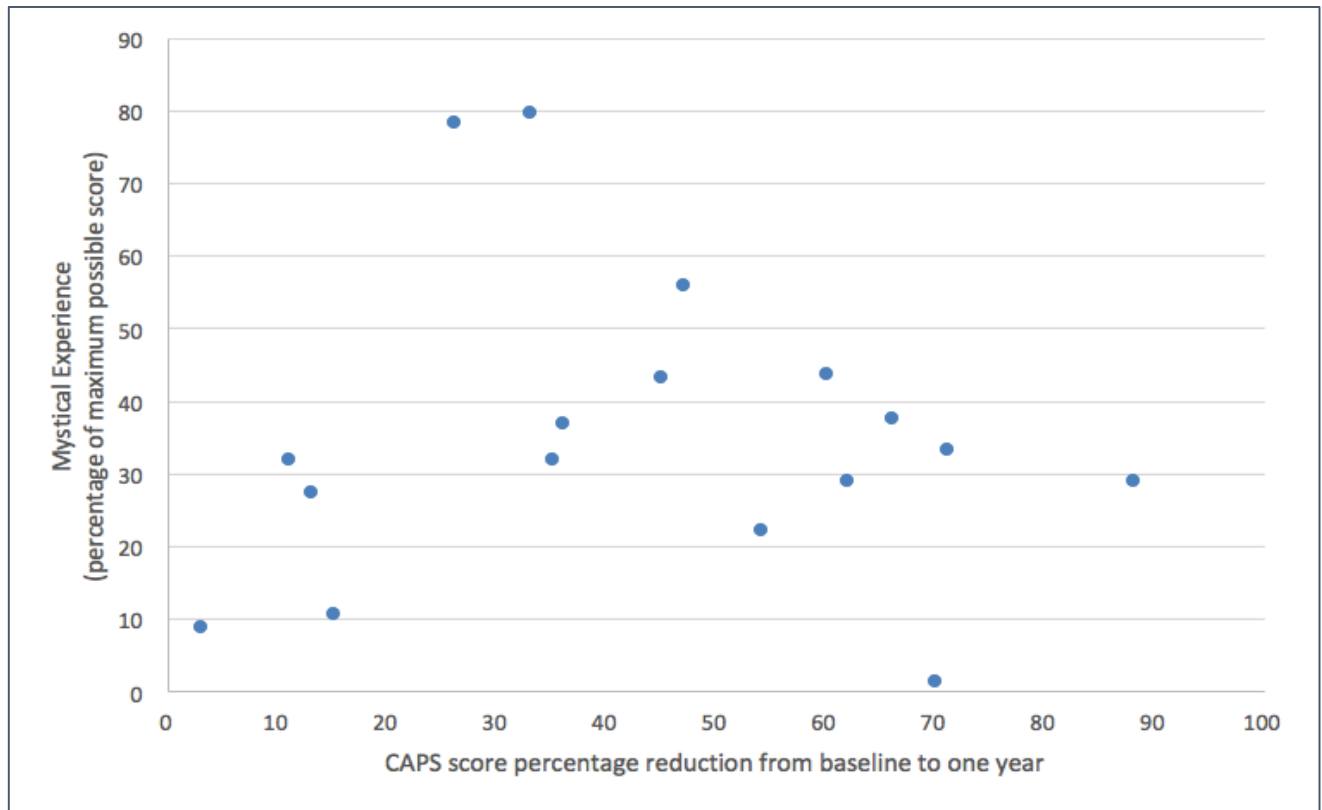
Table 2 shows that Pearson correlations between mean MEQ30 scores and CAPS score percentage improvement also are not statistically significant ($r=-0.036$, $p=0.890$).

Table 2: Correlations between mean mystical experience scores and CAPS Percentage Improvement from baseline and year-long follow up assessments

		CAPS % Improvement	Mean MEQ30 Scores
CAPS % Improvement	Pearson Correlation	1	-0.036
	Sig. (2-tailed)		0.890
	N	17	17
Mean MEQ30 Scores	Pearson Correlation	-0.036	1
	Sig. (2-tailed)	0.890	
	N	17	17

The following figure presents the relationship between MEQ30 scores and CAP score percentage improvement. Data points show individual experimental data. No significant correlation between MEQ30 and CAPS improvement was found ($r=-0.036$, $p=0.890$).

Figure 2. CAP score percentage improvement as reported by baseline and year-long follow up assessments as a function of mystical experience during the active-dose MDMA session (n=17).



Qualitative Data

This section presents the findings of a qualitative analysis of participants' experiences with MDMA-assisted psychotherapy as reported in their LTFU interviews. In accordance with the practices of IPA, the findings have been collected from a recorded interview in which each participant discussed their experiences with the treatment, participant perceptions on benefit of study participation, harm of study participation, helpfulness of an additional MDMA-assisted session, and perception of therapy prior to and after the study. LTFU interviews also gained information on psychiatric medication use before and after the study, any use of MDMA/ecstasy before or after the study, non-prescription substance use before and after the study, information on any significantly stressful events since study completion, symptom change, relationship

changes, and other pertinent information. The qualitative data analysis is organized in the following eight sections: (1) Enhanced quality of life (2) Reduction in negative PTSD-related symptoms; (3) Reduction of illicit or harmful substance use; (4) Relationship improvement; (5) Taking positive action or enacting lessons in life; (6) Improvement in self-awareness; (7) Overall experience with the study; and (8) Subject recommendations.

Enhanced quality of life. All participants (n=17) reported enhanced quality of life after completing the study. The following are quotes from LTFU interviews in which participants address the benefit and general improvement in their wellbeing and quality of life from participating in the study.

“There is improvement from every one of my problems I had when I first came here.”

“Now I do feel hopeful and... it’s just this feeling that things are going to get better. There’s going to be some time but it’s going to get better and better and better. I don’t know where it will go but the PTSD is manageable.”

“I don’t worry about things as much as I used to, I just don’t. I don’t feel I need to always carry a gun with me. I’ve come to the conclusion that I think I’m easy-going and well-mannered enough now to talk to people and talk myself out of most situations now. I don’t have to fight. if I think back, I think that I did feel that I needed to fight all the time before.”

“Now I actually live life and you know, I’m not living it for somebody else. I’m living it for myself”

“This study has worked out well. My life has improved. Night and day, quite dramatic.”

“I enjoy life, whereas before... Before I didn't care if I woke up or not.”

“I think that getting rid of all the, all the obstacles as far as my, my psychological type of things, it was nice to be able to get that out of the way so I can focus on actually improving my life. Which I think I've done quite, quite well here.”

Reduction in negative PTSD-related symptoms. Nearly all participants (n=16)

discussed their improvement in symptoms following treatment during LTFU interviews. Some quotes from the interviews are:

“It was really that first MDMA session that we had, where I had that I consider a breakthrough. Where I was able to clearly see that I had a big disconnect in compassion that I had for myself. After that first session, when I kind had that epiphany, I was able to get sleep. I don’t stay up until 5 or 6 in the morning anymore, unless I want to. It’s great.”

“I don’t feel as numb towards things. Prior to meeting y’all, I didn’t feel anything, literally. I didn’t feel anything. Happy, sad, mad, I just didn’t feel anything. I’m still somewhat numb about things but it’s not like it was.”

“The dreams that I am having are better, normal dreams, not terrors basically all the time, waking me up every night. That’s a lot better. That’s probably the most significant. And then that helps with stress, getting sleep.”

“There are a lot less fewer nightmares. I haven’t hardly had any flashbacks. The memories still pop up but they’re not as distressing. I understand where they come from.”

“If someone comes up and touches me, like behind me, before I would jump with hypervigilance; I don’t have that at all.”

Reduction of illicit or prescribed substance use. Existing research shows us that MDMA has potential to treat neuropharmacological abnormalities associated with addiction and could help provide a greater opportunity to address dangerous or unhealthy substance use (Jerome, Schuster, Yazar-Klosinski, 2013). The following are quotes that support this hypothesis by demonstrating how participants’ substance use was impacted after treatment.

“I’ve started learning the tools to where I don’t need to depend or rely upon medicine or alcohol or any kind of or even deviant behavior to feel better or get through things and things like that. So I think that’s been the most valuable.”

“When I first started I was taking 10 different things. And now no blood pressure medicine, no anxiety pills, no pain pills.”

“I would drink and find out I didn’t have enough to try and get rid of (the symptoms), but now I find out it just makes it worse.”

“I think that’s what pushed me away from the alcohol was that the MDMA proved to me that if you want something to help you it helps you continuously, not just for a moment and then the next moment you are feeling bad. The study helped me see that.”

“Before it was 15-20 drinks. And now it's down to three a week. I viewed drinking as a really cool thing to do anytime you didn't have anything else to do. It was just kind of this change of opinion of how I wanted to spend my time. I felt like a need to drink a lot. I just don't feel that anymore.”

“I would easily go through probably an eighth ever two days, beforehand. Now an eighth will last me two weeks.”

“I’ve come off all medicines. I’m on no kind of psycho medicine or anxiety medicine or anything.”

Relationship improvement. The majority of participants (n=12) also benefited by improving relationships with others in their lives following treatment in the study. While some participants experienced confounding variables during the LTFU interviews, such as going through a divorce, most reported a steady improvement in most aspects of their relationships as reported in the following quotes.

“It’s crazy. It’s changed every dynamic of my life. Every relationship. That means something to me... I couldn’t imagine this change. I didn’t think it was possible.”

“My ability to talk with my family and relax with them and be and be able to do things with them increased, and the communication. That was a positive thing that came from the study.”

