

Protocol

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A HUMAN PHASE II STUDY –
SAFETY AND EFFICACY OF
3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA)-
ASSISTED PSYCHOTHERAPY IN THE TREATMENT OF CHRONIC
POSTTRAUMATIC STRESS DISORDER (PTSD)

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VOLUME 1

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Volume 3

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Introductory Statement and General Investigational Plan

This application is for a Phase II pilot study into the use of 3,4-methylenedioxymethamphetamine (MDMA) to treat patients with chronic Posttraumatic Stress Disorder (PTSD). This study builds on FDA-approved research begun in the Phase I trials conducted at Harbor-UCLA Medical Center by Dr. Charles Grob (Grob et al. 1996), at The University of California, San Francisco by Dr. John Mendelson (Lester et al. 2000), and at Wayne State University by Dr. Manny Tancer and Charles R. Schuster, Ph.D. (Tancer, personal communication), and on ongoing Phase I research being done in Switzerland by Dr. Franz Vollenweider and his colleagues (Gamma et al. 2000; Liechti et al. 2000a; Liechti et al. 2001a; Liechti et al. 2001b; Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Vollenweider et al. 1998; Vollenweider et al. 1999b) and in Spain by Drs. R. de la Torre, Jordi Cami and Magi Farre (Cami et al. 2000; de la Torre et al. 2000a; de la Torre et al. 2000b; Mas et al. 1999; Pacifici et al. 2000; Pacifici et al. 1999; Pacifici et al. 2001).

On June 24, 1999, Dr. Cynthia McCormick chaired a teleconference between staff from the Division of Anesthetics, Critical Care and Addiction Drug Products (ACCADP) and Dr. Charles Grob, Dr. Rick Doblin, Loren Miller and Matthew Baggott (Memorandum of Telecon Meeting Minutes, July 23, 1999). The teleconference had been requested by Dr. Charles Grob and Dr. Rick Doblin, after FDA policy regarding MDMA research had been reviewed by Center-level policymakers. The purpose of the teleconference was “to discuss what preclinical studies, if any, would be required before further studies in humans would be permitted.”

Dr. McCormick reported that the “Center has decided to allow the sponsor [MAPS] to undertake a proof-of-principle study without further pre-clinical data” and that the proof-of-principle study should be “a solid clinical trial capable of demonstrating efficacy.” In response to a request by Dr. Rick Doblin “to begin with some pilot patients to allow the treatment team to develop their technique in administering the drug and concomitant therapy,” Dr. McCormick stated that “a case could be made for a pilot study with controls, to establish the effect size in order to appropriately power the main study.”

This protocol in patients with posttraumatic stress disorder (PTSD) involves a different patient population than the protocol discussed during the teleconference, which was in patients with terminal cancer. On the one hand, the acute risks associated with the administration of MDMA are less of a concern in PTSD patients than in cancer patients, due to the absence of significant physical disease in PTSD patients. On the other hand, the risks of long-term functional or behavioral consequences associated with the possibility of MDMA neurotoxicity are more of a concern in PTSD patients than in terminal cancer patients, due to the potentially longer life span of the PTSD patients. Based on the evidence presented in this protocol and the associated literature review, these risks are more than balanced by the potential benefits to the subjects.

This randomized double-blind placebo-controlled pilot study is designed to gather preliminary information about the safety and efficacy of MDMA-assisted psychotherapy

in stimulating therapeutic processing of traumatic experiences, with the goal of reducing or relieving symptoms of PTSD. If data from this pilot study reveals no unexpected safety issues, more definitive proof-of-principle studies will be submitted to FDA.

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the hallucinogen mescaline. MDMA does not cause hallucinations and other extreme changes in perception in the way that mescaline does. MDMA has some unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients (Shulgin, 1990, Greer and Tolbert, 1998). Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens (Nichols and Oberlender, 1990). The term refers to MDMA and similar substances that produce increased feelings of closeness to others, increased sensitivity to emotions and increased insights about the self, especially in the context of interpersonal relationships. The drug is a white, crystalline powder and will be administered orally in capsule form (FDA Drug Master File 6293).

Before MDMA became a Schedule I drug, it was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists (Greer and Tolbert 1986; Saunders 1993; Stolaroff 1997). There are a number of published case reports and uncontrolled studies of its effects. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways: Specifically, MDMA can “reduce or somehow eliminate fear of a perceived threat to one’s emotional integrity” (Greer and Tolbert 1998). Elimination of these “conditioned fear responses” can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. It has also been asserted that MDMA causes increased empathy for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience (Greer and Tolbert, 1998, Holland, 2001).

To date, no study in this country has attempted to evaluate the safety, efficacy or mechanism of action of MDMA as an adjunct to psychotherapy in PTSD patients or in patients with any other psychiatric disorder. There is presently an ongoing study in PTSD patients in Spain, which is still in the very early stages of treating subjects. (Bouso Saiz and Sopelana Rodriguez, AEM Protocol #99-309).

This proposed experiment will involve twenty subjects to be recruited from patient populations currently being treated for chronic PTSD at the Medical University of South Carolina and in the surrounding community. Patients will also be recruited through newspaper advertisements intended to attract patients who are not currently in treatment. Only chronic PTSD patients who have failed to benefit from or tolerate psychopharmacological or psychotherapeutic treatment will be included. The subjects in the experimental group will receive two MDMA treatment sessions (125 mg./treatment)

3 - 5 weeks apart, while controls will receive an inactive placebo during the same sessions. Both groups will experience identical psychotherapeutic treatment during the experimental sessions. All sessions will be conducted in a carefully controlled setting in the presence of a male and a female therapist (a male psychiatrist and a female nurse) with whom the patient has previously had the opportunity to develop a therapeutic alliance during several introductory non-drug psychotherapy sessions. There will be follow-up non-drug psychotherapy sessions with the therapists between MDMA or placebo sessions to aid in further processing and integration of the experiences.

The subject population of chronic PTSD patients was selected in part because of patient and therapist reports as to the effectiveness of MDMA-assisted psychotherapy in treating PTSD, from treatments conducted prior to the criminalization of MDMA in 1985. The qualities that have been associated with MDMA in anecdotal reports (i.e. decreased defensiveness and enhanced therapeutic alliance) seem to have the potential to be particularly useful in the treatment of this disorder. PTSD is a condition that involves prominent fear responses. Revisiting traumatic experiences in psychotherapy is recognized to be of therapeutic value. Early clinical experience with MDMA is consistent with the hypothesis that it can increase therapeutic effectiveness in this population. It is also a disorder for which there is, to date, only one FDA-approved medication, and about which there are still many unanswered questions regarding psychological and pharmacological interventions (Montgomery and Beck 1999). The lifetime prevalence of PTSD in the general population may be as high as 10% (Meltzer-Brody et al. 2000), so the search for additional and more effective treatments is extremely important.

The rise in illicit, recreational use of “Ecstasy” (MDMA) since it became scheduled has contributed to concern about its toxicity. Given the widespread use by millions of people around the world, remarkably few related problems have come to clinical attention. Nevertheless, there have been some serious complications and even deaths associated with the use of “Ecstasy” (often containing substances other than MDMA) at raves, primarily due to hyperthermia, dehydration or hyponatremia. There is evidence that the use of frequent, high doses of MDMA in uncontrolled settings exacerbates its risks. The majority of serious adverse events after illegal Ecstasy consumption have occurred in conditions of high ambient temperature, long periods of strenuous activity (dancing) and insufficient or uncontrolled fluid intake.

On the other hand, according to the data from several phase I trials conducted in the United States, Spain and Switzerland, when MDMA is used in therapeutic doses in a controlled setting, the risk/benefit ratio is favorable (Aghajanian and Lieberman 2001; Cami et al. 2000; de la Torre et al. 2000a; de la Torre et al. 2000b; Lester et al. 2000; Lieberman and Aghajanian 1999; Liechti et al. 2000a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Liechti et al, 2001; Mas et al. 1999; Vollenweider et al. 1998; 1999; See also data collected by CS Grob in Previous Human Experience and attached letters of support). There has been no evidence of significant or lasting toxicity in phase I studies. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e.g., Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle

neurocognitive changes may occur in a subset of repeated users of illicit MDMA and other drugs (e.g., Gouzoulis-Mayfrank et al. 2000; Gouzoulis-Mayfrank, attached letter of support). In contrast, our all available phase I data (published and yet unpublished) indicate that it is unlikely that the MDMA exposures proposed in this protocol cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Tests of neurocognitive function have found that performance is not affected by participation in clinical MDMA trials (Boone et al. in preparation, see also **Table 2.5** in Investigator's Brochure; Vollenweider et al. 2001; Vollenweider, attached letter of support). Vollenweider and colleagues (2000) recently presented positron emission tomography data at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine that found no change in estimated serotonin transporter binding sites four weeks after a dose of MDMA similar to our proposed dose of 125 mg was given to MDMA-naïve volunteers. Based on these data and an extensive review of the MDMA literature, we conclude that risks of neurocognitive, serotonergic, or other toxicity are low in the proposed protocol.

These low risks are more than balanced by the potential benefits to the volunteers. All participants have had at least one unsuccessful attempt at treatment with medications and psychotherapy and may find some relief associated either with MDMA-assisted psychotherapy or with the non-drug psychotherapy to be administered to the control subjects. Studies in humans and non-human animals suggest that ongoing symptoms and stress of untreated posttraumatic stress disorder may be neurotoxic in hippocampal areas (Bremner 1999; Ling 1981; Rauch 1996; Sapolsky 1990; Shin 1997; Wolkowitz, 1990). Hence the risks posed by MDMA-assisted psychotherapy are offset by the benefits of treating PTSD and its neurotoxic effects in one or more areas of the brain.

Based on these findings, which will be discussed further below in the section on Pharmacology and Toxicology, it is very unlikely that the doses we propose to administer in a controlled clinical setting will cause memory impairment or other neurological or physiological damage. These low risks are more than balanced by the potential benefits to the volunteers. All subjects have had at least one unsuccessful attempt at treatment with medications and/or psychotherapy and may find some relief associated either with MDMA-assisted psychotherapy or with the non-drug psychotherapy to be administered to the control subjects.

Rationale for Studying PTSD

A) Epidemiology of PTSD:

Posttraumatic stress disorder (PTSD) occurs in response to a traumatic event or events. Approximately 10% - 20% of people who experience a major trauma go on to develop PTSD, giving it an estimated 8% prevalence in the general population (Kessler et al. 1995). It is most likely to occur following an event involving perceived personal threat, such as rape or physical assault (Breslau 1998), and it develops approximately twice as often in women as it does in men. Vulnerability to PTSD is increased in people with a family or personal history of psychiatric illness, particularly anxiety or depression (McFarlane 1989). The most common comorbid conditions appear to be major depression, followed by generalized anxiety and substance abuse (Montgomery et al., 2000). In the National Comorbidity Study, 88% of men and 79% of women with PTSD reported a lifetime history of at least one other psychiatric disorder. Fifty percent of people with PTSD had 3 or more comorbidities. PTSD generally precedes most comorbidities, particularly affective and substance abuse disorders (Kessler et al., 1995). In addition to the psychiatric manifestations, individuals with PTSD have an increased incidence of physical problems and impairments in social and occupational functioning that lead to increased healthcare utilization and decreased quality of life (Brady et al. 2000; Kessler et al. 1999; Solomon and Davidson, 1997). PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. The search for more effective treatments and a wider array of treatments is crucial. In a recent update on PTSD by three experts in the field it was stated that,

“Pharmacologic agents and psychotherapeutic modalities are components of a multidimensional treatment strategy. ...PTSD often responds slowly and may not completely resolve, even with prolonged intervention. Because PTSD can devastate nearly every aspect of life, refinements in diagnostic accuracy and management options are clearly needed... Leaving aside cost issues in the healthcare system, patients with PTSD suffer significant impairments of work productivity, relationships, and overall health. The effects on society are no doubt enormous” (Brady et al. 2000, p. 25).

The DSM IV criteria for PTSD include: 1) Exposure to a significant traumatic event accompanied by an intense acute emotional response. 2) Persistent reexperiencing of the event or aspects of the experience. 3) Persistent avoidance of stimuli associated with the event, and/or withdrawal from some aspects of life. 4) Persistent symptoms of increased arousal. The above symptoms must last for more than one month for Acute PTSD and more than three months for Chronic PTSD (DSM-IV). In the National Comorbidity Study, the median time to remission was 36 months with treatment and 64 months without treatment. In either subgroup, more than one-third of patients still had symptoms several times per week after 10 years (Kessler et al., 1995). These data highlight the importance of research to develop new treatments and to thoroughly investigate any

treatments, such as MDMA-assisted psychotherapy, which have shown promise in anecdotal reports.