“(I feel) love, compassion, and it’s not just for family, it’s for everyone. My parents and I have a much better relationship now, no doubt. But it goes beyond family like if I see someone on the side of the road begging for money, I stop and give them money even if I have to stop and hold up traffic behind me, I will do it. The study helped me really get there.”

“My wife and I are getting a long a little better, talking about things more. So it's helped a lot.”

“I think I've improved my own personal relationship with myself.”

“I truly believe if I hadn't been in this study, I would have never even been able to, we would have, the relationship would have never even happened”

“I would say overall improved relationships on every level, because before I wasn't talking to my brothers, or my dad as often, and my family, and definitely not my friends. I had really isolated.”

Taking positive action or enacting lessons in life. Nearly all participants (n=16) reported in their LTFU interviews that they have become able to take healthy and rewarding action in their life after the study. They also report enacting lessons learned during treatment throughout life. The following quotes illuminate how participants have been able to concretely make changes for themselves following treatment.

“It’s more of a, just relaxing in life. This whole thing allowed me to slow down and enjoy, smell the roses instead of passing by the roses.”

“It changed my life...I mean I wouldn't be doing any of this stuff I'm doing now if it weren't for the study.”

“I’ve caught myself many times over the past year feeling things rise up in me like a bubbling teapot of, of emotion and actually physically saying to myself “OK just feel it, just feel it.”

“It made me, actually, want to go pursue these other things that before I had disregarded as possibly being helpful. And it made me actively pursue ‘em, on my own, to see if I could get the benefit from ‘em.”

“I've done some really weird and amazing shit since I've come out of this study. I had this drive before, but I had this thing holding me back. And it's like the gates were opened and I just said, "Fuck it," and ran. So I do end up butting up against triggers and stuff like that occasionally. But it's because I'm doing way more.”

Improvement in self-awareness. All study participants (n=17) experienced an improvement in self-awareness or understanding as reported in LTFU interviews. The following quotes highlight some of the ways in which participants gained insight into themselves and the processing of their trauma.

“I could see why I feel the way I do about a lot of things. I can now understand a lot of things about myself.”

“I was slipping down a really bad hole just in life. So I feel like I've gotten my life back that I lost. I had this life before I went to Afghanistan, I hadn't seen any part

of that person in the mirror since. So to me it feels like I'm kind of getting back to my old self slowly over time.”

“I have felt like I've come a long ways. I don't want to grow stagnant. I'd like to keep going and grow more and evolve.”

“It probably is linked to these past events and now it's just a matter of focusing on that and giving myself new meanings behind it.”

“I had a tragic childhood and this kind of woke me up to it. You can see yourself like you can read a book and see everything that you stand for and kind of analyze your own self, your own thought, your own reasoning.”

“It seemed before I was feeling as though I was like kind of self-conscious, or maybe I wasn't deserving of it. And now it seems I'm more confident. I have less to think about. I don't have regrets or anything like that, or I'm not thinking about other stuff. I'm not feeling self-conscious about being flawed or anything like that.”

Overall experience with the study. Nearly all participants (n=16) reported that the MDMA played a major role in their treatment bringing about change and most (n=14) discussed the importance of the therapists.

“It was really important to have a mother and father in the room with me. That was one of the most powerful parts for me.”

“It's not a clouded, druggy, trippy kind of thing. It's a weird way of your mind showing you your own memories. And then you can relive it; you can feel it, you can see it, you can smell it. But yet, you're safely away from it and you're still thinking from your adult mind, not from a child's mind, not understanding what's going on. You can see it.”

“I think that the MDMA gave me the ability to feel as though I was capable and safe of tackling the issues. Whereas before I feared those thoughts and I tried to avoid them at all times, and avoid things that reminded me of those thoughts, which is very typical of PTSD...I think it allowed me to feel safe in my space. Of being able to fight it. I felt like I had the ability and tools, whereas before I was unarmed, unarmored, and had no support. And this type of environment, with ya'll, the catalyst drug, and everything else, it felt as though I had backup. Now it was safe and I had my tools and weapons to be able to tackle the obstacles that I never had before.”

“There are no words that are going to explain this, but I have never in my life relaxed like I did during this. Like what you would feel in your mommy's tummy, back in the womb, very safe, very warm. And for me to get where I needed to be within my own mind, I had to relax that way.”

“I wouldn't be doing any of this stuff that I'm doing if it weren't for you guys, seriously. I owe you guys both my life.”

“It is the one thing that has helped me since 1995. The one thing that I've tried and done that's helped in any kind of way. None of the drugs they gave me, psychology, seeing a psychiatrist, none of it's the only thing I felt like I got benefit from. Not because it feels good or some kind of high. It helps.”

“I feel like this study helped speed up the processing and understanding because it could have been...It took me four years to just talk, to bring it up, and I just think it would have been several more years of painful maybe terrible therapy that went nowhere. I feel like this therapy really helped me get past the tears and get right to the problem and several other problems I didn't know were related to the feeling.”

Subject Recommendations. The primary recommendation from study participants is to have continued sessions. This has been suggested in a number of ways including having one more session in the same sequence, continuing sessions four times per year, or continued non-medication sessions with the therapists. The following quotes are examples of some recommendations from participants after they had completed the study.

“I think like now would be good. A year or so, because I think that it gives enough time to like, if you like do one two three, and then you did the other ones, you have to live through a rollercoaster for like months and months and months, I really thought I was getting more crazy as we did more, like I was really starting to lose it again. Like I thought, I think it was all part of the process or something. And then it all started to level out again once it was, you know what I mean? We really shook stuff up.”

“Maybe, where there was, like, a one year after the very last session reference point, where you have a chance to spend a year working with the process, and then come back to it to see where you're at and, maybe, get some useful insight in ways or areas that you could be more active in bringing about the change that you're trying to see in your life.”

“It could be a sort of an as-needed thing where, maybe somebody didn't need to have any additional MDMA because things were going so well for them. But, maybe, somebody else, they come up to another wall in their life, where they're just unable to get past whatever is in front of them, and the MDMA has helped them get through these walls before. So having the option of being able to use that as a medicine to get through the wall, and association with the therapy again.”

“That's why I think one more session, I don't want to go anymore than that, but that would do as I call it put icing on the cake.”

“I think like 6 months later, I would say around February, March that time period I was really wishing to have those feelings again. If not to discover anything new, but to give myself a break, because it was such a break from that mental anguish all the time.”

“Because I was just thinking like a year from now would be a good time to try and grow even further.”

“And I would think the first three and then a year to process that. Because I think so much happens and then to do my quarterly for the rest of my life, well our point's a year. But I think like even doing the three or six in a row and then let process that per year and then maybe do that next year maybe do them quarterly and then yearly early updates.”

“I think an additional session later on, maybe after there's been time to process and think about things, think about how it's all affected, maybe as another push. I don't know if that'd be a year, or two years.”

Summary

The main finding that emerged from this study is that mystical-type phenomena is not an essential experience for lasting symptom improvement for PTSD, but rather that there is a favorable benefit ratio for PTSD treatment with MDMA in a supportive environment, in conjunction with psychotherapy. The qualitative data from LTFU interviews reveal that the study provided beneficial change for all participants. Although the FDA approves treatment based solely on safety and efficacy, qualitative accounts of the lasting benefit are vital in understanding how to continue providing adequate support to patients, and set them up for long-term health.

Based on a Pearson correlation analysis, the current study found no correlation between MEQ30 scores and improvement in CAPS scores from baseline to year-long follow up ($r=-0.036$, $p=0.890$) or MEQ30 scores and long-term positive symptom improvement ($S_x+(LT)$) as reported in LTFU interviews ($r=0.171$, $p=0.512$). Therefore, mystical experiences are not correlated with the enduring symptom improvement participants in the Phase 2 trials described.