B) Biology of PTSD:

Although the biology of PTSD is not completely understood, animal models have been developed to study the neurobiology of the key PTSD symptoms, re-experiencing, avoidance/numbing, and hyper-arousal. The following two tables by Dennis Charney, MD (in Brady et al., 2000) summarize findings from the study of the conditioned-fear model in animals:

Table 1: Neurobiologic Changes in Animal Models of Conditioned Fear

Neuroanatomic:

4. Damage and/or cell death in the hippocampus
5. Stimulation of the amygdala
6. Stimulation of the red nucleus of the stria terminalis

Hypothalamic-pituitary-adrenal (HPA) axis

7. Elevated levels of corticotropin-releasing hormone (CRH) in the brain.

Neurotransmitters:

8. Elevated norepinephrine levels
9. Elevated serotonin levels
10. Elevated acetylcholine levels
11. Elevated dopamine levels in the prefrontal cortex

Other effects:

Reduced levels of messenger RNA (mRNA) encoding brain-derived neurotrophic factor

(Adapted by Charney from Rasmusson and Charney, 1997, and Davis 1999)

Table 2: Noradrenergic and Serotonergic Changes in Animal Models of Anxiety

Increased norepinephrine turnover:

- amygdala
- cerebral cortex
- hippocampus
- hypothalamus
- locus coeruleus

Increased serotonin turnover

- amygdala
- lateral hypothalamus
- nucleus accumbens
- prefrontal cortex

Occurs in conjunction with
Fear-associated conditioned
Response

Occurs in conjunction with
hyperirritability, hyperexcitability
and hypersensitivity

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Adapted by Charney from Charney and Bremner, 1999

In humans, MRI studies have now demonstrated decreased hippocampal volume in patients with PTSD. This is in keeping with the decreased neurogenesis and resultant stress-induced hippocampal atrophy in animal models. In addition, PET scans have revealed decreased metabolic rates in the temporal and prefrontal cortex in patients with combat related PTSD (Bremner et al. 1997). In another study, PTSD patients showed increased blood flow in limbic regions and decreased flow in mid-temporal, left inferior frontal and medial prefrontal cortex, compared with controls (Bremner 1999; Rauch 1996; Shin 1997). It is not known how rapidly the neurobiologic changes develop after trauma or to what degree they are enhanced or sustained by the ongoing stress of the re-experiencing and hyper-arousal symptoms of PTSD. Changes in blood flow patterns on PET scans have been observed when patients are exposed to reminders of the original trauma (Bremner 1999). This is consistent with what seems intuitively likely, that the ongoing stress of the disorder is in some sense self-perpetuating and contributes to the adverse neurobiologic effects as well as the suffering that stems from PTSD. If that is true, then the ongoing neurotoxicity of the chronic disorder itself is an important factor to weigh against any concerns regarding toxicity from drug treatment. Charney points out that, "in animals, the amygdala, hippocampus, locus coeruleus, and prefrontal cortex are involved in the fear reaction (Grillon 1996). In humans, however, idiosyncratic differences contribute to the development of PTSD in some individuals but not in others exposed to the same stressor. Chronic noradrenergic activation can lead to down-regulation of noradrenergic receptors and depletion of norepinephrine, both of which can increase susceptibility to future stress (Grillon 1996). Chronic elevation of glucocorticoids can result in neurotoxic effects in the hippocampus that adversely affect learning and memory. (Ling 1981; Sapolsky 1990; Wolkowitz 1990). Re-experiencing the trauma through intrusive symptoms or other reminders can serve as a chronic or intermittent stressor. This effect reinforces the neurobiologic disturbance and establishes a process of "kindling" in which the patient is chronically prepared to respond to specific reminders of the trauma or even to neural stimuli (such as loud noises) with the same intensity experienced during the original traumatic event. (Van der Kolk 1997)

Treatment goals for posttraumatic stress disorder include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. Ideally, treatment should reduce or reverse any hippocampal atrophy arising from post-traumatic stress disorder. One approach is to discover drugs that directly counteract these neurobiologic changes. Sertraline, currently the only drug with an FDA approved indication for treating PTSD, is known to affect the noradrenergic and serotonergic components of PTSD. It may also block the down-regulation of brain-derived neurotrophic factor, but it is not known whether it can arrest and reverse the hippocampal atrophy found in PTSD. Another approach to these problems is to develop drugs and/or psychotherapeutic treatments that will indirectly interrupt the destructive neurobiological changes by decreasing or eliminating the stress reactions to triggers and the chronic hyperarousal of PTSD. Reports of past experience with MDMA-assisted psychotherapy suggest that it may be such a treatment. In fact, the biologic and the psychotherapeutic approaches overlap and re-enforce each other. Knowledge about the connections between the neurobiologic effects and the therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left

amygdala (Gamma et al 2000). This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD (Charney 1997, Davis 1999).

Investigators and Institutional Review Board

Principal Investigators:

Michael Mithoefer, MD is a practicing psychiatrist and Clinical Assistant Professor of Psychiatry at the Medical University of South Carolina. He is board certified in Psychiatry and was also board certified in Internal Medicine in 1981 and in Emergency Medicine in 1987. Dr. Mithoefer will be the primary therapist for all the patients and will be responsible for participant safety during protocol participation. He will be present during all MDMA sessions.

Mark T. Wagner, Ph.D. is an Associate Professor of Neurology at the Medical University of South Carolina, and is the Director of the Neuropsychology Section at the University. He is an expert in the assessment of cognitive and psychological function. His clinical work often involves assessment of patient response to pharmacological agents and assessment of efficacy of medical/surgical treatment modalities. He has an extensive research background and numerous publications related to the topic of neuropsychology.

Additional Investigators:

Ann T. Mithoefer, BSN is a registered nurse who works with her husband, Michael Mithoefer, MD, as a psychiatric office nurse and as co-facilitator in their monthly Holotropic Breathwork groups. She completed training and certification in Holotropic Breathwork with Stanislov Grof, MD in 1997. Ann Mithoefer will be acting as co-therapist throughout the study, and she will be present during all MDMA sessions.

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Institutional Review Board:

This research will be submitted to the I.R.B of The Medical University of South Carolina.
The I.R.B. can be reached at:

Office of Research Integrity
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165 Cannon Street
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The Investigator's Brochure

Please find the entire text in Volume 3 "The Investigator's Brochure."

The Protocol

Experimental Design and Methods

Study design:

The proposed project is a double-blind placebo-controlled Phase II pilot study designed to investigate the safety and efficacy of two MDMA-assisted psychotherapy sessions. The effects of 125 mg. of MDMA delivered within a controlled therapeutic setting to patients with chronic PTSD will be compared with placebo administered in otherwise identical sessions. All subjects will meet current criteria for PTSD. Subjects will be recruited through newspaper advertisement and referrals from physicians or psychotherapists. They will be screened through intake interviews, physical examinations, neuropsychiatric exams and psychiatric diagnostic interviews. Twelve of the twenty subjects will receive two MDMA-assisted therapeutic sessions scheduled 3 - 5 weeks apart, and the eight remaining subjects will receive inactive placebo. All subjects will also receive 13 – 14 hours of non-drug psychotherapy before and after the experimental sessions. Physical and psychological status will be continuously monitored throughout the test sessions. Subjects will be reassessed for physical status by the physician-investigator immediately following and weekly for at least 3 weeks after each session. Psychiatric status will be objectively reassessed 4 days after each session and 3 months following the first session (2 months following the second session). Neurocognitive status will be measured again at 2 months following the second MDMA session. A full medical exam and laboratory screening will be done before the study and 2 months after the second MDMA session.

Specific Hypothesis:

- There will be a trend for volunteers participating in MDMA-assisted therapy to experience a greater decrease in signs and symptoms of PTSD than will controls, with signs and symptoms measured by a change in the Clinician Administered PTSD Symptom Scale (CAPS-2: Blake et al. 1990), the Impact of Events Scale (IES: Horowitz et al. 1979) and the Symptom Checklist 90 (SCL-90) administered at study initiation and again at 4 days after each MDMA session and at 2 months after the second treatment session.

- Exposure to MDMA will not be associated with neurocognitive toxicity as measured by The Repeatable Battery for Assessment of Neuropsychological Status (RBANS), the Paced Auditory Serial Addition Test (PASAT) and the Rey-Osterrieth Complex Figure Test administered at study initiation and 2 months after the second MDMA session. Likewise, it will not be associated with hepatic, electrolyte or other metabolic toxicity as measured by biochemical profiles and serum electrolytes determined at study initiation and 4 days after the last treatment session. Subjects in the experimental group will not perform any differently than controls on measures of neurocognitive performance when measured three months after treatment administration.

Subjects:

Twenty subjects, including males and females, aged 18-65, will be recruited for study participation. Prospective subjects will be recruited through newspaper advertisements and referrals from physicians or psychotherapists. Subjects will be screened with intake interviews, physical examinations and psychological diagnostic testing. The first twenty who meet inclusion criteria without any exclusion criteria will be included in the study. All subjects will receive the treatment (MDMA or placebo) within an experimental setting (described below) designed to facilitate optimal trust, relaxation, and catharsis. Data from this initial set of twenty volunteers will be analyzed for preliminary information about safety and efficacy before any additional patients are treated in the context of a full-scale controlled clinical trial. Any volunteers who drop out or are excluded between the first and the second MDMA or placebo sessions will be replaced. Researchers will, nevertheless, attempt to collect outcome data on drop-outs and excluded volunteers. ■

Inclusion Criteria:

1. Subjects must meet DSM IV criteria for current PTSD (within the past 6 months) in response to crime victimization (CR-PTSD), including childhood sexual or physical abuse.
2. They must have had at least one unsuccessful attempt at treatment with medications and/or psychotherapy, including a trial of treatment with a selective serotonin uptake inhibitor. Treatment will be deemed to have been unsuccessful if the patient continues to meet criteria for current PTSD following the treatment.
3. Subjects may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of subjects with other mood and anxiety disorders is essential because recent literature (Brady et al., 1994; Faustman & White, 1989), indicate the marked frequency of the co-existence of other psychiatric disorders among patients with PTSD.
4. Subjects must also be willing to commit to medication dosing, therapy sessions, and follow-up sessions and to complete evaluation instruments.
5. Subjects must be willing to refrain from taking any psychiatric medications from the outset of the study until the final follow-up evaluation, which will occur two months after the second MDMA session. If they are being treated with psychoactive drugs at the time they are recruited into the study, agreement to suspend treatment must be obtained in writing from their outside treating physician. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life).

6. Subjects who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. If they desire that the investigators communicate directly with the therapist, they must sign a release for the investigators to communicate directly with their therapist. They may not change therapists, increase the length and frequency of treatments, or commence any new type of therapy until after the evaluation session 2 months after the second MDMA session.
- 7.
8. Subjects must agree that, for one week preceding each MDMA session:
 - a. They will refrain from taking any herbal supplement (except with prior approval of the research team).
 - b. They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
 - c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).
9. Subjects must agree to take nothing by mouth except clear alcohol-free liquids after 12 A.M. (midnight) the evening before each MDMA session. Patients must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA-assisted therapy session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of MDMA.
10. Female subjects of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.

Exclusion Criteria:

Potential subjects with the following conditions will be excluded:

1. Women who are pregnant or nursing, or of child bearing potential not practicing an effective means of birth control.
2. Patients with a history of or current primary psychotic disorder or bipolar affective disorder type 1.
3. Patients with dissociative identity disorder or an eating disorder with active purging.
4. Patients with evidence or history of significant hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, immunocompromise, or neurological disease, including seizure disorder. (Patients with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).

5. Patients with hypertension, hepatic disease (with or without abnormal liver enzymes), or history of or existing hyponatremia.
6. Patients weighing less than 50 kg or more than 105 kg.
7. Patients with prior use of “Ecstasy” more than 5 times or at any time within the previous 6 months.
8. Patients who would present a serious suicide risk or who are likely to require hospitalization during the course of the study.
9. Patients requiring ongoing concomitant therapy with a psychotropic drug.
10. Patients meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.
11. Any subject who is not able to give adequate informed consent will be excluded.

Initial screening visit and diagnostic evaluation:

The purpose of the initial screening visit is to determine whether or not the potential subject fits the inclusion criteria and is free from any exclusion criteria. This visit will consist of:

The Clinician Administered PTSD Scale (CAPS-1; Blake et al. 1990: Appendix C) will be used to provide a DSM-IV CR-PTSD diagnosis. If the subject meets DSM-IV PTSD criteria, the rest of the SCID (First et al. 1994) will be administered for the purpose of ruling out patients for exclusionary Axis I diagnoses (i.e., exclusion criteria of substance dependence, psychotic disorder, eating disorder, or bipolar disorder).

DSM-IV criteria will be used as the diagnostic criteria for psychiatric assessment because they represent a standardized set of criteria that are easily interpreted and followed. They yield consistent diagnoses for treatment for research purposes across sites and between studies.

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

Patients who meet the above psychiatric criteria and agree to participate in the study will receive further medical evaluation as follows:

- general medical history and physical exam

- EKG
- metabolic profile
- serum electrolytes
- thyroid hormone levels and TSH
- HIV serology (like all other results, these results will be kept confidential, and appropriate referral for counseling will be made if necessary)
- urine pregnancy test for females

Following this pre-study evaluation, patients who meet the study criteria as outlined above will be scheduled for a baseline assessment battery to be administered 14 days prior to their first MDMA session. They will also be scheduled for the two preparatory psychotherapy sessions that will occur within this same time period.

Baseline assessment visit:

An assessment battery will be performed during the 2 weeks prior to the first MDMA session in order to provide baseline measures of PTSD symptomatology, mood state and global functioning. Inter-rater reliability will be established on all clinician or research-administered rating instruments prior to the initiation of the trial as we have done for other clinical research projects. The assessment instruments to be used represent state-of-the-art instruments in PTSD and neuropsychology testing fields. They are outlined below. The baseline assessment battery should take approximately 2-3 hours to complete. The rationale for the use of these particular instruments and a detailed description is provided below:

A. Screening and diagnostic instruments:

1. SCID-IV (First et al. 1994). The SCID is a semi-structured interview, typically performed by a psychiatrist that permits accurate diagnosis of lifetime and current psychiatric disorders, using DSM-IV criteria. Tests for inter-rater reliability will be performed with SCID interviewers (Nunes et al. 1989; Drake and Walloch 1989).
2. Clinician-Administered PTSD Scale (CAPS; Blake et al., 1990). The CAPS is a structured clinical interview designed to assess the seventeen symptoms of PTSD along with eight associated features. The CAPS provides a means to evaluate (a) the frequency and intensity dimensions of each symptom (b) the impact of symptoms on the patient's social and occupational functioning (c) the overall severity of the symptom complex (d) global improvement since baseline and the validity of the ratings obtained. Form 1 of the CAPS allows for a current and lifetime PTSD diagnosis. This instrument will be used to determine current PTSD diagnosis. Form 2 allows the interviewer to assess PTSD symptom status over time (CAPS-2). The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability (Blake et al, 1990; Nagy et al., 1993).

3. Impact of Event Scale (IES; Horowitz et al, 1979). The Impact of Event Scale is a 15-item self-report scale designed to measure the extent to which a given stressful life event produces subjective distress. Each item, which represents either a symptom of intrusion or avoidance, is rated on a 4-point scale (0, 1, 3, and 5) for the extent to which the item was true for the participant during the past seven days. Scores range from (0) for "not at all" to (5) for "often". The Intrusion subscale, Avoidance scale, and Total IES scores will be used in the analyses. Internal consistency and reliability of the IES has been found to be adequate. IES scores were found to be meaningful in discriminating between psychotherapy patients and non-patients (Zilberg et al. 1982).
4. Subjective Units of Distress. This is a standardized subjective rating scale by which a subject can quickly rate comfort level throughout the session (1-7 scale). The parameters of the scale are explained at study initiations.
5. NEO Personality Inventory (Piedmont, 1998). The NEO is a well-established measure of personality with sound properties of reliability and validity that operationally define personality structure according to a five-factor model. The factor structure includes the major domains of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Each factor consists of six facet subscales that sample constructs such as anxiety, hostility, vulnerability, warmth, positive emotions, fantasy, compliance, self-discipline, etc. This model of personality structure provides insight as to the internal psychological forces that have resulted in Axis I psychopathology, or in this case, PTSD. The instrument consists of a series of items to which the subject responds via a (1) strongly disagree to (5) strongly agree Likert-type scale. This measure will be administered during the baseline, then repeated 4 days post session and then again at the final 3 month follow-up session.

B. Neuropsychological Measures:

1. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1997) has two parallel forms, with identical administration but different stimulus content, ideal for measuring change in a patient's neuropsychological status over time. The use of alternate forms eliminates content practice effects and simplifies interpretation of repeat test performance. Each version has one stimulus booklet and one record form with a shared manual. Examining multiple neurocognitive domains RBANS provides a quick sampling of major neurocognitive domains, using subtest content. The RBANS is brief (20-30 minutes), portable, and hand-scorable. Only the easel-backed stimulus booklet and record form are required for administration and scoring. RBANS is used to support the broad-based assessment of multiple cognitive domains with index scores for the following neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory.
2. The Paced Auditory Serial Addition Task (PASAT) (Roman, Edwall, Buchanan, &

Patton 1991) is a sensitive measure of information-processing speed and efficiency, concentration skills, and immediate memory which has an extensive literature associated with the effects of brain dysfunction. Comparison of attention and working memory using the PASAT test and fMRI within the same individual has been shown to be valuable in grading response to drug therapy or in following the natural recovery of cognitive function in individuals with deficits. The test consists of a taped sequence of numbers. The subject's task is one of serial addition in 4 conditions of increasing complexity.

3. Rey-Osterrieth Complex Figure (Mitrushina, Boone, D'Elia, 1999) consists of a complex two-dimensional line drawing. The subject's task is to copy the design with pencil on paper. The Rey-Osterrieth assesses visuo-perceptual skills, spatial organizational skills and memory. It has frequently been found to be sensitive to nondominant hemispheric functioning and right temporoparietal area integrity in particular.
4. Symptom Checklist 90: This is a standardized instrument used to measure subjective, feeling states. It gives subscales on several dimensions.
5. Subject Beliefs on Condition Assignment: All subjects will be asked to indicate whether they believe they have received MDMA or placebo during the experimental sessions.

Table 3: Assessment Timetable

	Pre-Study	Baseline Evaluation	Session 1	Post session (4-Day) Follow-up	Session 2	Post session (4-Day) Follow-up	3-Month Follow-up
Inclusion / Exclusion	X						
Informed consent	X						
SCID	X						
Physical Exam & Medical History	X					X	
B-HCG	X		X		X		
EKG	X						
Metabolic Profile, HIV Thyroid Panel	X					X (metabolic only)	
Electrolytes	X		X			X	
Liver Enzymes	X					X	
Urine Drug Screen	X		X		X		
Vital Signs	X		X		X		X
Neuropsych. Evaluation		X					X
CAPS-1		X					
CAPS-2				X		X	X
IES		X		X		X	X
SCL-90		X		X		X	X

Psychological measures to be used on the day of the experimental (MDMA or placebo) session:

Subjective Units of Distress (SUD): Will be administered immediately before the MDMA or placebo is administered and every 60-90 minutes during the session. The exact timing will be at the discretion of the therapists so that testing will not interfere unnecessarily with the therapeutic process.

Dosing Plan: (See table 4)

A dose of 125 mg MDMA has been selected for use in this study on the basis of prior reports of therapeutic effectiveness and tolerability. Patient testimonials of the effectiveness of MDMA-assisted psychotherapy conducted prior to the scheduling of MDMA indicate that 125 mg MDMA is an appropriate dose for psychotherapeutic treatment. Doses equal to or greater than 125 mg have been well-tolerated in previous studies wherein MDMA was administered to humans (Cami et al, 2000; Grob et al, In preparation; Mas et al, 1999). Some prior clinical trials have employed dosing on an mg/kg basis, while others have used fixed amounts. With mg/kg dosing, milligram dosage can vary widely (see Appendix B). The use of a standard dosage of 125 mg was chosen in an effort to optimize the therapeutic dose while assuring safety.

The MDMA will be weighed into 125 mg doses and placed in gelatin capsules by a research pharmacist at the Medical University of South Carolina licensed to handle Schedule I compounds. The pharmacist will also place lactose into gelatin capsules of identical appearance.

Drug treatment will be randomly assigned to each subject, with therapists and subjects blind to treatment condition. Twelve subjects will be assigned to the MDMA condition and eight subjects will serve as controls.

See table 4, “Timing of Visits” and table 5 “Study Timetable Within-Session Evaluation” for a summary of what follows.

Following the initial screening and the baseline data visits, all subjects will receive two ninety-minute introductory sessions with the therapists. There will then be two individual drug treatment sessions conducted 3-5 weeks apart, each lasting approximately six to eight hours depending upon the subject’s response.

A total of 11 sixty to ninety minute preliminary and follow-up therapy sessions will occur in the following schedule:

- 1) Two introductory sessions, ninety minutes each, will occur within the two weeks preceding the first drug treatment session. Informed consent will be obtained at this time.
- 2) First treatment session: One hour before the beginning of the treatment session, a urine specimen will be collected for a drug screen and, for females, a pregnancy test. These results must be negative for the subject to receive the treatment (MDMA or placebo) and to continue in the study. After the patient has acclimated to the environment and reviewed their intentions with the therapists the SUD will be administered. The patient will then receive either 125 mg of MDMA or placebo p.o. Therapists and subjects will be blind to treatment condition. The therapists will stay with the subjects during the entire period of the experience until the patient reaches a satisfactory point of resolution and initial integration of the experience. Blood pressure, heart rate and temperature will be measured at regular intervals for subjects in both groups throughout the test session.

The SUD will be repeated at 60-90 minute intervals and at the conclusion of the session. Serum electrolytes will be measured at the conclusion of session 1 (see table 3 and “Nature of Treatment Sessions” below).

3) There will be a ninety-minute follow-up session with the therapists on the day following the first treatment session and 3 or 4 sixty to ninety-minute additional sessions, at approximately weekly intervals between the first and the second treatment sessions. (Whether there are 3 or 4 therapy sessions will depend on the length of time between MDMA or placebo sessions. A clinical judgment will be made as to whether the second MDMA or placebo session should occur 3 or 4 weeks after the first).

4) Psychological measures will be performed 4 days after the MDMA or placebo session.

5) Second treatment session: 3-5 weeks after the first drug session, the subject will again be administered placebo or 125 mg of MDMA p.o. One hour before the beginning of the treatment session, a urine specimen will be collected for a drug screen and, for females, a pregnancy test. These results must be negative for the subject to receive the treatment and to continue in the study. The therapists will again stay with the subjects during the entire period of the experience and until the patient reaches a satisfactory point of resolution with initial integration of the experience. Monitoring of BP, pulse, temperature and SUDS will be the same as in session 1. Serum electrolytes will not be measured if they were normal at the conclusion of session 1.

6) There will be a ninety-minute follow-up session with the therapists on the day following the second treatment session and 3 additional sessions at approximately weekly intervals. There will be two additional sixty to ninety-minute follow-up therapy sessions at 3 months following the first MDMA or placebo session.

7) Psychological measures will be performed 4 days after the second MDMA or placebo session (See table 4). Serum liver enzymes and metabolic profile will be drawn during that visit, and serum electrolytes will be measured if necessary.

8) Three months after the first treatment session (approximately 2 months after the second MDMA or placebo session), an independent rater will assess the response to treatment using the instruments indicated below in table 4. Neuropsychological measures will also be repeated at this time. ■

Table 4 Timing of Visits

Time: d=days w=week m=month	- 14 d	0	+ 1- 7 d	+ 7- 13 d	+ 2 w (s. 1)	+ 2 w, 1 d	+ 2 w, 4 d	+ 3 w	+ 4 w	+ 5 w	+ 6 w (s. 2)	+ 6 w, 1 d	+ 6 w, 4 d	+ 7 w	+ 8 w	+ 9 w	+ 3 1/ 2 m
Pre-Study Eval	X																
Baseline Eval.		X															
Psycho Therapy			X	X		X		X	X	X		X		X	X	X	X
MDMA Session					X						X						
Psycho Logical Measure		X					X						X				X
Neuro Psych. Measure		X															X
Metabolic profile	X												X				
Electro-Lytes	X				X								X				
Liver FCT	X												X				
Drug Screen & B-HCG	X				X						X						
Medical exam	X												X				
Time from First MDMA session					0	1 d	4 d	1 w	2 w	3 w	4 w	4 w 1 d	4 w 4 d	5 w	6 w	7 w	+ 3 m

Nature of the treatment sessions: (See Appendix A. for additional details and table 5 for summary)

The two 90 minute introductory sessions with the therapists will be used to facilitate the therapeutic alliance, identify the subject's significant issues and concerns, prepare for the nature of the drug sessions, and set goals for the treatment.

The experimental treatment sessions themselves will be supervised and facilitated by the male investigator/psychiatrist (M.C.M.) accompanied by an experienced female registered nurse (A.T.M.). Both therapists will be present throughout the sessions. The sessions will be conducted following the principles developed by Stanislav Grof, MD for LSD psychotherapy (Grof, 1980, pp. 123-147) and for Holotropic Breathwork (Grof, 2000: pp. 178-183) and adapted for MDMA-assisted psychotherapy by Metzner and by

Greer and Tolbert (Metzner 1988; Greer & Tolbert 1998). (see Appendix A). Both therapists have been trained and certified in Holotropic Breathwork facilitation by Grof, and have years of experience working therapeutically with this model in non-drug Holotropic Breathwork sessions. M.C.M also has extensive experience treating PTSD in his psychiatric practice using both medications and psychotherapy. The treatment protocols will be exactly the same for each experimental session.