CHAPTER V

Discussion

Major Findings Relative to the Literature Review

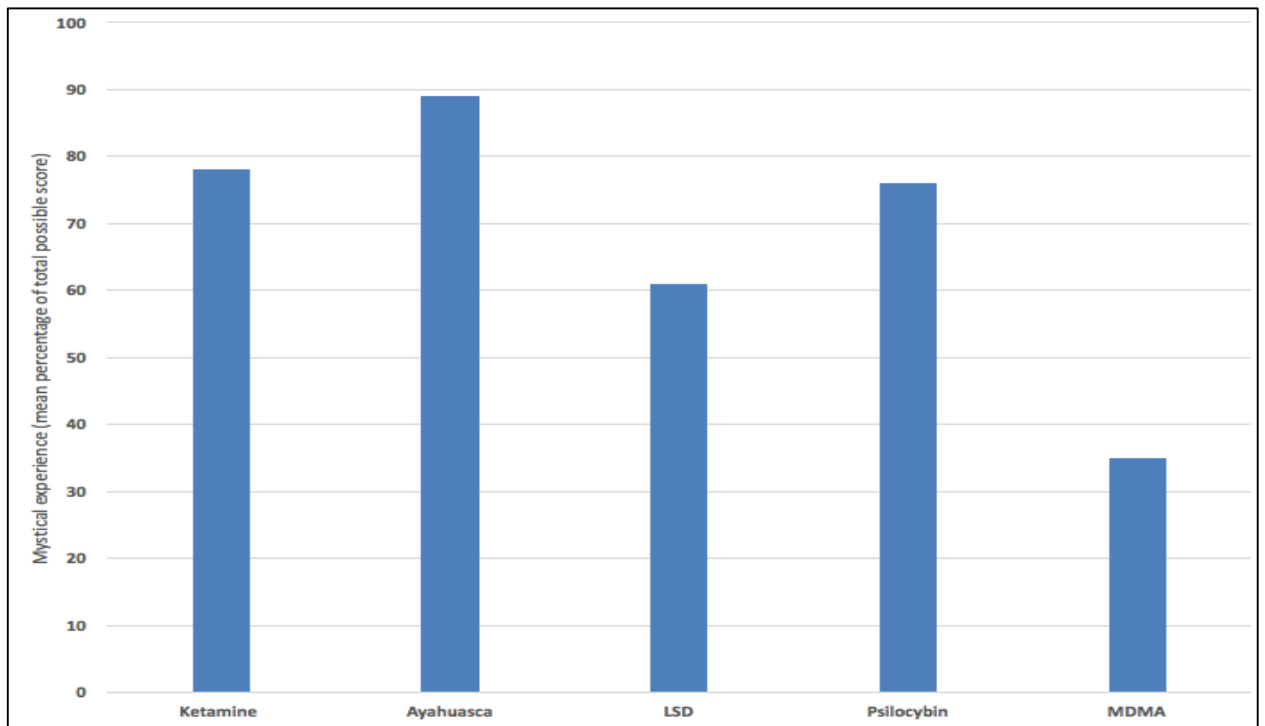
The results of the current study align with previous neurobiological research on psychedelics (Carhart-Harris, et. al., 2014, Beck, 1994). MDMA does not induce mystical experiences as profoundly as other psychedelics such as LSD, Psilocybin, Ayahuasca, or Ketamine. While some research studies conclude that MDMA is an auspicious therapeutic agent, it has mostly been used recreationally. This study aimed to provide evidence for the benefits of MDMA without the influence of its recreational use impeding on its illegality. The current study is significant because the use of MDMA-assisted psychotherapy, in a controlled setting that provided a combination of psychological and pharmacological treatments, proved fruitful in achieving the desired effects of MDMA-assisted Psychotherapy on Patients with Recurring treatment resistant PTSD Symptoms. Findings from this study support that this treatment method when used with chronic, treatment-resistant PTSD can be safely applied in supervised settings with no drug-related serious adverse events occurring.

Efficacy failed to reach statistical significance ($p = 0.171$) as measured by the primary outcome measure whereas self-assessment of the participants' PTSD symptoms, as measured by the LTFU self-reporting questionnaire, showed beneficial results for the participants in this study.

Figure 3 demonstrates mean mystical experience scores from existing studies on other psychedelics, including Ketamine, Ayahuasca, LSD, and Psilocybin. Compared to other entactogens, MDMA appears to insight a smaller percentage of total possible mystical experience score. This finding sheds light on why MDMA is useful for PTSD as compared to

other psychedelic substances. The post-session mystical experience score (mean percentage) that compared Ketamine (Dakwar, et al., 2014), Ayahuasca (Bouso, et al., 2016), LSD (Liechti, et al., 2016), Psilocybin (Griffiths, 2008), and MDMA (current study) documented positive outcomes (See Figure 3).

Figure 3: Post-session mystical experience score (mean percentage) comparing five researched entactogens



It is well worth mentioning that no participants in this study reported any harm or decline from their participation and all participants reported various degrees of benefit. Often these benefits extended beyond decreased PTSD symptoms. Considering the degree of support, monitoring and follow-up, these findings are not unusual; many forms of psychotherapy produce benefits in terms of psychological growth and development that are not restricted to improvements in a specific disorder or problem that was identified at the original target of therapy. These findings, however, are of particular significance for the present study because

they indicate a valuable feature of MDMA-assisted psychotherapy that extends beyond the core issues. Some of the areas of benefit that were endorsed on the LTFU questionnaire, such as an increased self-awareness, improved relationships, an enhanced spiritual life, and more involvement in the community or world, represent effects that are not fully measured by the PTSD symptom scales.

Findings from this study are consistent with Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., & Doblin, R. (2012) who found in their study that on average subjects maintained statistically and clinically significant improvements in PTSD symptom relief and reported no harm from participating in their study. The Mithoefer et al. study, like the present study, showed that no participant developed a problem with any illicit substance after MDMA-assisted psychotherapy, which supports the hypothesis that MDMA can be administered in a regulated, clinical setting without creating a dependence or addiction.

The current study also supports findings from Maclean, Johnson, Leoutsakos, & Griffiths (2012), which shows that the MEQ30 is a reliable and valid measure that correlates with other mysticism scales, and that it is a useful tool in studying psychedelic experiences. Also the current study's findings are consistent with Thomas, Lucas, Capler, Tupper, & Martin (2013) study on problematic substance use and stress that after four days of group counseling and two ayahuasca-assisted therapy sessions, participants showed improvements on scales assessing hopefulness, empowerment, mindfulness, and quality of life meaning and outlook. Feedback from the LTFU interviews almost mirrored Thomas et al. (2013) findings.

The worthiness of the current study is validated by participant comments and feedback on the LTFU interviews and questionnaire describing the positive MDMA treatment effects. Their descriptive feedback provides an important context in which the outcome data is evaluated and

understood. Their benefits endorsed and described extended beyond the realm of symptom reduction. Specifically, the participants shared deeply meaningful therapeutic experiences and ongoing improvements in their lives. The majority of participants in the current study endorsed benefits such as, “increased self-awareness and understanding” and “enhanced well-being.” These responses, similar to other researchers’ findings, point to a process of psychological and spiritual exploration and growth that could logically be expected to facilitate trauma processing and symptom reduction, and to promote healthy psychological development.

Weaknesses and Limitations

The primary limitation to this study was the lack of control group for the follow-up interviews. It would be ethically problematic under the National Social Work Code of Ethics and American law to conduct a placebo control group over such a long period of time. Other limitations also reflect the preliminary nature of this study. Data were extrapolated from a larger qualitative exploration that did not focus on MDMA-induced mystical experiences. Although the basic dimensions of the MEQ30 were utilized, shortening the initial 100-item questionnaire (SOCQ-100) may have also impacted our capacity to obtain more nuanced information about the psychoactive effects, particularly when comparing the difference in dosage.

Another limitation of the current study was the varying lengths and nature of interviews. Although most interviews covered similar topics, it is possible some participants experienced certain phenomena, but did not express them. Data analyzed the number of times a participant mentioned long-term, positive symptom change in their LTFU interview, however, this number may not be directly related to the realistic improvement of their symptoms. Therapists from the study gave the LTFU interviews; while this had some benefits for rapport and safety, it may have altered responses.

The sample was small (n=17) and homogenous, reflecting a largely Caucasian demographic (n=15). Current research about these medications falls short regarding issues of diversity. No study addresses race, socioeconomic status, gender, ability or other important identities when assessing effectiveness of this treatment. While this study does not purport to show definite differences in experiences of varying demographics, it may open doors to the kind of future research that needs to be conducted. Information about other races or multiculturalism is lacking.

Demographic information such as religious affiliation, spiritual beliefs, or attachment history was also omitted from the data collection. This information might have provided more insight about mystical experience scores and personal predispositions towards lower or higher scores.

Implications for Social Work

It is possible that the changes observed by participants in this study were dependent on a related experience of emotional safety and engagement in therapy, but these do not match the criteria for mystical experiences on the MEQ30. The results support the goal of MDMA-assisted therapy, which is not to have a mystical experience, but rather to confront and work through trauma. The minimal mystical-type effects MDMA induces may relate to reasons why this particular entactogen is so useful, specifically for PTSD. Instead of mystical experiences, MDMA promotes a profound feeling of safety which allows people with PTSD to confront and make meaning of their trauma without being physiologically activated. Some PTSD symptoms are the very obstacles to treating it, such as avoidance, dissociation, or panic attacks. MDMA may prevent these defenses from occurring, allowing patients to benefit from therapy in a way their PTSD has prevented in the past.

The implication of the current study for social work is, therefore, that MDMA-assisted psychotherapy is not beneficial because of an inherent effect of the psychedelic on the brain, but rather, that participants could access and benefit from talk-therapy.

Future questions. Future research can evaluate whether mystical-type effects influence the therapeutic effects of MDMA in larger clinical samples and in other clinical frameworks. The upcoming Phase 3 trials provide a great opportunity to continue learning about the participant experience and external factors that contribute to persistence of benefit. Although mystical experiences are not correlated with symptom improvement, the LTFU interviews revealed the importance of feeling safe and calm when working through trauma. Future research should investigate the influence of MDMA on the amygdala and other parts of the brain or use qualitative measures to explore the implications of feeling safe during MDMA-assisted therapy. Phase 3 trials also offer an important opportunity to explore how participant attachment styles, religious or spiritual histories, or sociopolitical identities may relate to long-term treatment outcomes.

Long-term follow-up studies allow researchers to investigate the lasting efficacy of treatment and predict the need for maintenance treatment. A thorough long-term qualitative investigation in Phase 3 and further exploration of Phase 2 would supplement the existing data surrounding MDMA-assisted psychotherapy.

Conclusion

In the realm of psychedelic-assisted therapy, mystical experiences have been linked to long-term positive treatment outcomes (Pahnke, 1963; Doblin, 1991). The current study presents results from a correlation analysis of the Mystical Experience Questionnaire (MEQ30) with PTSD treatment outcomes to determine if lasting symptom improvement is related to mystical

experiences occasioned by MDMA-assisted therapy. Many people report mystical experiences during their time under the influence of psychedelics; however, that experience with MDMA is not correlated with lasting symptom change as reported by participants during LTFU interviews and Clinician-Administered PTSD Scale (CAPS) score improvement.