All treatment sessions will begin at 10:00 am and will take place at the Medical University of South Carolina General Clinical Research Center (see Appendix D). The furnishings of the room will be arranged to create as comfortable and welcoming a setting as possible. The ambient temperature will be kept comfortably cool to decrease the likelihood of hyperthermia. Subjects will have had nothing by mouth except clear alcohol-free liquids since 12 AM the evening before. They will be asked to arrive at 9:00 AM for collection of a urine specimen for drug screening and, for females, a pregnancy test. These results must be negative for the subject to continue in the study. At the beginning of the session, the therapists will discuss with the subject his or her intentions for the session, including intentions regarding working with psychological issues related to their PTSD. The SUD will be measured just prior to the administration of placebo or MDMA. After the session begins, subjects will recline in a comfortable position with eyes closed or wearing blindfolds if preferred. They will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material. (Bonny and Savary 1990; Grof 2000: pp.186-191; Grof 1980; Unkefer 1990). After the first hour, if the subject has not spoken spontaneously, the therapists will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapists will engage with the subject to support and encourage emotional processing and resolution of whatever psychological material is emerging. The therapists will also encourage periods of time in which the subject remains silent with eyes closed and with attention focused inward in order to allow for the further unfolding of the inner experience. Electrolyte containing fluids will be available ad lib throughout the session within the limits described under "monitoring for toxicity." Food will be available during the latter part of the session.

Blood pressure and pulse will be measured at the outset and then once every 15 minutes for 3 hours, and then every 30 minutes for 3 more hours. Temperature will be measured at the outset and then hourly for 6 hours. If at any time the blood pressure exceeds 180 systolic or 110 diastolic or the pulse exceeds 130, measurements will then be taken every 5 minutes until the values fall below these levels. The physician may also call for more frequent measurements of pulse, blood pressure or temperature in the event of clinically significant changes in any of the measurements or any other clinical signs of hypertension, cardiovascular problems or hyperthermia. The SUD will be repeated at 60-90 minute intervals. The exact timing will be at the discretion of the therapists so that testing will not interfere unnecessarily with the therapeutic process.

All treatment sessions will be audiotaped in their entirety. Sessions will last from six to eight hours, depending on when the subject feels that he or she has arrived at a point of

completeness with the process and on the therapists' determination of the mental and physical state of the subject. Rides home will be pre-arranged so that subjects will not have to drive after the sessions. One of the investigator psychiatrists will be on call 24-hours a day, seven days a week to handle any concerns or emergencies related to the protocol.

Table 5 Study Timetable Within-Session Evaluation

TIME	
9:00 AM	Urine drug screen and pregnancy test, Patient acclimated to environment
9:45 AM	Baseline BP, Pulse, Temp, Subjective Units of Distress Rating (SUDS)
9:55 AM	2 nd Baseline BP, Pulse, SUDS
10:00 AM	Drug Administration
10:15 AM	BP, Pulse
10:30 AM	BP, Pulse.
10:45 AM	BP, Pulse
11:00 AM	BP, Pulse, Temp, SUDS
11:15 AM	BP, Pulse
11:30 AM	BP, Pulse
11:45 AM	BP, Pulse
12:00 Noon	BP, Pulse, Temp
12:15 PM	BP, Pulse
12:30 PM	BP, Pulse, SUDS
12:45 PM	BP, Pulse
1:00 PM	BP, Pulse, Temp
<i>Every half-hour, and as needed</i>	BP, Pulse, Temp
<i>Every 60-90 minutes</i>	SUD

Nature of follow-up therapeutic sessions:

During the 90-minute follow-up sessions, the subjects will be encouraged to describe their experiences during the experimental sessions and to express freely any thoughts, feelings, questions or concerns they have. Subjects will also be asked to indicate whether they believe they received MDMA or placebo at each follow-up session. The primary purpose of these sessions will be to support the subject in further processing, understanding and integrating the experience. It will also be an opportunity for the

therapists to gather information, in an unstructured format, about the effects of MDMA or placebo and to evaluate whether the blind was maintained for subjects in either condition.

Methods of Evaluating Efficacy and Monitoring for Toxicity::

Research follow-ups:

The follow-up will begin 4 days after the first experimental (MDMA or placebo) treatment session. There will be a total of three research follow-up interviews. The first two will be done 4 days after the first and second experimental sessions respectively. A research follow-up will also be done at 2 months after the second experimental session. During these follow-up visits the CAPS-2, IES and SCL-90 will be administered as outcome measures to be compared with baseline scores. The research and treatment intervention aspects of this project will be kept as separate and distinct as possible. The research assistants obtaining the follow-up information will not be involved in monitoring patients during the medication portion of the protocol. They will, therefore, be naïve to complaints of medication side effects.

Monitoring for Toxicity

There is now a considerable body of information indicating that the likelihood of significant toxicity from this dose of MDMA used in this kind of setting is very low. The three FDA-approved Phase I studies in this country have failed to demonstrate toxicity (Grob et al. 1996; Lester et al. 2000; Tancer, personal communication). Doses of up to 2.5 mg/kg were employed in one of these three studies, with eight subjects receiving doses equal to or exceeding the 125 mg. The same is true for studies that have been conducted in Switzerland and for ongoing studies that are being conducted there and in Spain (Vollenweider et al. 1998a; de la Torre et al. 2000b; Liechti et al. 2001a). Likewise, psychiatrists in the US and Europe used MDMA safely in a large number of patients before it became illegal (Greer and Tolbert 1986; Downing 1986; Gasser 1994).

In spite of this reassuring data, we intend to monitor closely for the unlikely possibility of an untoward reaction. A physician will be in attendance throughout each MDMA treatment session. The sessions will be conducted in a general medical setting where a crash cart and other emergency equipment will be immediately available, experienced nurses will be on hand and there will be ready access to specialty medical back up and intensive care beds if necessary. Blood pressure and pulse will be measured at the outset and then once every 15 minutes for 3 hours, and every 30 minutes for 3 more hours. Temperature will be measured at the outset and hourly for 6 hours. The physician may also call for more frequent measurements of pulse, blood pressure, or temperature in the event of clinically significant changes in any of the measurements or any other clinical signs of hypertension, cardiovascular problems or hyperthermia. After approximately eight hours, if all medical parameters are acceptable and the patient is alert, ambulatory and emotionally stable, the session will be ended. The patient will be given Dr. Mithoefer's pager number to call immediately if any problems occur. He or she will then be allowed to leave via a previously arranged ride from a friend or family member. We

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

Hypertension and related cardiovascular complications:

Blood pressure and pulse will be measured at the outset of each treatment session, then once every 15 minutes for the first 3 hours, and then every 30 minutes for the next 3 hours. If at any time the blood pressure exceeds 180 systolic or 110 diastolic or the pulse exceeds 130, measurements will then be taken every 5 minutes until the values fall below these levels. During this time the physician/therapist will continually evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. The physician/therapist will make a clinical judgement about whether additional monitoring or treatment is required. Reasons for moving a patient to the ICU would include, but not be limited to, severe headache in the setting of hypertension, angina or neurologic deficits regardless of blood pressure. A crash cart will be immediately available and will contain nitroprusside in addition to the usual resuscitation drugs and equipment. This will allow treatment to be instituted without transferring the patient if that should become necessary. The physician/therapist may, at any time, make a clinical judgment to transfer the patient to the ICU for closer monitoring and additional treatment.

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

Psychological Toxicity

During the preparatory sessions, patients will be made aware of the fact that difficult emotions, including grief, rage and fear or panic, may arise during the MDMA sessions. They will be told that such symptoms will not be treated pharmacologically during the sessions because they present an opportunity to therapeutically address the symptoms and underlying causes of PTSD. Using the methods described in Appendix A, every effort will be made to help patients move through difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the session. In the event that a patient is experiencing severe emotional distress, such as panic attacks, severe generalized anxiety or insomnia, following an MDMA session then the physician-investigator may prescribe a benzodiazepine or zolpidem as an “rescue medication”.

Hyperthermia:

Temperature will be taken as above. If the temperature rises more than 1° C attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the patient. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, a cooling blanket will then be used, blood will be drawn for

stat CBC, electrolytes, BUN, creatinine, glucose, CPK, PT, PTT, platelets, liver enzymes and urine will be collected for urinalysis. If there are significant abnormalities in these tests, if the temperature continues to rise, or if an elevated temperature is associated with delirium, or muscle rigidity the patient will then be transferred to the ICU.

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

Dehydration:

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

Hyponatremia

Patients will be given electrolyte solutions such as Gatoraid instead of water in order to decrease the likelihood of dilutional hyponatremia. They will not be allowed to drink more than 3 L. of fluids, and fluid intake will be spread out appropriately during the session. If there are any signs or symptoms of hyponatremia such as confusion, vomiting, myoclonus or ataxia, a stat serum sodium will be drawn and fluids will be withheld until the results are obtained. If the serum sodium is less than 125mEq/L, serum and urine osmolality and sodium will be measured, and the patient will be admitted to the medical ward for further monitoring and for water restriction and possibly hypertonic saline and furosemide administration if the symptoms are severe. Even in the absence of symptoms, as a precaution, serum electrolytes will be measured at the conclusion of the first MDMA session.

Liver toxicity:

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

Neuropsychological toxicity:

Psychological and neurological status will be clinically monitored by the therapists during the MDMA sessions and during therapy sessions at frequent intervals thereafter. Formal neuropsychological testing will not be done between sessions, but any patient who, on clinical examination during that period, is found

to have cognitive deficits which persist for more than two weeks will not be given a second MDMA session. Any patient who develops mania or psychosis will not be given a second MDMA session and will receive appropriate psychiatric treatment. Neuropsychological effects will be formally measured by repeating neuropsychological testing 2 months after the final MDMA session using the RBANS, PASAT and Rey-Osterrieth Complex Figure tests.

Chemistry, Manufacturing and Control Information

Complete details on the chemistry, manufacturing and control of the MDMA HCl to be used are described in Drug Master file # 6293. As described in that file, MDMA was prepared for human consumption by David Nichols, Ph.D., Dept. of Medicinal Chemistry and Pharmacology, Purdue University. The identity and purity of this MDMA was confirmed using HPLC in 1997 as described in DMF # 6293 and was found to be 99.87% pure. There was no evidence of deterioration at that time, 11 years following original synthesis in 1986.

MDMA is a Schedule I compound and will be stored and handled in compliance with relevant Federal, State and University regulations.

MDMA will be weighed into 125 mg doses (calculated as the weight of the hydrochloride salt) and placed in gelatin capsules by a pharmacist at The Medical University of South Carolina who is licensed to handle Schedule I compounds.

Lactose will be used as a placebo, and will be prepared in gelatin capsules identical in appearance to the capsules containing MDMA. Placebo capsules will be prepared by a pharmacist at the Medical University of South Carolina.

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

Pharmacology And Toxicology

Primary Pharmacodynamics

Mechanisms of Action

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

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

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

Direct MDMA stimulation of postsynaptic α -2 adrenoceptors may modify this state by altering the balance of α -1 and α -2 stimulation, allowing the individual to remain emotionally calm

despite noradrenergic activation. MDMA is an α -2 agonist (Lavelle et al. 1999). Like other α -2 agonists, such as guanfacine and clonidine (Arnsten 1998), MDMA produces feelings of calmness and relaxation (Cami et al. 2000). It is worth noting that open label trials suggest that clonidine may be helpful for treating symptoms of PTSD (Harmon and Riggs 1996; Kinzie and Leung 1989).

Drug Activity Related to Proposed Indication

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive psychotherapy. In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection (Greer and Tolbert 1998; Grinspoon and Bakalar 1986). Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion (Cami et al. 2000; Liechti et al. 2000a; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Vollenweider et al. 1998). These effects make it likely that MDMA would be useful in psychotherapeutic treatment of many different complaints.

The subject population of chronic PTSD patients was selected because of patient testimonials concerning the effectiveness of MDMA-assisted therapy and because the effects of MDMA have the potential to be particularly useful in the treatment of this disorder. PTSD is a condition that involves prominent fear responses. Revisiting traumatic experiences in psychotherapy is recognized to be of therapeutic value, and early clinical experience with MDMA is consistent with the hypothesis that it can increase therapeutic effectiveness in this population. Downing (1985) testified that MDMA was very helpful in treating a woman who experienced incapacitating panic attacks after sexual assault. Anecdotal reports have been published of improvement in PTSD among people who took MDMA in therapeutic or quasi-therapeutic settings (Adamson 1985). These reports are consistent with the observations of other therapists that MDMA-assisted psychotherapy is particularly useful in patients with a history of child abuse or sexual assault (Greer 1985). Preliminary results were encouraging in a pilot study of MDMA treatment for 20 soldiers with combat-related PTSD, but political instability in Nicaragua prevented further research (Doblin 1995). In 2000, a currently ongoing MDMA/PTSD therapy study was approved in Spain (AEM #99-309).