PTSD has plagued people since the beginning of humanity and there are still not sufficient treatment options for this complex mental disorder. MDMA-assisted psychotherapy has emerged as a promising option to permanently reduce PTSD symptoms. MAPS Phase 2 trials showed that MDMA-assisted psychotherapy is reliable, safe, effective, and offers enduring benefit, without necessitating complete mystical experience.

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Appendix A

Informed Consent Form



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SUBJECT INFORMATION AND CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE PERSONAL HEALTH INFORMATION FOR RESEARCH

Study Title: A Randomized, Triple-Blind Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in conjunction with manualized psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-resistant Posttraumatic Stress Disorder (PTSD)

Protocol #: MP8 Amendment 5

Study Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
309 Cedar Street, #2323
Santa Cruz, CA 95060

Principal Investigator Name: Michael C Mithoefer MD

Research Site Address(es):

208 Scott St
Mount Pleasant SC 29464-4345

Daytime Telephone Number(s): 843-849-6899

24-hour Contact Number(s): 843-849-6899

Cellular number(s): 843-412-8375

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM

This consent form describes a research study and your role as a participant. Please read this form carefully before you decide to take part in this study. You may ask the study doctors anything about the information provided. You are being asked to participate in this research study because you are a military veteran, firefighter or police officer and you have been diagnosed with posttraumatic stress disorder (PTSD) related to your service, and because your symptoms have not gone away after psychotherapy, medicines, or both, or you stopped your treatment because you could not tolerate it.

Please ask the study therapists to explain any words or information in this consent that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE AND BACKGROUND

This small ("pilot") study is designed to provide information on whether psychotherapy ("talk therapy") combined with the drug MDMA is safe and helpful for subjects with posttraumatic stress disorder (PTSD). The researchers plan to use the results of this study to design further studies.

MDMA is an experimental drug, which means that it has not been approved by the United States Food and Drug Administration (FDA) for medical use except in research studies. MDMA is also a controlled drug (illegal to use outside of research) and is sometimes known as "Ecstasy" (which is supposed to contain MDMA but often contains other drugs instead of or in addition to MDMA). MDMA has already been used legally in research and illegally in uncontrolled environments, such as nightclubs. While much is known about MDMA and its risks, much remains unknown about this drug.

The study is sponsored by a US-based non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org). MAPS' first small study of MDMA-assisted psychotherapy in 21 people with PTSD is finished in the US, with promising results. MAPS has other MDMA/PTSD pilot studies in Switzerland and is planning new studies in the US, Canada, and Israel.

Before it became illegal in 1985, some psychologists and psychiatrists combined MDMA with psychotherapy to help people with psychological problems, including PTSD. Though we do not know why it may help people with PTSD, we know that MDMA increases positive mood and changes the way we see and think about the world around us, making it easier to think about and recall things that happened to us that are upsetting. People say they feel caring and forgiving toward themselves and others during the MDMA experience. It is possible that these drug effects, when combined with psychotherapy, help people work through thoughts, memories and emotions related to PTSD.

This study will compare three doses of MDMA: 30, 75 and 125 mg, possibly followed one and a half to two and a half hours later by a second dose half the size of the first dose.

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LENGTH OF STUDY

This study can take up to 1.5 years or 20 visits if you receive 125 mg MDMA in "Stage 1." It can last for an additional three months or 15 more visits if you receive 30 or 75 mg MDMA in "Stage 1," and decide to go on to have an active dose of MDMA in the second part of the study, "Stage 2." This time period includes a long-term follow-up visit 12 months after the last experimental or open-label session.

TYPE OF STUDY

This study is double blind, meaning that neither you nor the study researchers will know what dose of MDMA you get. The dose of MDMA you get will be decided at random, as if by tossing a coin. Each person in this study has a 50% chance of getting 125 mg, a 25% chance of getting 30 mg and a 25% chance of getting 75 mg. You will find out what dose of MDMA you received approximately 1 month after your second experimental session. There will be approximately 24 subjects in this study.

PROCEDURES/WHAT WILL HAPPEN TO YOU

Screening/Evaluation and Beginning of Study

If you agree to take part in this study, you will first sign this Subject Information and Consent Form before any study-related procedures are performed. You will not be asked to stop taking any of your current medications until you are enrolled in the study. If you are taking psychiatric medications when you are enrolled you will be required to slowly stop taking them under the supervision of your prescribing physician or the study doctor. It is possible that stopping some medications could lead to recurrent or new symptoms, including thoughts of wanting to kill yourself.

Before you can be in the study, the study doctor must first make sure that you qualify for the study and that you are generally physically healthy. The screening process can take up to 4 months, and there will be one or more office visits during this time. The study therapists may ask your permission to contact your doctor or psychotherapist to get information about your medical history. They may need to do this so that they will know if you can be in the study or not.

The tests will include the following:

- A questionnaire about your PTSD symptoms and how you deal with them in your everyday life. Your score on this questionnaire will be used to decide if you can be in the study. The person asking you these questions will be a different person from the therapists. This session may be recorded to video.
- Questions about your medical history, including questions about your emotional and psychiatric history. This may include any previous medical or psychiatric problems or treatment and may include questions about difficult experiences you may have had during childhood or at other times of your life. The study doctor will rate how well you are doing in general.
- A questionnaire about feelings of depression or other symptoms or feelings you might experience.

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- A questionnaire about thoughts or feelings you might have about hurting or killing yourself.
- A questionnaire about your personality.
- A questionnaire about your quality of sleep.
- Another questionnaire about your PTSD and its effects on your life
- A questionnaire about any dissociation symptoms.
- A visual scale of pain and tinnitus (ringing in the ears) levels if you have these symptoms.
- A physical examination that will include measures of your blood pressure, pulse, temperature, and body weight.
- An ECG (electrocardiogram) will also be taken, which is a recording of the electrical activity of your heart.
- A sample of your blood (about 2 tablespoons) and a urine sample for routine laboratory testing, including tests of metabolism and liver function. Laboratory tests will also include testing for the human immunodeficiency virus (HIV) and hepatitis C virus (HCV).
- A urine test for drugs of abuse. Your urine drug screen must be negative to take part in the study.
- A urine pregnancy test if you are a woman and are able to get pregnant. Your urine pregnancy test must be negative for you to take part in the study.

You may have to have extra medical tests to make sure you can be in the study.

People who control their high blood pressure with medication may have to see a cardiologist (heart doctor) for more tests, and people with a liver disease called hepatitis C may have to visit a liver specialist. If you have hepatitis C, you will have to complete treatment the liver specialist or your physician (your doctor) prescribes for HCV. If the tests find out that you test positive for HCV or HIV, then the study doctors will have to tell the South Carolina department of Health and Environmental Control within seven days, as stated by law. If you live outside South Carolina, the study doctors may need to report the results according to the laws of the state you live in.

You may be asked if you want to participate in another study while you are in this study. If you are interested in learning more about this study, you will receive information about it separately and it will involve additional tests.

Beginning of Study

Once you are in the study, you will schedule your first introductory (preparatory) psychotherapy session with the study therapists. It may happen that the first preparatory session will be done at the Screening visit, after you have signed this consent form. You will need to be enrolled in the study before the second psychotherapy session. If you were taking psychiatric medicines before enrolling in the study, you will have to stop taking them after you are enrolled. The study doctors and your physician will help you do this. If it takes over a month between when you stop taking your medication and your first MDMA session, then you may have to answer questions about your PTSD symptoms again. You must let the study therapists know about any medical conditions or procedures, like surgery, within 48 hours of their occurrence.

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You will have to give the study therapists the name and contact information (as telephone number, cell phone number or email) of a relative, spouse or close friend to contact in case of medical emergency, as when you might be at risk of hurting yourself, or someone else, so they can reach that person to let them know what is going on.

Schedule of Events

Time is counted from the first study visit after you are selected to be in the study. The tables below show the type of visits you will have in Stage 1 and Stage 2 (if you are in the low or medium dose groups).

Stage 1	Screening	Start study	Intro and Preparation		MDMA and Non-Drug Therapy 1					MDMA and Non-Drug Therapy 2					Evaluation	MDMA and Non-Drug Therapy 3					Evaluation	Long Term Evaluation	
For All Groups													For full dose group only										
Study Visit #	1 Enroll	2*	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18					
Screening	X																						
Measure symptoms	X												X							X	X		
Psychotherapy			X	X	X	X	X	X	X	X	X	X			X	X	X						
Psychotherapy With MDMA					X				X					X									
Medical Exam	X																						
Learn dose you received													X										

* Visit 2 may happen at the time of screening, before Visit 1.

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Stage 2	Preparation	MDMA and Non-Drug Therapy 1					MDMA and Non-Drug Therapy 2					Evaluation	MDMA and Non-Drug Therapy 3					Evaluation	Long Term Evaluation
		19	20	21	22	23	24	25	26	27	28		29	30	31	32	33		
For Low and Medium Dose Groups Only																			
Study Visit #	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33				
Measure symptoms	X*									X					X	X	X		
Psychotherapy	X		X	X	X		X	X	X			X	X	X					
Psychotherapy With MDMA		X				X						X							

* Symptoms may be measured again if more than a month passes between Stage 1 and Stage 2.