PTSD causes a great deal of suffering, impairing work productivity, relationships, and overall health. PTSD is also a disorder for which there is, to date, only one FDA-approved medication with efficacy only reported in one gender (women). There are still many unanswered questions regarding this pharmacological intervention. (Montgomery and Beck 1999). The lifetime prevalence of PTSD in the general population may be as high as 10% (Meltzer-Brody et al. 2000), so the search for additional and more effective treatments is extremely important. The terrible burden that PTSD places on patients, lack of effective treatments, and high prevalence of PTSD lend the proposed research considerable importance.

Secondary Pharmacodynamics

The psychotherapeutic effects of MDMA are accompanied by dose-dependent physiological effects including vasoconstriction and increased heart rate and blood pressure. These acute effects of MDMA are well documented in the dose-response safety study described in Previous Human Experience and in placebo-controlled double-blind studies published in peer-reviewed journals (de la Torre et al. 2000a; de la Torre et al. 2000b; Gamma et al. 2000; Grob et al. 1996; Lester et al. 2000; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Mas et al. 1999; Vollenweider et al. 1998). Physiological effects of MDMA reach their maximum within 1 and 2 hrs after oral MDMA administration and have largely subsided within 6 hrs of drug administration. Available data on maximum changes in heart rate and blood pressure are summarized in Table 3.1 in the Investigators' Brochure. In the currently proposed study, the effects of 125 mg MDMA are not expected to increase heart rate above 100 BPM and blood pressure above 170/100 mmHg. As described elsewhere, blood pressure and heart rate of volunteers will be monitored at regular intervals and appropriate action will be taken if clinically significant changes occur.

MDMA dose-dependently and acutely increases cortisol, prolactin, and adrenocorticotrophic hormone concentrations (Grob et al. 1996; Grob et al. In preparation; Mas et al. 1999), while growth hormone is unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peak at about 2 hours after MDMA administration. 40 mg MDMA was found to acutely increase circulating levels of antidiuretic hormone (arginine vasopressin) in 8 male volunteers (Henry et al. 1998). Antidiuretic hormone reached maximum between 1 to 2 hrs after MDMA administration. Increased retention of fluid is unlikely to be of any consequences in a clinical setting. Nonetheless, precautions will be taken to avoid dilutional hyponatremia.

Studies conducted in Spain suggest that MDMA acutely affects the immune system (Pacifci et al. 2000; Pacifci et al. 1999; Pacifci et al. 2001). These acute changes in immunologic function include reduced CD4 T-cell count, increased NK cell count, and decreased phytohaemoagglutinin A-induced lymphocyte proliferation. Generally, MDMA appears to decrease the concentration of Th1 cytokines and increase the amount of Th2 cytokines measured in blood. These acute changes are unlikely to be of consequence in healthy individuals and are of a similar magnitude to changes produced by other pharmacological agents. For example, the CD4 T-cell count decrease was similar in magnitude to that produced by 0.8 g/kg oral ethanol (the equivalent of 4-5 drinks) in the same report (Pacifci et al. 2001). The mechanism of this MDMA-induced immunomodulation is unclear but may involve MDMA-induced glucocorticoid release or sympathomimetic activity. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 2000a; Connor et al. 2000b; Connor et al. 1998). This immunomodulation is an acute effect of MDMA and is not likely to persist for more than 48 hours after MDMA administration.

Safety Pharmacology

Neurological Effects

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

MDMA appears to produce modest acute changes in neurocognitive performance during peak drug effects. The acute effects of MDMA, generally at doses of either 125 mg or 1.7 mg/kg, have been assessed using the digit symbol substitution task (Cami et al. 2000), a simple reaction time task (Cami et al. 2000), a continuous performance attention task (Gamma et al. 2000), the Stroop task (Vollenweider et al. 1998), and a prepulse inhibition measure of sensorimotor gating (Liechti et al. 2001b; Vollenweider et al. 1999b). Of these tasks, only the digit symbol substitution task and the prepulse inhibition task have detected MDMA-induced performance alterations.

Participation in clinical MDMA studies has not been associated with chronic alterations in neurocognitive performance. Data collected by Grob and associates (described in Previous Human Experience) and by Vollenweider and colleagues (Vollenweider et al, 2001, Vollenweider, attached letter of support) indicate that performance on tests of neurocognitive function is not altered after receiving one or two doses of MDMA in a clinical setting. In contrast, studies of illicit ecstasy users have suggested that repeated MDMA use may be associated with lowered neurocognitive performance. This has not been consistently found in studies and it appears that these changes are only associated with some conditions of use. In a retrospective study that did find some impairment in very high dose recreational users of ecstasy, there was no effect seen among those who had taken up to an estimated 440 mg of "ecstasy" per month for a year or longer and had used it a minimum of 25 times (unpublished table from published study, Bolla et al. 1998a). Similarly, a yet unpublished study failed to find decreased memory in ecstasy users reporting a lifetime dose of 20 to 40 tablets, with decreased memory function only appearing in ecstasy users reporting a lifetime dose of 80 or more tablets (Gouzoulis-Mayfrank, data presented at the 2001 National Institute on Drug Abuse MDMA Conference and described in attached letter of support).

Clinical studies have investigated the effects of MDMA on cerebral blood flow. MDMA acutely alters regional cerebral blood flow (rCBF) and may decrease rCBF for several weeks after drug exposure. Gamma et al. (2000a) used [$H_2^{15}O$]-Positron Emission Tomography (PET) to measure rCBF at 75 min after 1.7 mg/kg MDMA in 16 volunteers. They detected increases in prefrontal, inferior temporal, and cerebellar cortex rCBF. Decreased rCBF was detected in limbic, paralimbic, central frontal, and temporal areas. These acute effects of MDMA on rCBF may be followed by decreases in rCBF (Chang et al. 2000), as found in a study where SPECT was performed upon eight volunteers 10 to 21 days after receiving the second of two doses of MDMA administered in a clinical

setting. These decreases appeared to be time-limited. Two additional volunteers assessed at 41 and 80 days after last MDMA exposure did not show decreases. Similarly, Gamma et al. did not detect differences in cerebral blood flow between ecstasy users and nonusers during a vigilance task (Gamma et al. 2001). Finally, in the study of acute changes in rCBF (Gamma et al. 2000), the eight volunteers who received 1.7 mg/kg MDMA in their first session did not have altered cerebral blood flow in their second session, which was conducted at least two weeks later (Dr. Alex Gamma, personal communication).

Cardiovascular Effects

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

Abuse Liability

MDMA is classified as a Schedule I compound with a high potential for abuse, primarily because of its use in settings such as “rave” dance parties. Whether or not MDMA’s abuse potential will negatively affect PTSD patients exposed to MDMA in a therapeutic context is an open question for which there is no direct data. However, instead of experiencing euphoria, PTSD patients undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions and memories related to the original traumatic incident. As a result, it seems unlikely that PTSD patients undergoing this emotionally challenging psychotherapy will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings.

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

There is known to be significant comorbidity for substance abuse among patients with PTSD, though specific data on the relationship between MDMA use and PTSD have not been reported. Currently, there is no definite evidence concerning the casual relations between the two disorders, and it is unclear whether posttraumatic stress disorder precipitates substance abuse or whether people with pre-existing substance abuse are at greater risk for PTSD. Currently, the most commonly accepted hypothesis for the

relationship between PTSD and substance abuse is that of self-medication (Meisler, 1996). Since individuals undergoing the proposed treatment will be encouraged to confront the traumatic events during MDMA-assisted therapy rather than defending against them or avoiding them, it seems likely that these individuals will subsequently be less inclined to choose to self-medicate through the self-administration of MDMA. If our hypothesis is correct that MDMA assisted psychotherapy will alleviate symptoms of PTSD, it is possible that subjects will be at reduced risk for substance abuse in general following MDMA treatment because they will have a reduced motivation to self medicate.

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

Pharmacokinetics/Toxicokinetics

Summary of Pharmacokinetic Parameters

MDMA Dose	N	C _{max} μg/l	T _{max} H	AUC ₀₋₂₄ μg*h/l	AUC/dose μg*h/(l*mg)	Reference
50	2	19.8 and 82.8	2 and 3	100.1 and 813.9	2 and 16.3	de la Torre et al. 2000a
75	8	130.9 ± 38.6	1.8 ± 0.38	1331.5 ± 646.03	17.8 ± 8 .6	Mas et al. 1999
100	8	222.5 ± 26.06	2.3 ± 1.1	2431.38 ± 766.52	30.5 ± 11.2	de la Torre et al. 2000b
125	8	236.4 ± 57.97	2.4 ± 0.98	2623.7 ± 572.9	21 ± 4.6	Mas et al. 1999
150	2	441.9 and 486.9	1.5 and 2	5132.8 and 5232	34.2 and 34.9	de la Torre et al. 2000a

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

The pharmacokinetics of MDMA, summarized above, have been primarily characterized by a group of Spanish researchers. Additional pharmacokinetic parameters for MDMA and metabolites are given in the papers cited in the table. For example, after 125 mg MDMA, total clearance for MDMA was 51.1 ± 14.1 per hr, while renal clearance was 13.0 ± 5.4 per hr (de la Torre et al. 2000a). The findings of Spanish researchers are consistent with other investigations using limited doses (Fallon et al. 1999; Hensley and Cody 1999) or illicit users (Crifasi and Long 1996; Moore et al. 1996; Ramcharan et al. 1998).

As can be seen above, MDMA kinetics are dose dependent within the range of commonly administered doses (de la Torre et al. 2000b). These dose-dependent kinetics appear to be due to dose-dependent metabolism rather than changes in absorption or excretion. Mas et al. (1999) reported that 75 mg and 125 mg doses of MDMA had similar

absorption constants and absorption half-lives. On the other hand, non-renal clearance for 125 mg MDMA was approximately half that of 75 mg MDMA. The dose-dependent metabolism of MDMA is at least partially due to inhibition of CYP2D6, as discussed below. It has also been established that the fraction of MDMA bound to dog plasma proteins is approximately 0.4 and is concentration-independent over a wide range of concentrations (Garrett et al. 1991). Therefore, changes in plasma partitioning are not likely to be significant.

Absorption/Distribution/Metabolism/Excretion

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

The oxidation of the methylenedioxy group can take place via enzymes such as cytochrome p450 (Hiramatsu et al. 1990; Kumagai et al. 1991; Lim and Foltz 1988; Tucker et al. 1994) or by a nonenzymatic process involving the hydroxyl radical (Lin et al. 1992). The enzymes catalyzing this reaction have been examined in the rabbit (Kumagai et al. 1991), rat (Gollamudi et al. 1989; Hiramatsu and Cho 1990; Hiramatsu et al. 1990; Hiratsuka et al. 1995) and human (Kreth et al. 2000; Lin et al. 1997; Maurer et al. 2000; Tucker et al. 1994; Wu et al. 1997). In human liver microsomes, Michaelis-Menten kinetics for formation of dihydroxylated metabolites are biphasic (Kreth et al. 2000). The low K_m component for demethylenation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher K_m also contribute to MDMA demethylenation, including CYP1A2 and CYP3A4.

Although it was hypothesized that genetic variations in CYP2D6 activity might influence risk of MDMA toxicity, this is no longer a concern. Several *in vitro* studies have shown that MDMA is not just a substrate for CYP2D6 but also binds to it, forming an inhibitory complex (Brady et al. 1986; Delaforge et al. 1999; Wu et al. 1997). Compelling *in vivo* evidence of enzyme inhibition was provided by de la Torre et al. (de la Torre et al. 2000a) who showed that plasma levels and 24-hour urinary recovery of HMMA are dose-independent. This is likely the result of inhibition of CYP2D6-mediated DHMA formation. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant. In fact, there currently seems to be no evidence that the poor metabolizer genotype is by itself a major risk factor for acute MDMA toxicity. Kreth et al. (2000) reported that the poor metabolizer trait did not lead to significant alteration in maximal drug plasma concentrations in an individual participating in a clinical study of the MDMA analogue, MDE. This provides further

evidence that the role of CYP2D6 in MDMA metabolism is sufficiently limited that it is not a major risk factor in healthy individuals in a clinical setting.