Introductory Psychotherapy Sessions:

You will meet with the study therapists on three separate occasions before the first experimental session. These visits will last 90 minutes. During each introductory session, you will talk about the traumatic incidents that led to your PTSD, the ways PTSD symptoms are affecting your life and what you would like to achieve during these sessions. You will be asked the same questions about thoughts or feelings you might have about hurting or killing yourself during one of these preparatory sessions. You will also learn more about what to expect during experimental sessions. The introductory sessions will be recorded to video, so that the study doctors will have accurate records of the sessions and so that they can gather more information about drug-assisted psychotherapy sessions. You can ask the study therapists to let you see these recordings if you wish. In addition, you will be asked to read a brief script that does not contain any information related to the study for a computer program that will allow converting audio recordings to text from these sessions.

Experimental Sessions:

There will be two day-long experimental sessions, when you will have MDMA (30, 75 or 125 mg) and psychotherapy, each happening three to five weeks apart. The first experimental session will occur after you have had three introductory sessions. If you are in the 125mg or Full Dose Group, you will have a third day-long experimental session with 125 mg MDMA. If you received 30 or 75 mg (low or medium dose MDMA), you will be offered one of two active doses of MDMA sessions during the Stage 2 experimental sessions. Your therapists will discuss the optimal dose of MDMA with you for the second and third experimental sessions.

One week before each of the MDMA sessions you will need to avoid taking:

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- any herbal supplement (except with prior permission);
- any nonprescription medications, unless you have permission (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen (Tylenol));
- any prescription medications, unless you have permission (with the exception of birth control pills, thyroid hormones or other medications).

You must not eat or drink any alcohol after midnight on the night before each session, though you can drink non-alcoholic liquids during this time, such as water or juice. You cannot use any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA session. You cannot use nicotine or caffeine for two hours before and six hours after MDMA treatments.

First, you and the study therapists will discuss your goals for the experimental session, and the study therapists will answer any other questions you may have.

Before an experimental session:

- Your urine will be tested for drugs of abuse, including stimulants, sedatives, opiates and cannabis.
- If you are a woman who can become pregnant, you will take a urine pregnancy test.

Throughout an experimental session:

- Your blood pressure and pulse will be measured periodically (every 15 to 30 minutes).
- Your temperature will be measured every hour.
- You will also complete a very brief, simple test of how comfortable or distressed you feel by marking a number on a sheet of paper that matches the way you feel at that moment. You will complete it every 60 to 90 minutes throughout each experimental session.
- About an hour before receiving the drug and about six hours afterward, you will complete the questionnaire about thoughts you might have about hurting or killing yourself.
- The study therapists will check in on you every hour or so to see how you are doing.

The experimental session will be video recorded, so that the study therapists will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. You will be given access to view these recordings if you wish.

After urine test results come back, you will receive a capsule containing MDMA mixed with some lactose to make all capsules appear and weigh the same. The capsule can contain either 30, 75, or 125 mg MDMA. After taking the capsule, you will then sit or lie down in a comfortable position. You can ask for an eye shade if you wish. You will listen to music during much of each experimental session, either through headphones or room

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speakers. Periodically you will be asked to talk to the study therapists. If you are wearing headphones, you may remove them yourself if you want to talk to the study therapists or have periods of silence. Lying or sitting in a comfortable position and listening to music are meant to bring out thoughts and feelings, including thoughts and feelings about the trauma. Both study therapists will remain with you, and they will help you if you need them to do so. They will speak with you and ask you to talk to them at least once an hour, but you can talk to them whenever you wish. There may be times when the study therapists will suggest that you stop talking for a while in order to pay attention to your thoughts and feelings. There will be beverages available, including water, juices and Gatorade or similar sports drinks, and you will be encouraged to drink an adequate amount of fluid. You can drink it whenever you wish to do so, within the limits of the amount that is safe for your body. Later on, food will also be provided.

Approximately one and a half to two and a half hours after you took the first capsule, you and the study therapists will talk about taking a second dose of MDMA. The second dose will contain half the amount MDMA of the first dose. If you and the study therapists agree, you will take the second dose. If you or the study therapists notice problems after the first dose of MDMA, then you will not get the second dose of MDMA.

The study therapists will keep measuring blood pressure, pulse and temperature, and the study therapists will watch for any side effects (unwanted effects or health problems), which will be treated if they see them. If this happens, the study therapists will let you know what they are doing.

If you are confused or upset eight or more hours after the start of an experimental session, the researchers will stay with you until you have fully recovered. If the researchers think you are at risk of hurting yourself or others, they will either remain with you all night or have you admitted to a hospital until you are no longer at risk of hurting yourself or others. The researchers will ask you about thoughts of killing or harming yourself before and after MDMA administration and throughout the follow-up period. You will also be asked to complete a questionnaire about thoughts, feelings or other things you might have experienced during the experimental session. You can complete this questionnaire at any time between the end of the experimental session and you leave the study site the next day.

If you request it and the study therapists agree to it, you can have a person of your choosing stay with you during some or all of the experimental session, starting at an agreed-upon time, or when you stay at the office of the study doctors after the session. When he or she arrives, this person will stay in the waiting room until there is a good time for them to come into the session.

You will be spending the night in a room at the office of Dr. Michael C Mithoefer MD with an attendant who will be staying in another room nearby. You can use the kitchen or walk around outside if you want. If you find you need to talk with the researchers or you are having other problems and need to contact the researchers, the attendant will contact them immediately.

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On the next day, you will have a non-drug (integrative) therapy session with the study therapists. You will need to have someone drive you to wherever you are staying (home, hotel or another location) from the non-drug therapy session on the day after the experimental session because we do not know how MDMA will affect your ability to drive, and because some people report feeling tired, less alert or having trouble concentrating a day after having taken MDMA. If you cannot find anyone to take you home, the researchers will find someone to drive you.

After you return from the non-drug therapy session, the researchers will telephone you every day for a week to inquire about how you are feeling and determine whether you should see the study doctors before your next scheduled non-drug psychotherapy session. These telephone calls will take approximately 5 to 15 minutes, though they can be as long as you need them to be. You may schedule additional meetings with the study therapists besides those that are scheduled as part of the study. You can contact the study therapists at any time. The study therapists will be reachable by telephone 24 hours a day throughout the research study, except on occasions when he is out of town. At those times another psychiatrist familiar with the study will be on call and can be reached through his phone number which will be given to you as well.

The researchers will give you a card with telephone numbers for reaching Dr. Michael C Mithoefer MD and the Copernicus Group Independent Review Board (IRB), which is an independent committee that protects the rights and welfare of study participants. You can keep this card in your wallet to make it easier for you to contact the researchers if you need to do so.

If there are delays in following the usual study schedule, the study therapists will telephone you at least once a week to talk about how you're doing. These telephone calls will take approximately 15 minutes, and you agree to call the investigators if any of these things happen: you have an increase in symptoms for which you previously took medicine, you need to contact your outside therapist other than for the usual appointments, and/or you start or stop taking prescribed medicine.

If you have very high blood pressure, get sick, or have an important and strong lasting negative reaction (unwanted effect or health problem) after the first experimental session, you or the study therapists may decide that you should not participate in the second experimental session. You may make this decision to stop being in the study for any reason. If the study therapists decide to take you out of the study, they will let you know that they are doing this and their reason for doing this. If you are taken out of the study or decide you do not want to be in the study, the study doctor will ask you to complete some final questionnaires about your PTSD symptoms. If you decide you do not want to continue in the study during an experimental session, you will still have to stay in the office until the study therapists think that you are well enough to leave and that all the effects of the drug have worn off.

The experimental sessions will occur three (3) to five (5) weeks apart. All experimental sessions will be carried out in an identical manner to the first session.

Psychotherapy after Experimental Sessions

You will have regular psychotherapy to help you express, understand, bring together and connect any thoughts or feelings you may be having about your symptoms and their causes, and to think and talk about your experience during experimental sessions. You will have psychotherapy with the study therapists the morning of the day after each experimental session and then two more visits during the next three to five weeks after each experimental session. These sessions will last 60 to 90 minutes. You and the study therapists will also talk about ways to use what you learned to help work on treating your PTSD, face and solve difficulties you may have faced during the experimental sessions and gain maximum benefit and understanding from experimental sessions. Each regular psychotherapy session will be recorded to video, just like the introductory and experimental sessions, and you can see these recordings if you wish.

Before starting psychotherapy on the day after each experimental session, you will be asked to guess whether you got 30, 75 or 125 mg MDMA. You will not be told if your guess is correct. The researchers will ask you about thoughts about killing or harming yourself during each follow-up session, and during the second and seventh day of telephone contact with the study doctors.

Measuring PTSD after Experimental Sessions

Approximately four months after the start of the study (one month after the second experimental session), you will meet with a study researcher who is not one of the study therapists. You will be asked not to tell this researcher what your guess is about what dose of MDMA you think you received. The study researcher will ask you questions about your PTSD symptoms, (which may be video recorded with your permission). You will also complete a questionnaire on feelings of depression, dissociation symptoms, a questionnaire on your sleep quality, a personality questionnaire, and one more questionnaire related to your PTSD. This visit should last up to two hours. The researchers will ask you about thoughts about killing or harming yourself. You will also complete the scale of pain and tinnitus levels if you had these problems before the study.

After you complete these tests, you will meet with the study therapists and all of you will find out if you received 30, 75 or 125 mg MDMA. The study researcher who measured your PTSD symptoms will not find out.

If you learn that you had the low (30 mg) or medium (75 mg) dose of MDMA, you can then enroll in "open label" study sessions, or "Stage 2," described below. If you decide not to participate in Stage 2, then you will complete a questionnaire about your experience as a research subject before you leave the first part of the study.

If you are in the full dose group (125 mg), you will be asked about your thoughts on having a third experimental session.