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

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

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

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

The urinary excretion of MDMA and its metabolites has been characterized by de la Torre and colleagues and is summarized in the table above. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

Toxicology

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

Serious MDMA toxicity is rare in uncontrolled settings, considering the millions of users taking “ecstasy” of unknown identity, potency, and purity. Under these conditions, the most common serious adverse event involves hyperthermia, which often appears to be influenced by prolonged physical exertion (dancing) and other unsafe conditions of use. Reports of toxicity in illicit ecstasy users are summarized in the Investigator’s Brochure. In addition to hyperthermic syndromes, other rare adverse events include dysphoric responses, hyponatremia, and hepatotoxicity. In the proposed clinical study, volunteers will be carefully monitored for signs and symptoms of these unlikely events, as discussed in the section on Monitoring for Toxicity. As described in Previous Human Experience, exposure to MDMA in a controlled clinical setting has not been associated with toxicity. As previously noted in the rationale section, the ongoing neurotoxicity of untreated PTSD is an important factor to weigh against any concerns regarding toxicity from MDMA exposure.

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

Hepatotoxicity

Because hepatotoxicity has been noted in ecstasy users, three *in vitro* studies have examined the hepatotoxicity of MDMA. These studies show that MDMA can impair liver cell viability, but that this is very unlikely to occur in the proposed clinical study. The peak liver exposure to MDMA in the proposed clinical study should be approximately one-eleventh the concentration shown to impair cell viability in these *in vitro* studies.

In one study, MDMA caused increases in ALT, AST, and LDH activities in rat hepatocytes (Beitia et al. 2000). These increases were statistically significant with high concentrations of MDMA (1 mM for six hours) or lower concentrations for prolonged exposures (0.1 mM for 24 hours). Further evidence of MDMA-induced toxicity to hepatocytes came from moderate decreases in ATP (after three, but not one, hour incubation with 0.1 mM MDMA). A second *in vitro* study examined the possible pro-fibrogenic effects of MDMA on the liver by measuring expression of procollagen mRNA in a cell line of hepatic stellate cells (Varela-Rey et al. 1999). These cells produce the

collagen characteristics of a fibrotic liver. Expression of $\alpha 1(I)$ procollagen mRNA was significantly increased by 0.5, but not 0.1, mM MDMA for 24 hr. This effect required sustained exposures, as 1 mM MDMA for 8 hr did not increase mRNA expression. A third *in vitro* study using mice hepatocytes showed that MDMA increases the lipid peroxidation and loss of cell viability produced by hyperthermic conditions (Carvalho et al. 2001). 1.6 mM MDMA slightly but significantly decreased cell viability but did not affect lipid peroxidation over 60 to 180 min under normothermic (37° C) conditions. When temperature was raised to 41° C, the hepatotoxicity of MDMA was dramatically increased. At this temperature, 1.6 mM MDMA approximately doubled lipid peroxidation after 180 min and decreased cell viability after as little as 60 minutes. A lower concentration, 0.8 mM MDMA, also decreased cell viability after 180 min at 41° C but not at 37° C.

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

Neurotoxicity

Extensive studies in animals indicate that high or repeated dose MDMA exposure can oxidatively damage serotonergic axons originating in the dorsal raphe nucleus of the brainstem. This is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter. Although some regrowth occurs, seemingly permanent redistribution of axons was noted in a study with squirrel monkeys (Hatzidimitriou et al. 1999). These serotonergic changes have not been associated with lasting behavioral impairment in the vast majority of animal studies, despite dramatic serotonin depletions.

We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity in previous clinical MDMA studies. Moreover, a series of letters in the journal *Neuropsychopharmacology*

discussed the risks of neurotoxicity in MDMA studies (Gijsman et al. 1999; Lieberman and Aghajanian 1999; McCann and Ricaurte 2001; Vollenweider et al. 1999a; Vollenweider et al. 2001), leading two of the journal editors to conclude that there is no evidence that the MDMA exposures in the studies of Vollenweider and colleagues (similar to those currently proposed) were neurotoxic (Aghajanian and Lieberman 2001).

Vollenweider and colleagues recently measured serotonin transporter density using positron emission tomography (PET) with [¹¹C]McN5652 before and after a single clinical MDMA exposure. This research was presented at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine, and is described in the attached letter of support. Vollenweider and colleagues were unable to detect any lasting effect of 1.5 or 1.7 mg/kg MDMA in a pilot study with six MDMA-naive healthy volunteers and in a second study with additional volunteers (n = 8). This ligand and measurement technique had been previously reported by another group to be sensitive to apparent serotonin transporter changes in illicit ecstasy users with at least 70 drug exposures (McCann et al. 1998). This measurement technique was validated in a study using a baboon exposed to a neurotoxic MDMA regimen. The validation study found that, in most brain regions, PET tended to overestimate serotonin transporter changes (Scheffel et al. 1998). Given the small sample size in the study by Vollenweider et al., it is possible that a modest change in SERT density could have gone undetected. However, very little variance in ligand binding was found in baseline measures of ligand binding. The possibility of neurotoxicity will be discussed with all volunteers, even though strong evidence from studies in humans and non-human animals suggests that the risk of neurotoxicity posed by participating in this study is low.

Interspecies pharmacokinetic comparisons support the safety of 125 mg MDMA in humans. Vollenweider et al. (2001) compare published pharmacokinetic data for humans and rats and conclude that human exposure to MDMA after 125 mg is significantly less than the lowest known consistently neurotoxic MDMA dose in Sprague-Dawley rats, 20 mg/kg, sc, (Battaglia et al. 1988; Commins et al. 1987). At these doses, human MDMA plasma AUC are approximately 30% of the rat AUC. Similarly, human C_{max} are approximately 10% of rat C_{max}.

We note that this comparison is limited by several considerations. First, it is not known whether rats and humans have different vulnerability to the same MDMA exposure. Second, it is not known whether metabolites of MDMA contribute to neurotoxicity. If they do, then the margin of safety for 125 mg MDMA should be even wider because formation of metabolites is more extensive in rodents than in humans. Third, rats and humans may differ in the brain concentration of drug produced by a given blood concentration. In rats, MDMA concentrations in the brain are 7 to 10 times higher than in plasma (Chu et al. 1996). In a human fatality, postmortem MDMA concentrations were about 6 times higher in the brain than in the plasma (Rohrig and Prouty 1992), although postmortem drug redistribution may have occurred. If these data are reliable, rats may have similar peak brain levels to humans when plasma levels are the same. Fourth, neurotoxicity in rodents appears to be increased by hyperthermia in many studies. Finally, the threshold for neurotoxicity is not well established in rats. The threshold for

neurotoxicity in Sprague-Dawley rats appears to be above 10 mg/kg (Battaglia et al. 1988) and below 20 mg/kg (Commins et al. 1987). Therefore, a conservative comparison indicates that human MDMA exposure (measured as plasma AUC) after 125 mg is likely between 30% and 60% of the exposure required for neurotoxicity in rats. We think that the margin of safety is probably wider due to the presence of hyperthermia and increased formation of toxic metabolites in animal studies but not in clinical MDMA trials.

In conclusion, the lack of apparent toxicity in previous clinical MDMA studies, evidence of unaltered serotonin transporter density after similar doses, and toxicokinetic comparisons suggest that 125 mg MDMA is unlikely to lead to neurotoxicity in the proposed study.

MDMA-Induced Neuronal Apoptosis (Programmed Cell Death)

Two *in vitro* studies have suggested that MDMA may trigger programmed neuronal cell death (apoptosis) under certain conditions. This phenomenon has not been verified *in vivo*. No cell death occurs in regions containing the cell bodies of serotonergic neurons after MDMA exposure (Fischer et al. 1995; Hatzidimitriou et al. 1999; O'Hearn et al. 1988). However, one study detected evidence of non-serotonergic cell body damage in the rat somatosensory cortex after 80 mg/kg MDMA (Commins et al. 1987). It is theoretically possible that this damage was due to apoptosis. MDMA-induced apoptosis appears to require high concentrations and exposure times. It is unlikely that 125 mg MDMA in the currently proposed clinical study will trigger programmed cell death in neurons. In the currently proposed study, the peak brain concentration of MDMA is estimated to be approximately 6% of a concentration that produced no toxicity after 96 hr of exposure *in vitro*.

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

It is unlikely that MDMA exposures in the currently proposed clinical study will approach those demonstrated to trigger programmed cell death in neurons. If MDMA levels in the brain are about 6 times higher than in plasma (Rohrig and Prouty 1992), then 125 mg MDMA should produce peak plasma levels of $236.4 \pm 57.97 \mu\text{g/l}$ MDMA (de la

Torre et al. 2000b) and peak brain levels of 1.4 ± 0.3 mg/L. This estimated peak level is significantly less than the lowest drug concentration used in either apoptosis study. While 0.4 mM MDMA or 77.3 mg/L had modest effects in the first study, 125 μ M or 24.2 mg/L had no significant effect in the second study. Given these concentration differences and the long exposure times used in these studies, it does not seem likely that human oral doses of MDMA would be sufficient to induce programmed cell death in neurons.

Reproductive and Developmental Toxicity

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

Previous Human Experience

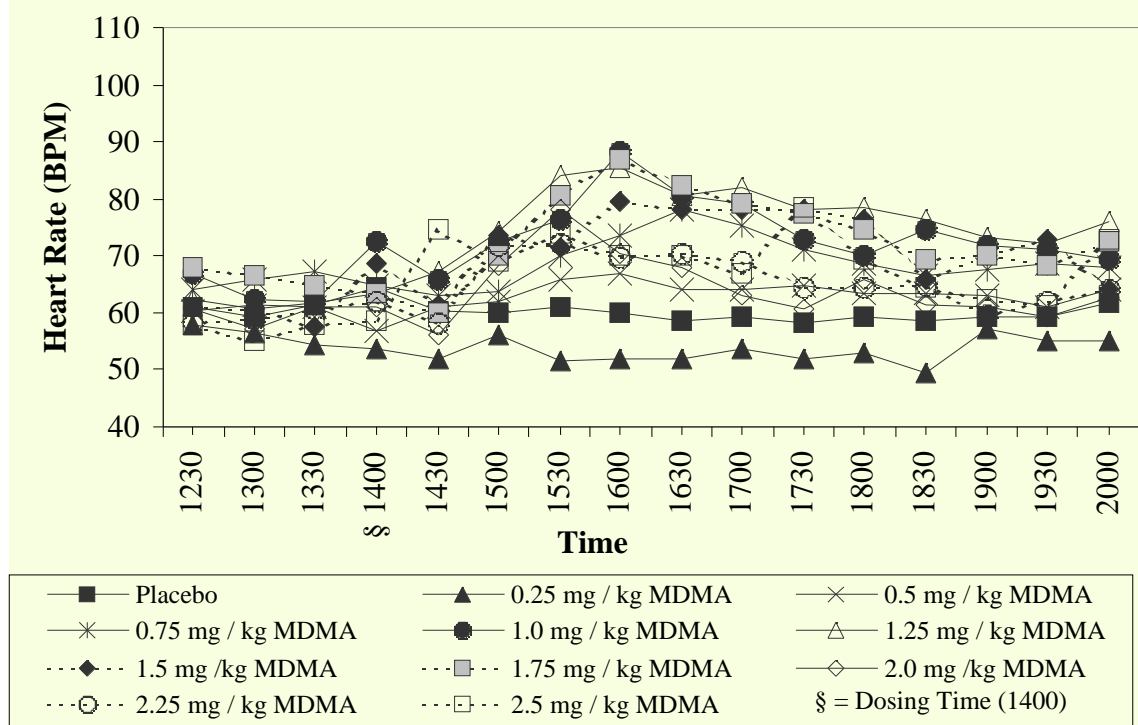
Clinical MDMA research using healthy volunteers has been conducted by at least five research groups, including three in the United States. Double-blind placebo-controlled MDMA studies that have been published in peer-reviewed journals include a review of the physiological and self-reported effects of up to 1.7 mg/kg MDMA in 74 volunteers (Liechti et al. 2001a), an 8-volunteer study of cardiovascular effects of 0.5 and 1.5 mg/kg MDMA (Lester et al. 2000), a 16-volunteer positron emission tomography study of the effects of 1.7 mg/kg MDMA on cerebral blood flow (Gamma et al. 2000), a 13-volunteer study of the physiological and self-reported effects of 1.7 mg/kg MDMA (Vollenweider et al. 1998), an 8-volunteer study of the pharmacokinetics and physiological and neuroendocrine effects of 75 and 125 mg MDMA (Mas et al. 1999), a 6-volunteer study of the acute immunomodulating effects of 100 mg MDMA alone and in combination with ethanol (Pacifici et al. 2001), an 8-volunteer study of the pharmacokinetics and neuroendocrine effects of 40 mg MDMA (Fallon et al. 1999; Henry et al. 1998), and a 6-volunteer study of the physiological and neuroendocrine effects of 0.25 to 1.0 mg/kg MDMA (Grob et al. 1996). This research is discussed in the Investigator's Brochure, which presents information drawn from unpublished research data as well as from all published research reports. Structured abstracts of each published study are available as an appendix in the back of that document.

In summary, researchers have measured the cardiovascular, physiological, neuroendocrine, cerebrofunctional, psychiatric, and subjective effects of MDMA at doses ranging from 0.25 to 2.5 mg/kg. MDMA has been generally well tolerated in these studies, and we are aware of no serious adverse events. Participants with and without previous experience with MDMA reported that the effects of MDMA were mostly pleasant and otherwise tolerable (Cami et al. 2000; Grob et al. 1996; Grob et al. In preparation; Vollenweider, 1998). Occasionally, dysphoric responses to MDMA have occurred, but have always resolved within several hours. Clinically significant hypertension has occurred in several volunteers; these cases are discussed below. Researchers have not detected any evidence that exposure to MDMA in a clinical context produces neurocognitive changes, serotonergic neurotoxicity, or any other lasting toxicity. As shown in Table 2.5 of the Investigator's Brochure, Grob et al. did not detect any change in neurocognitive function in their volunteers. Similarly, Vollenweider et al. (2001) report that retrospective analysis of their studies did not detect any lasting effect of MDMA on psychological and neuropsychological measures, cerebral blood flow ($H_2^{15}O$ -PET), and electrophysiological indices of information processing such as prepulse inhibition of the startle reflex (PPI) and brain wave activity (EEG/ERP). Most importantly, preliminary analysis using positron emission tomography (PET) and the radioligand McN-5256 revealed no significant changes in estimated serotonin transporter density four weeks after a single dose of MDMA (1.5–1.7 mg/kg) in MDMA-naive volunteers (Vollenweider et al. 2001). It is worth noting that MDMA was administered to hundreds of patients in the context of psychotherapy in the 1970s and 1980s (Greer and Tolbert 1998; Grinspoon and Bakalar 1986; Wolfson 1986) and more recently in Switzerland (Gasser 1994; Widmer 1997) without evidence of toxicity.

The remainder of this section will discuss the Phase I study conducted by Dr. Charles Grob and colleagues at the UCLA-Harbor Medical School with doses ranging from 0.25 mg/kg to 2.5 mg/kg. Eighteen healthy individuals (five females and 13 males) with histories of previous use of ecstasy received two doses of MDMA in a randomized, double blind placebo-controlled dose-response study. The doses administered to each volunteer differed by an increment of 0.25 mg/kg, with dosage in milligrams ranging from 16.6 mg to 204.8 mg. Eight out of 18 volunteers received at least one dose of MDMA that was equal to or greater than 125 mg, which is the proposed dose in the current study. (Appendix B gives complete information on individual doses.) Participants arrived at the laboratory at 700. The first physiological measures were made at 1230, and placebo or MDMA was administered p.o. at 1400, one and a half hour after the first measures were taken. Measures of heart rate, systolic blood pressure, diastolic blood pressure, and body temperature were taken at 30-minute intervals, before and for 6 hr after MDMA administration.

Safety data from this study are summarized in the following charts and tables depicting drug effects at each dose level. Individual data from each volunteer are shown in Appendix B. MDMA was well tolerated by all individuals participating in this study, and no adverse effects requiring medical intervention arose during any session. However, hypertensive urgencies occurred in two volunteers. Blood pressure was elevated above 200/100 in a 61-year-old male (subject #16) who received 2.25 mg/kg (162.0 mg) MDMA and in a 24-year-old male (subject #10) who received 1.75 mg/kg (204.8 mg) MDMA. Elevated blood pressure in the 24-year old male may have been related to undisclosed use of Ventolin (salbutamol/albuterol), an β_2 -adrenergic agonist and CYP3A substrate (Manchee et al. 1996), on the morning of the study. Blood pressure returned to normal limits in both individuals within 20 minutes to 1 and a half hours, and neither individual required additional treatment to reduce blood pressure. Clinically significant hypertension after MDMA has been reported by other investigators, with clinical significance defined as being 220/130 or higher (see “Monitoring for Toxicity.”) Vollenweider et al. (1998) conducted a 16-volunteer study employing 1.7 mg/kg MDMA. One volunteer, a 49-year-old male with no previous MDMA experience, displayed peak blood pressure values of 240/145 mm Hg (but no other signs of hypertensive crisis) for about 20 minutes. Plans for monitoring for and treating hypertension are described in the section on Monitoring for Toxicity.

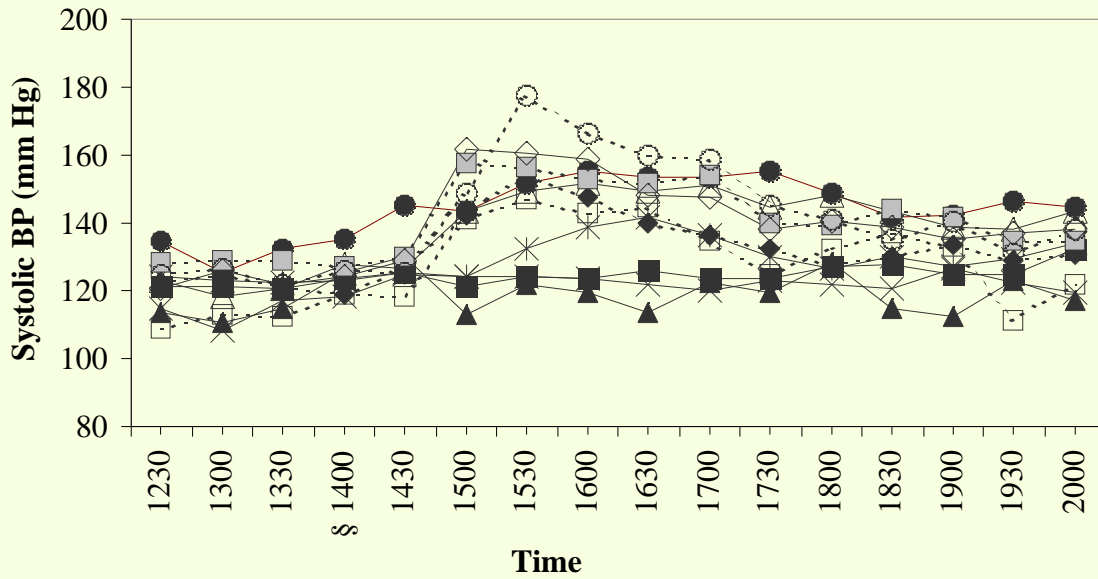
Heart Rate After MDMA or Placebo



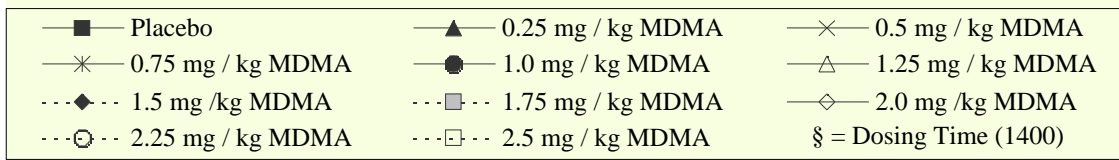
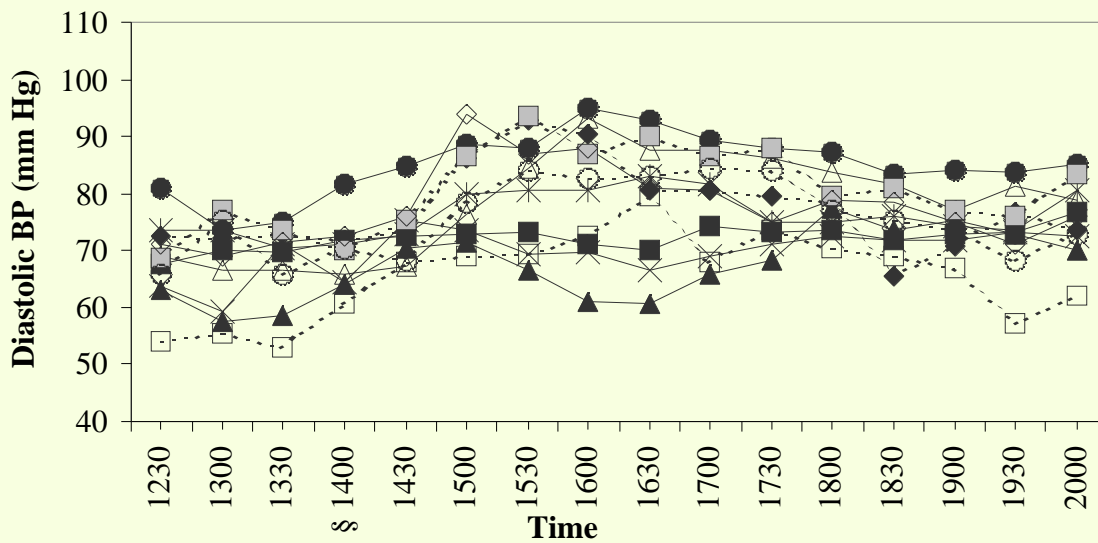
Heart Rate (BPM)

Time	Dose (mg / kg) MDMA										
	0	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2.0	2.25	2.5
1230	61.1	58.0	60.3	64.3	67.0	62.5	61.0	68.0	60.8	58.3	58.0
1300	59.2	56.5	61.3	66.0	62.3	60.5	60.5	66.5	57.0	59.0	55.0
1330	61.3	54.5	61.0	67.3	62.0	61.8	57.5	64.8	61.0	60.8	58.0
1400	64.3	53.5	56.8	64.8	72.5	63.5	68.8	63.5	61.0	62.0	58.5
1430	60.4	52.0	61.0	63.0	65.8	67.3	61.5	60.0	56.3	58.3	74.5
1500	59.9	56.0	62.0	63.8	72.5	74.3	73.8	70.0	68.5	72.0	69.0
1530	61.0	51.5	65.8	70.0	76.5	84.3	71.5	80.5	78.0	72.3	74.0
1600	60.1	52.0	67.0	73.5	88.3	85.5	79.5	87.0	70.5	69.8	70.0
1630	58.7	52.0	64.3	78.0	80.5	80.5	78.0	82.3	68.0	70.5	70.0
1700	59.4	53.5	64.3	75.5	79.3	82.0	78.3	79.3	63.0	69.0	67.0
1730	58.3	52.0	65.0	71.0	72.8	78.3	78.3	77.5	60.8	64.5	78.5
1800	59.2	53.0	63.5	68.8	70.0	78.5	76.3	74.5	66.0	64.5	69.5
1830	58.4	49.5	63.5	66.8	74.5	76.3	66.0	69.3	61.3	64.8	64.5
1900	59.4	57.0	63.0	67.5	72.0	73.3	70.0	70.0	61.0	59.8	62.5
1930	59.2	55.0	61.0	68.8	71.3	72.3	72.8	68.3	59.3	62.0	61.5
2000	61.6	55.0	64.0	68.0	69.5	76.0	64.0	72.5	62.8	64.3	73.0
n	18	2	4	4	4	4	4	4	4	4	2

Systolic Blood Pressure After MDMA or Placebo



Diastolic Blood Pressure After MDMA or Placebo



Systolic Blood Pressure (mm Hg)

Time	Dose (mg/kg) MDMA										
	0	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2.0	2.25	2.5
1230	120.9	113.5	115.0	124.0	135.0	123.0	122.3	128.3	120.8	124.5	109.0
1300	121.1	110.5	108.3	122.8	125.3	118.5	124.5	129.0	126.0	126.3	113.0
1330	120.5	115.0	117.0	122.3	132.3	120.8	121.3	129.0	122.0	121.5	112.5
1400	123.8	125.5	118.0	123.0	135.3	127.5	119.0	127.3	124.0	126.0	119.0
1430	125.3	130.0	124.8	125.5	145.3	126.3	126.5	130.3	128.8	125.5	118.0
1500	120.9	113.0	124.3	124.3	143.8	143.5	142.5	157.8	161.8	149.0	141.0
1530	124.1	121.5	124.3	132.5	151.8	149.5	154.0	156.5	160.5	177.5	147.0
1600	123.6	119.5	123.5	139.0	155.5	151.5	147.5	153.0	159.0	166.8	143.0
1630	125.8	113.5	121.5	141.8	153.5	149.5	140.0	152.0	148.3	160.0	144.5
1700	123.8	122.5	119.8	136.8	153.8	151.3	136.3	154.0	147.8	159.0	134.5
1730	123.7	119.5	122.8	130.3	155.3	145.0	132.5	140.0	138.5	145.5	125.0
1800	126.8	128.5	122.0	126.8	148.8	148.3	127.5	139.3	140.5	141.3	132.5
1830	127.7	114.5	120.5	130.3	141.5	143.3	130.0	144.0	139.0	135.5	137.0
1900	124.7	112.5	126.3	127.3	142.3	138.8	133.8	142.0	135.5	140.8	133.0
1930	124.5	123.0	122.5	129.3	146.5	138.3	129.0	135.0	137.3	131.0	111.0
2000	132.2	117.0	119.3	134.0	144.8	143.5	130.5	135.0	138.0	138.0	122.0
n	18	2	4	4	4	4	4	4	4	4	2