Full Dose (125 mg) Group Only – Approximately six months after the start of the study (two months after the third experimental session), you will meet with the study researcher again. The researcher will ask about your PTSD symptoms (which

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may be video recorded, with your permission), and you will fill out a questionnaire on feelings of depression, another questionnaire on PTSD, a dissociation symptoms questionnaire, and a sleep quality questionnaire. You will also be asked if you have had any thoughts about hurting or killing yourself. This visit should last about 2.5 and 3.5 hours.

The tests will help the study therapists tell if your symptoms have changed or stayed the same over time.

You will complete a questionnaire about your experience as a research subject before you leave the first part of the study. You will be asked about your thoughts on having a third experimental session. The study therapists will give you a memory aid card. This card is to help you to remember any new problems or medical conditions, or changes in medication during the months between this visit and your last visit, the 12-month follow-up visit. On this card you will record any new important health problems, changes to your mental health, hospitalizations and medications to treat these problems.

Open-Label MDMA Sessions for People who Received 30 or 75 mg MDMA (Stage 2)

If you are one of the twelve subjects who received 30 or 75 mg MDMA, you can take part in three open-label MDMA-assisted sessions scheduled 3 to 5 weeks apart as part of Stage 2. In this study segment, you will receive an active dose of MDMA (either 100 mg possibly followed by 50mg or 125 mg possibly followed by 62.5 mg) , with the 125 and 62.5 doses possible during the second and third sessions. . Stage 2 can start any time after you learn what dose of MDMA you received but not later than five months after that point. Signing this consent form means you agree to take part in the second part of the study though you can change your mind at any time and still take part in the 12 month follow up without participating in Stage 2. **The twelve people who receive a full dose of MDMA during the first stage of the study cannot take part in Stage 2.**

If more than 8 weeks pass between Stage 1 and Stage 2, you will need answer questions about your PTSD symptoms, and the questionnaires about depression, dissociation, and sleep quality again before you start Stage 2. If you take part in Stage 2, you will have 15 more visits. These sessions will be like the experimental ones you had during the first part of the study, except that you will know you are getting an active dose of MDMA and will have 3 experimental sessions instead of only two. You will also only have one review and introductory session instead of three. Otherwise, you will have three experimental sessions scheduled three weeks apart followed by an overnight stay and non-drug integrative therapy afterwards. You will complete the scale of pain and tinnitus levels if you notice changes in your symptoms that you had before the study. You will have tests of your PTSD symptoms and complete a questionnaire on symptoms of depression, dissociation symptoms, and sleep quality one and two months after the third open-label session, and a personality questionnaire two months after the third session. You will also be asked if you had any thoughts about hurting or killing yourself during that time. You will be asked about your thoughts on the experimental sessions before and after your third session. At the 2-month follow-up, you will complete a questionnaire about your experience as a research subject. The study

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therapists will give you a memory aid card. This card is to help you to remember any new problems or medical conditions, or changes in medication during the months between this visit and your last visit, the 12-month follow-up visit. On this card you will record any new important health problems, changes to your mental health, hospitalizations and medications to treat these problems.

Long-Term Follow-Up 12 Months after Last Experimental Session for All Participants

Approximately 12 months after your last MDMA-assisted session, you will answer questions about your PTSD symptoms, dissociation symptoms, feelings of depression and sleep quality, and a personality questionnaire, and you will fill out a questionnaire on the positive and negative effects of being in the study. You will complete the scale of pain and tinnitus levels if you had them before the study. If you were only in Stage 1, then this will happen 12 months after your third experimental session, and if you were in Stage 2, then this will happen 12 months after the third open-label session.

The same study researcher who asked you about your PTSD symptoms will do so again, either in person or over the telephone. The study therapists will ask you about any changes in medications or your psychiatric health, including any benefits or harms, during the follow-up period between your last visit and the 12-month follow-up visit.

You will also answer the questionnaire about feelings of depression, your personality, your sleep quality and another PTSD-related questionnaire. The questionnaires will include questions about any thoughts, feelings or events that happened after being in the study. You will also answer a questionnaire about your attitudes and feelings about being in the study, any thoughts you have about the good and bad points of MDMA-assisted therapy, and your thoughts about taking MDMA. There are no right or wrong answers to these questions.

A researcher who is a part of the study team will ask you about any changes in medication or your psychiatric health, including any benefits or harms, during the follow-up period between your last visit and the 12-month follow-up visit.

The questionnaires will be mailed to you for you to fill out. It will come with an envelope that is already stamped and has only the researcher's address on it. Do not put your name on the questionnaire.

The researchers will use your answers to these questionnaires to see if there are any long-lasting effects of being in the study, such as changes in PTSD symptoms or other life events. They may be able to learn what happens to people who started out receiving full dose MDMA versus people who received lower doses of MDMA first, and then received full dose MDMA.

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A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

POSSIBLE RISKS OR DISCOMFORTS

MDMA has not been widely tested in humans, but as of December 2015, more than 1185 people have received MDMA in clinical research settings without any serious unexpected problems happening. There may be unknown side effects or risks from the use of MDMA. Some of the effects that have been observed are listed below.

Side effects that are most frequently reported by 25% or more of participants during the MDMA experience (100 to 125mg) are:

- Muscle tightness (jaw) (55%)
- Decreased appetite (42%)
- Muscle tightness (27%)
- Nausea (27%)
- Feeling Cold (27%)
- Sweating (25%)
- Restlessness (25%)

In these studies, participants (mostly with PTSD) also experienced anxiety, headache, and fatigue at a similar rate during MDMA or placebo. Less than 25% of participants receiving MDMA reported dizziness, insomnia, thirst, problems walking or with balance, dry mouth, difficulty concentrating, depressed mood, and nystagmus (eye wiggles), from most to least common. When these side effects occur, they usually last less than four hours. However, some effects have been reported to last for more than 24 hours and (rarely) for as long as four days.

There may be unknown side effects or risks from the use of MDMA.

Other possible risks of MDMA may include the following:

Serious problems: There have been some serious problems, and even deaths, associated with the use of Ecstasy outside of controlled clinical or laboratory settings. These problems have included high fever, brain swelling associated with drinking too much liquid, convulsions, and liver damage. Some recreational users of Ecstasy have become severely anxious, depressed or paranoid (thinking that other people are out to get them). Since you will be receiving moderate amounts of uncontaminated MDMA in a controlled setting with trained therapists who will be closely monitoring your physical and psychological reactions, these problems are not expected to occur either during or after the experimental session. While this does not guarantee that they will not occur, it does mean that if they do occur, the study doctors are prepared to respond in a safe and professional manner.

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Changes in vision, hearing or other senses: In previous studies in which MDMA was given to volunteers (including a total of about 365 participants without emotional disorders and 21 with PTSD) most participants reported experiencing temporary and minor changes in vision and hearing, such as sounds seeming closer or farther away than usual or objects seeming brighter than usual. These changes typically lasted 2 to 3 hours. People also reported unusual feelings in their bodies, such as tingling or numbness (between 12% and 33%).

Blood pressure and heart rate: The effects of MDMA usually last 4 to 6 hours. At the dose in this experiment, the increases in blood pressure and heart rate are likely to be moderate. Average increase in systolic blood pressure is 28 mmHg (measurement unit for blood pressure) and average diastolic blood pressure increase is 13 mmHg. Heart rate may increase by approximately 30 beats per minute (BPM) on average.

In previous studies, blood pressure rose well above normal levels in a few subjects (a little less than 5%) after receiving MDMA, but these subjects did not report any discomfort and did not require any treatment. Although these increases in blood pressure are similar to what happens after heavy exercise, they could cause serious problems in individuals with pre-existing heart or vessel conditions. These serious problems could include heart attack or stroke. We will screen all potential subjects for preexisting heart problems before they are allowed to be in this study. While this doesn't guarantee that no heart problems will occur, it does reduce the risk of this happening.

Anxious or jittery feeling: Some participants in past studies with an anxiety disorder who received MDMA (48%) or placebo (58%) reported feeling over-stimulated or anxious at a similar rate. These feelings usually lasted less than 30 minutes. Letting yourself accept and feel these emotions deeply can be part of the psychotherapy. If you are not able to deal with these experiences in a way that helps you, the study doctors will work with you to deal with these feelings. It is possible that if such periods of heightened emotion do not clear up or grow weaker during the session, you could be at increased risk for suicide or other self-harm afterwards. You will be encouraged to ask your support person or attendant to call the study doctors immediately if you have any thoughts about hurting or killing yourself so they can help you resolve them safely. If necessary, they may prescribe anti-anxiety medication or medication for sleep.

If you are in immediate danger of hurting or killing yourself or hurting someone else, then the researchers may require you to be admitted to a hospital.

Insomnia & drowsiness: In previous studies, between 7% and 23% of subjects have reported insomnia (difficulty sleeping) or feeling tired, irritable, or drowsy for as long as 3 days after receiving MDMA. If needed, the study doctor may prescribe medication for sleep. **You should not drive or use machinery immediately after each experimental session (up to 24 hours afterwards).** This is because the study drug may cause drowsiness, lack of coordination or slower reaction time.

Mood: Some after-effects of MDMA may be noticeable up to 2 or 3 days later. While some subjects feel that their mood is better, 11% feel that it is worse.

Immune System: You may have a less active immune system for 2 or 3 days after receiving MDMA. This may make you more likely to become sick with a cold or other infection during this time. The study describing this finding did not report how many people in the study showed these changes.

Addiction: There is a small chance that you will become dependent on (addicted to) MDMA. One study found that up to 6% of people using Ecstasy for recreational purposes were dependent on it. However, a study of people who had received MDMA for the first time in a legal laboratory setting found that they did not want to try MDMA again outside of the laboratory.

People who have recently (in the last 2 months) had problems with drug abuse should not take part in this study.

Possible Brain Damage: Experiments in rats and monkeys show that high and repeated doses of MDMA can change certain brain cells that release a chemical called serotonin; in mice (though not in humans), the affected cells release dopamine. The changes include loss of the parts of the cell (called "axons") that connect different brain areas. Rodents given repeated, high doses of MDMA are less sensitive to a later dose of MDMA, are more likely to become overheated when placed in a warm room, and some studies find they perform worse in difficult memory tests. Recent studies in monkeys and rodents suggest that the doses used in these studies are far higher than those typically taken by humans in either recreational or laboratory settings.

Many studies found that people who had used Ecstasy many times in recreational contexts were not able to recall words, pictures or patterns as well as people who did not use Ecstasy, and performed less well on tests of planning and impulse control. These differences are not great, but they have lasted for at least a year after people had stopped taking Ecstasy. Not all studies have found Ecstasy users to have difficulty recalling words or pictures or to have impulse control problems. When compared with people who do not use Ecstasy, studies found Ecstasy users were more likely to report feeling generally anxious or depressed. Many of these studies found that using alcohol or other drugs was also associated with feeling anxious or depressed. At least two studies found that people who are anxious, depressed or have psychological problems before taking any drugs are more likely to take Ecstasy than people without these problems, but there is no proof that MDMA might not cause these problems in some people.

Only one study has looked at brain scans of people before they got MDMA and then again after they have received one or two moderate doses of MDMA. This study did not show any changes in the brain following MDMA, though it is possible that there were changes that were too small to notice. Other studies looked at people before and after they decided to take a few tablets of Ecstasy in a recreational setting, and found one small change in the amount of blood flow in a specific part of the brain, but did not show

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signs of brain injury. The decrease in blood volume might be from temporary lowering of a type of brain receptor, or it might be a sign of reduced function in this area. Findings from these studies suggest that the amount of MDMA you will receive in this study will not produce any lasting changes in your brain, though this is not guaranteed.

Studies of people receiving one or two doses of MDMA in a laboratory setting have not found any lasting changes in memory or planning. Studies comparing people before and after they decided to take a few tablets of Ecstasy in a recreational setting with people who did not take them found less improvement in memory in the people who took Ecstasy, and no other changes in thinking or planning. It is believed that the amount of MDMA you will receive will not produce any lasting changes in memory or planning, though this cannot be guaranteed.

If you are in immediate danger of hurting or killing yourself or hurting someone else, then the study therapists may require you to stay in a hospital.

Other Risks of Being in the Study:

If you are tested for drugs of abuse within three days of each experimental session, you may test positive. The study therapists will provide you with an information card in case you are tested for drugs of abuse, and if you are tested for drugs of abuse while you are in this study, you can have the person(s) testing you call Dr. Michael C Mithoefer MD to verify that you are in this study.

The interviews you have during the study involve no specific risks or discomforts beyond those of a standard clinical interview situation. You may feel upset at the review of your emotional experiences, or you may feel boredom or fatigue. Answering questions about thoughts you might have of hurting or killing yourself may be upsetting.

The medical evaluation involves some blood tests. The risks of blood drawing include temporary discomfort from the needle stick, bruising and, rarely, infection at the site of the needle stick. Fainting could also happen.

It is possible that after you stop taking psychiatric medicine (as for depression or anxiety) as part of the study, you may start to have symptoms again. There is also a risk that you may have thoughts of hurting or killing yourself when you stop taking medicine and are in psychotherapy, especially if you have had these thoughts before. If this happens, you should talk with your outside therapist and Dr. Michael C Mithoefer MD. If you have to start taking medicine again, then the study doctors will have to take you out of the study.

REPRODUCTIVE RISKS

Effects of MDMA on the growth and development of an unborn baby are not known. Birth defects could include physical deformities, mental retardation and premature birth; therefore you will not be allowed to enter the study if you are pregnant. If you become pregnant after you have had at least one experimental session, the study doctors and the sponsor (MAPS) will ask you about and keep track of the pregnancy and will need to know about the outcome of your pregnancy.

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Women who are able to become pregnant must use one of the allowed birth control methods, such as birth-control pills or shots, IUDs, and diaphragms used along with spermicide and with partner use of condoms, or sexual abstinence while they are in the study and for at least one month afterward. The study therapists will explain these methods to you and will help you decide which might be best for you, and they can suggest to you where you can get more information and advice.

If you are a woman of childbearing potential, you will be tested at the start of the study and again before each MDMA session to see if you are pregnant. If, at any time during the study, you think that you may be pregnant or are worried that you may become pregnant, you must contact Dr. Michael C Mithoefer MD immediately. If you should become pregnant during the study, the study doctors will help you get proper advice and help you and your unborn baby get proper care while you are pregnant.

NEW FINDINGS

If any new information becomes available about MDMA while you are taking part in this study, the study therapists will tell you about it as soon as possible. You may contact the study doctor at any time after your participation ends to find out if any new information about this study has become available.

POSSIBLE BENEFITS

Your symptoms of PTSD may improve while participating in this study. There is no guarantee that you will benefit from taking part in this research study, however, information obtained from this study may help doctors and researchers to improve treatment for PTSD in the future.

COSTS

The sponsor of this study, Multidisciplinary Association for Psychedelic Studies (MAPS), will cover the costs that are directly related to this study. This includes the costs for all psychotherapy sessions that are a part of this study, for the psychological and laboratory testing, for medical examinations, including any extra tests you might have solely to see if you can be in the study (if you are eligible) and for the study drug. You, your private medical insurance (if any), and the public health insurance plan will not be charged for any procedures done solely for the purpose of the study. You or your insurance company will remain responsible for on-going treatment unrelated to the study.

PAYMENT FOR PARTICIPATION

The Sponsor, MAPS, will reimburse you for travel related expenses as follows:

Subjects who drive to the study site:

If you must drive more than 50 miles round trip for visits, you will be reimbursed at a rate of \$0.25 per mile. If you live far enough away that it is not practical or desirable to make the round trip in one day, MAPS will pay up to \$150.00 a night for all motel bills and up to \$50.00 per day for meals.

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Subjects who fly to the study site:

MAPS will pay for all travel expenses submitted by you for reimbursement. MAPS will pay up to \$150.00 a night for all motel bills and up to \$50.00 per day for meals.

If you must pay for travel or parking, the researchers will pay you back the costs of travel or parking.

ALTERNATIVES

One alternative to being in this study is to decide not to participate. You may decide to try other treatments for PTSD. There are other medicines, such as Paxil (paroxetine) or Zoloft (sertraline) and anti-anxiety medications such as Xanax (alprazolam) and other forms of psychotherapy that you could try. If you are currently having psychotherapy and/or taking medicine, you could continue with those for a longer period of time. The study doctor can discuss the alternatives and their potential risks and benefits with you.

CONFIDENTIALITY

To ensure confidentiality, your information will be stored in secure electronic systems or in a locked office. Absolute confidentiality and security cannot be guaranteed, but every effort will be made to maintain your confidentiality.

People outside of your treatment team will need access to your information to monitor the study and conduct further research and training. Any paperwork copied will have any information that could be used to identify you removed first, except for videos, which will still show your face. If records are copied, only your participant number and initials will identify you to the study sponsor unless you give specific permission, for example at a time when you sign a media release.

Medical records, including video, which identify you, and the consent form signed by you will be looked at and/or copied for research or regulatory purposes. These records may be looked at by:

- The sponsor, MAPS and the people they hire.
- Researchers who cooperate with MAPS to conduct further research, and people who conduct therapist trainings on behalf of MAPS.
- The FDA and similar agencies in other countries.
- Governmental agencies in other countries.
- The Copernicus Group Independent Review Board (CGIRB).

All records in South Carolina are subject to subpoena by a court of law.

The results of this research study may be presented in meetings, presentations, or in publications, where your identity will not be disclosed. Video of your sessions may be used in training sessions for research therapists or other researchers only in controlled settings as described below.

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Video recordings: The study therapists will video record each visit. The purposes for this recording that you are agreeing to by signing this informed consent are:

- So that you will have access to review your own therapy sessions.
- So the study therapists will have accurate records of the session.
- So that trained raters working for the sponsor can verify that the therapy is being carried out according to the protocol and the methods described in the Treatment Manual, or for further development of the Treatment Manual.
- For further research on the therapy and how it is performed.
- For training other therapists and scientists to develop and work on additional research.

For the above purposes the adherence raters, researchers and therapists who may be viewing these recordings will be selected by the sponsor, and will sign confidentiality agreements to ensure they do not share the identifying information they may receive.

Information contained in recordings that could be used to identify you may include:

- Your physical appearance
- Your voice
- Your name (if it is spoken on the recording)
- Situations from your life that might be discussed

You may watch the recordings if you wish, but you do not have to. Due to processing time required, they will not be available immediately after your visit. Once the recordings are processed you may request access to your own recordings. Your name or other identifying information will not be used to label these recordings. Sometimes audio or transcripts from these video files will be processed separately and used for additional research.

With your permission, the investigators and/or sponsor may use portions of your videos to educate a broader audience at medical conferences or other settings. In these settings the audience will not be specifically screened and selected, and confidentiality agreements will not be obtained from the audiences. You are not required to agree to use of your video in these settings in order to participate in the study. Signing this consent form does not mean you have given permission for your videos to be used in this way. You will have the opportunity to sign an additional release for these situations if they arise and if you choose to allow this use. At the end of the treatment period when you have completed all of the questionnaires and measures, you can make a decision about whether or not you wish to grant this additional consent.

These recordings will be stored on hard drives stored in a locked and secure location when not in use. No personally identifying information will be used to label the video recordings. A copy will be transferred to the sponsor for electronic storage on the web to allow for viewing purposes described above. Electronic systems used will include measures to protect confidentiality of your identity and video data. Total security cannot be guaranteed, but the sponsor is consistently working to maintain and improve the

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security of its data systems. Your videos may be viewed in online trainings or in-person trainings with pre-screened therapists. People viewing these videos will be required to sign a confidentiality agreement.

During your study sessions you may ask to stop the recording at any time, but your therapists will ask your permission to turn it back on when you are ready.

By signing this consent form, you consent to the collection, access, use and sharing of your information as described above. You have the right to check your study records and ask for changes if the information is not correct.

TREATMENT AND COMPENSATION FOR INJURY

In the event of a study-related injury, the physician who treats you will bill your insurance company. If your insurance company denies coverage or insurance is not available, then MAPS will pay for any costs that arise from treating a study-related injury, including hospitalization. Neither the Sponsor nor the study doctor has a program in place to provide additional compensation in the event of an injury.

Your health insurance may not be willing to pay for the costs of treating a study-related emergency. The study sponsor (MAPS) will pay for any study-related procedure that your insurance will not cover.

LEGAL RIGHTS

The above section does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this Subject Information and Consent Form.

VOLUNTARY PARTICIPATION

Your decision to take part in this research study is completely voluntary. There will not be any penalty or loss of benefits to you if you decide not to take part.

In addition, you may withdraw from (leave, stop being in) the study at any time. There will be no penalty if you decide to withdraw from the research study. Before withdrawing from this study, notify your study doctor that you wish to withdraw. This notice will allow your study doctor to inform you if there are any potential medical risks of withdrawal. You may be asked to return to the clinic for tests.

WITHDRAWAL

Your doctor, the sponsor company, or the FDA has the right to stop your participation in the study at any time, with or without your consent, for any of the following reasons: if you have an adverse effect from the study drugs, if you need a treatment not allowed in this study, such as restarting medication for depression or anxiety, if you do not keep appointments, if you do not take the study drug as instructed, if you become pregnant, or if the study is canceled by the FDA or the sponsor company.

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CONTACT FOR QUESTIONS

If you have any questions or concerns about your participation in this research study or if you feel that you have experienced a research-related injury or reaction to the study drug, or have a complaint about the research study, contact:

Investigator Name: Michael C Mithoefer MD

Daytime Telephone Number(s): 843-849-6899

24-hour Contact Number(s): 843-849-6899

If you have any questions or concerns about your rights as a research subject or want to discuss a problem, get information or offer input, you may contact Copernicus Group Independent Review Board (IRB) at 1-888-303-2224 (toll free). An IRB is a group of scientific and non-scientific individuals who perform the initial and ongoing ethical review of the research study with the study subject's rights and welfare in mind. Copernicus Group IRB has reviewed and approved the research study described in this Subject Information and Consent Form. If you have study-related comments, complaints or concerns, you should first contact the study investigator. Please call the IRB if you want to talk to someone other than the study investigator or have difficulty reaching the study investigator. For further information regarding the clinical trials process and your role as a research subject, you may visit the Copernicus Group IRB website at www.cgirb.com.

The researchers will give you a wallet card containing contact information for the researchers, the sponsor and the IRB.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

SUBJECT'S STATEMENT OF CONSENT

"A Randomized, Triple-Blind Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in conjunction with manualized psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-resistant Posttraumatic Stress Disorder (PTSD)"

My participation in this study is voluntary. I may refuse to take part in or I may stop taking part in this study at any time. I will call the researchers if I decide to do this. My decision will not affect my current or future regular medical care or any benefits to which I am entitled at this site. The researchers and/or the sponsor may stop my participation in this study at any time without my consent if they decide it is in my best interest or if I do not follow the researchers' instructions.

I agree to have my sessions video recorded during this study.

I have read the information in this consent form and it has been discussed with me. I have been given sufficient opportunity to consider whether to participate in this study. All of my questions so far about the study and my participation in it have been answered. I freely consent to participate in this research study.

By signing this consent form, I have not waived any of the legal rights which I otherwise would have as a subject in a research study. I have been told that I will be given a copy of this consent form signed by you and the investigator.

	SUBJECT	INVESTIGATOR
Printed Name		
Signature		
Date		

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**AUTHORIZATION TO USE AND DISCLOSE
PERSONAL HEALTH INFORMATION FOR RESEARCH**

The United States government has issued a privacy rule to protect the privacy rights of patients. This rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule is designed to protect the confidentiality of your personal health information. The document you are reading, called an "Authorization", describes your rights and explains how your health information will be used and disclosed (shared).

In working with the sponsor, the study doctor, Michael C Mithoefer MD, will use and share personal health information about you. This is information about your health that also includes your name, address, telephone number or other facts that could identify the health information as yours. This includes information in your medical record and information created or collected during the study. This information may include your medical history, physical exam and laboratory test results. Some of these tests may have been done as part of your regular care. The study doctor will use this information about you to complete this research.

In most cases, the study doctor will use your initials and assign a code number to your information that is shared with the sponsor. The sponsor and its representatives may review or copy your personal health information at the study site. Regulatory authorities and the Copernicus Group Independent Review Board may also review or copy your information to make sure that the study is done properly or for other purposes required by law.

By signing this Authorization, you allow the study doctor to use your personal health information to carry out and evaluate this study. You also allow the study doctor to share your personal health information with:

- the sponsor and its representatives
- the Copernicus Group Independent Review Board
- the U.S. Food and Drug Administration (FDA)
- other regulatory agencies

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Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, these groups are committed to keeping your personal health information confidential.

You have the right to see and get a copy of your records related to the study for as long as the study doctor has this information. However, by signing this Authorization you agree that you might not be able to review or receive some of your records related to the study until after the study has been completed.

You may choose to withdraw this Authorization at any time, but you must notify the study doctor in writing. Send your written withdrawal notice to:

**Michael C Mithoefer MD
208 Scott St
Mount Pleasant SC 29464-4345**

If you withdraw from the study and withdraw your Authorization, no new information will be collected for study purposes unless the information concerns an adverse event (a bad effect) related to the study. If an adverse event occurs, your entire medical record may be reviewed. All information that has already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

If you withdraw from the study but do not withdraw your Authorization, new personal health information may be collected until this study ends.

This Authorization does not have an expiration date. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely. Your study doctor will keep this Authorization for at least 6 years.

If you do not sign this Authorization, you cannot participate in this research study or receive study drug. If you withdraw this Authorization in the future, you will no longer be able to participate in this study. Your decision to withdraw your Authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

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AUTHORIZATION

I authorize the release of my medical records and personal health information related to this study to the sponsor and its representatives, the Copernicus Group Independent Review Board, the FDA, and other regulatory agencies as described above. I have been told that I will receive a signed and dated copy of this Authorization for my records.

	SUBJECT	INVESTIGATOR
Printed Name		
Signature		
Date		

Appendix B

Human Subjects Review Board Approval Letter



August 28, 2013

Amy Emerson PhD
Multidisciplinary Association for Psychedelic Studies
1215 Mission St.
Santa Cruz CA 95060

Re: Protocol #: MP8
IRB Tracking #: MAP3-10-051

" A Randomized, Triple-Blind Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in conjunction with manualized psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-resistant Posttraumatic Stress Disorder (PTSD) "

Dear Ms. Emerson,

This letter is to inform you that the following document(s) received IRB approval on 08/27/2013:

- Protocol (incorporating Amendment #5) dated 08/16/2013
- Dissociative Experiences Scale
- Perceptions of Experimental Sessions Scale dated August 19, 2013
- Questionnaire for Long Term Follow-up dated August 2, 2013
- Visual Analog Scale dated August 19, 2013
- Revised Subject Information and Consent Form
and Authorization to Use and Disclose Personal Health Information for Research

This letter also serves to acknowledge review of the Investigator's Brochure for MDMA (7th Edition) dated August 1, 2013.

If you have any further questions, please do not hesitate to contact us.

Sincerely,

Angela F. Coleman
Manager, Study Operations

cc: Amy Emerson, Multi-disciplinary Association For Psychedelic Studies (Email)
Berra Yazar-Klosinski, Multi-disciplinary Association For Psychedelic Studies (Email)

Copernicus Group IRB
One Triangle Drive Suite 100
Durham, NC 27713
Mailing Address:
P.O. Box 110605
Research Triangle Park, NC 27709

Experience and Innovation in Ethical Review™

Telephone: 919-465-4310
Toll-Free: 888-303-2224
Fax: 919-465-4311
E-Mail: irb@cgirb.com
Web: www.cgirb.com

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Investigator List

IRB Tracking Number: MAP3-10-051

Protocol ID: MP8

Sites: 1

Investigator	Approved	City State	Translation	Site IC	Notes
Mithoefer, Michael C.	2010-03-30	Mount Pleasant SC			

Copernicus Group IRB
One Triangle Drive Suite 100
Durham, NC 27713
Mailing Address:
P.O. Box 110605
Research Triangle Park, NC 27709

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Telephone: 919-465-4310
Toll-Free: 888-303-2224
Fax: 919-465-4311
E-Mail: irb@cgirb.com
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