Diastolic Blood Pressure (mm Hg)

Time	Dose (mg/kg) MDMA										
	0	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2.0	2.25	2.5
1230	67.6	63.0	63.8	73.8	81.0	69.0	72.5	68.8	71.0	65.8	54.0
1300	70.0	57.5	59.3	73.5	73.5	66.8	72.3	77.0	69.0	75.5	55.5
1330	69.8	58.5	71.3	70.5	75.0	66.5	72.8	73.5	71.5	66.0	53.0
1400	71.8	64.0	64.5	71.0	81.8	65.8	72.0	70.0	72.5	70.5	60.5
1430	72.7	70.5	75.3	72.8	84.8	67.3	73.5	75.3	76.0	68.5	68.0
1500	73.1	71.5	73.5	79.8	88.8	76.5	86.3	86.5	94.0	78.5	69.0
1530	73.2	66.5	69.3	80.5	88.0	84.5	93.0	93.5	87.0	84.0	69.5
1600	71.3	61.0	69.8	80.5	95.0	93.3	90.5	87.0	88.0	82.8	72.5
1630	70.2	60.5	66.8	83.0	93.0	87.8	80.5	90.0	81.0	83.0	79.5
1700	74.4	66.0	69.0	81.5	89.3	87.5	80.8	86.5	80.5	84.5	68.0
1730	73.2	68.5	71.3	75.0	88.0	86.3	79.5	88.0	75.0	84.0	73.5
1800	73.6	77.5	72.5	75.0	87.3	83.8	78.5	79.5	78.8	77.3	70.5
1830	71.9	73.5	72.0	76.0	83.3	81.5	65.5	81.0	78.5	75.3	69.0
1900	72.9	75.5	71.8	74.3	84.0	77.0	70.8	77.0	75.0	73.5	67.0
1930	73.4	73.0	73.3	73.8	83.8	81.3	76.8	76.0	71.0	68.3	57.0
2000	76.9	70.0	72.5	80.5	85.3	79.0	73.8	83.5	76.0	73.0	62.0
n	18	2	4	4	4	4	4	4	4	4	2

Appendix A: Method of Conducting the MDMA or Placebo Session

Method of conducting MDMA psychotherapy: The therapeutic method to be used was developed and has been practiced extensively by Stanislav Grof, MD, first in LSD psychotherapy research and later in non-drug Holotropic Breathwork. (Grof 1980, pp.123-147; Grof 2000: pp. 178-183). The adaptation and use of this method for MDMA assisted psychotherapy has been described by Ralph Metzner, PhD and by George Greer, MD and Requa Tolbert, MSN. (Greer and Tolbert 1998; Metzner 1988). The therapy will be done by a male-female team in accordance with Grof and Greer and Tolbert's recommendations.

The preparation period:

All the above authors stress the importance of adequate preparation time during non-drug therapy sessions preceding drug-assisted psychotherapy. In the present study this will be accomplished during the two 90-minute sessions in the weeks preceding the MDMA session and will be reinforced during the first hour of the MDMA session before the drug is ingested. The goals of the preparation process will be:

2. To establish a therapeutic alliance between therapists and patient.

The development of an adequate level of trust and understanding between therapists and patient is critical, and will be the primary focus to the preparation process. In the course of developing a therapeutic alliance, several specific agreements will be made: The patient will agree not to leave the treatment area before the therapists have declared the session over, and to accept a pre-arranged ride home after the session. The therapists will likewise both agree to stay until the end of the session. In addition, they will both be in the room with the patient during the vast majority of the time and at least one of them will be with the patient at all times. The subject of touch will be discussed. The patient will be told that there may be times during the session when they would like to ask for nurturing touch in the form of hand holding or being held. The therapists will agree to provide this nurturing touch if the patient desires and to immediately discontinue any physical contact if the patient says "stop". The patient will be told that they may experience sexual feelings as a normal part of the experience and that the therapists will support them in expressing these feelings but will not have any form of sexual contact with them.

3. To answer any questions and address any concerns, fears or doubts the patient may have about any part of the study protocol.

In particular this will involve conveying to the patient therapists' commitment to providing a safe setting and to supporting the patient in working therapeutically with whatever experience arises.

4. To familiarize the patient with the general approach to be taken during the MDMA sessions.

The therapists will describe the physical setting, and explain the following: Patients will start the session lying down with eyes closed and with music playing. They will be encouraged to direct their attention toward their inner experience. As the MDMA takes effect, they may notice a sense of stimulation or increased autonomic arousal. They will be taught diaphragmatic breathing as a tool to use if they experience anxiety or other discomfort at this stage or at any time during the session. It will be recommended that the general stance toward any emotional difficulty that arises should be to use the breath as an aid to experiencing and moving through, rather than away from, whatever is coming into consciousness. The stance that will be taken toward verbal interaction will be consistent with the recommendations of Grof, Metzner and Greer and Tolbert: Patients will be welcome to open their eyes and talk to the therapists at any point. If they have not done so after an hour, the therapists will ask them to describe briefly what they're experiencing. The therapists will continue to check in with the patient in this way throughout the session each time vital signs are being taken. On the other hand, it is also possible for talking to become a distraction from the inner experience. For this reason the therapists may at times suggest that the patient close their eyes and silently redirect their attention toward their inner process for a period of time before resuming verbal interaction.

5. To discuss the patient's intention or purpose for the session.

Patients will be encouraged to include working with PTSD related material as part of their intention. They will also be introduced to the concept that the specific course of their therapeutic process related to PTSD may be different from what might be predicted by the intellect. They will be instructed that it may be helpful to set aside specific expectations and to open themselves to working with the experience in whatever way it unfolds.

5. For the therapists to become familiar with the patient's history, present life situation, symptoms, and personality.

The Experimental (MDMA or Placebo) session:

On the morning of the experimental session, the therapists will arrive at the General Clinical Research Center before the patient in order to prepare the room. This will involve assuring that the equipment for medical monitoring is present and taking steps to arrange and decorate the room to make it as comfortable, welcoming and aesthetically pleasing as possible. (As has been noted in the clinical observations of

Grof, Metzner, and Greer and Tolbert, attention to the nature of the physical setting is an important aspect of the therapy sessions). When the patient arrives, urine will be collected and sent to the laboratory for drug screen and (for females) a pregnancy test. While waiting for the urine results, the therapists will talk with the patient to answer any remaining questions and to complete preparation for the session as described above. If the urine tests are negative, the patient will be administered 125 mg. MDMA p.o. and will be asked to lie down, to close their eyes (with or without an eye shade according to their preference). At that time, music will be started. The music to be played will be the same for each patient, with the exception that the therapists may move ahead in the program at their discretion according to the nature of the patient's experience. In addition, a patient's request to discontinue a particular piece of music or to have a period of silence will be respected. The musical program will have been selected beforehand by the therapists. Music will be chosen to support emotional experience while minimizing suggestion. For this reason the music will not contain English words, and well known music to which people are likely to have strong associations will be avoided. The music program will have a trajectory designed to match the likely trajectory of the MDMA experience. In the beginning, it will be soothing and relaxing. Toward the end of the first hour it will become somewhat more energetic and supportive of emotions, and toward the end of the session it will become quieter and supportive of integration.

When there is verbal interaction with the patient, the therapists' responses will be oriented toward following and supporting the way in which the patient's experience is unfolding rather than toward directing the experience. As appropriate, the therapists may offer insights or ask questions to help the patient track and further explore the experience. Often, however, the therapists' role will be to listen carefully and empathically. If difficult material arises, they will help the patient keep the perspective that it is being presented by the psyche as part of the healing process. With this perspective, which tends to be strongly enhanced by the effects of MDMA, the re-experiencing of traumatic events can be profoundly healing rather than re-traumatizing. Toward the end of the session, the patient will be encouraged to talk about the experience in as much detail as they are ready to communicate. During this period, particular attention will be paid to any residual emotional or physical discomfort and the therapists will help the patient to further process, understand and integrate the experience.

Throughout the session, medical monitoring will be maintained as outlined in the protocol. After approximately eight hours, if all medical parameters are acceptable and if the patient is alert, ambulatory and emotionally stable, the session will be ended. The patient will be given an appointment time for a follow-up visit the following day and will be given Dr. Mithoefer's pager number to call immediately if any problems occur. He or she will then be allowed to leave via a previously arranged ride from a friend or family member.

Appendix B: Individual Safety Data from Phase 1 Ascending Dose Study

This appendix summarizes individual acute safety data from the Phase I study conducted by Dr. Charles Grob and colleagues at the UCLA-Harbor Medical School with doses ranging from 0.25 mg/kg to 2.5 mg/kg MDMA. Eighteen healthy individuals (5 females and 13 males) with histories of previous use of ecstasy received two doses of MDMA in a randomized, double blind, placebo-controlled, dose-response study. The doses administered to each subject differed by an increment of 0.25 mg/kg, with dosage in milligrams ranging from 16.6 mg to 204.8 mg. Participants arrived at the laboratory at 700. The first physiological measures were made at 1230, and placebo or MDMA was administered p.o. at 1400, one and a half hour after the first measures were taken. Measures of heart rate, systolic blood pressure, diastolic blood pressure, and body temperature were taken at 30-minute intervals, before and for 6 hr after MDMA administration.

As can be seen, MDMA was generally well tolerated. MDMA dose-dependently increased heart rate and blood pressure. At the highest doses tested, these changes were robust but not clinically significant. Two volunteers (subjects #10 and #16) experienced clinically significant hypertension but were without other signs of hypertensive crisis. These episodes resolved spontaneously within 20 minutes and 2 hours, respectively.

MDMA Doses (in mg) Used in Phase I Study

Subject	Session 1	Session 2		Session 3	
	mg/kg	mg	Mg/kg	mg	mg/kg
1	0.0	16.6	0.25	33.2	0.5
2	0.0	28.2	0.25	56.3	0.5
3	0.0	46.1	0.5	69.2	0.75
4	0.0	29.6	0.5	44.4	0.75
5	0.0	55.5	0.75	74.0	1.0
6	0.0	60.0	0.75	80.0	1.0
7	0.0	88.0	1.0	110.0	1.25
8	0.0	99.0	1.0	123.8	1.25
9	0.0	94.3	1.25	113.1	1.5
10	0.0	175.5	1.5	204.8	1.75
11	0.0	112.5	1.25	135.0	1.5
12	0.0	115.5	1.5	134.8	1.75
13	0.0	97.0	1.75	110.8	2.0
14	0.0	125.3	1.75	143.2	2.0
15	0.0	156.0	2	175.5	2.25
16	0.0	144.0	2	162.0	2.25
17	0.0	137.3	2.25	152.5	2.5
18	0.0	172.8	2.25	192.0	2.5

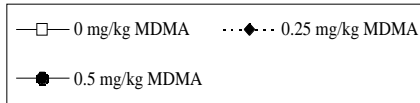
Doses of 125 mg or above have been bolded.

SAFETY DATA FROM SUBJECT 1: 43-Year-old Female

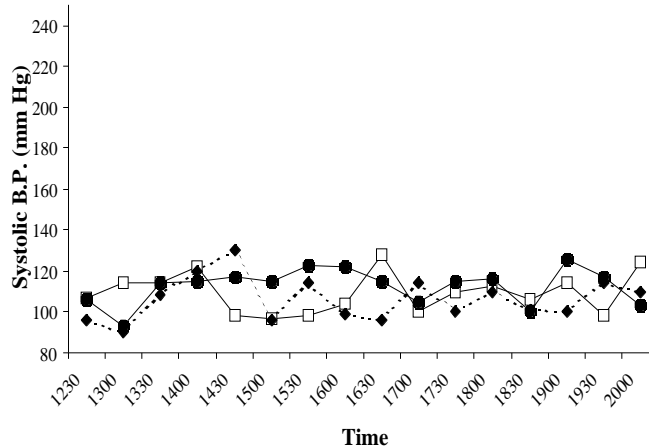
SESSION ONE

Dose = 0.00 mg/kg MDMA

TIME	SYS	DIAS	H.R.	TEMP
1230	107	52	40	100.1
1300	114	45	40	99.7
1330	114	60	40	99.9
1400	122	54	43	100.0
1430	98	52	39	98.1
1500	97	50	44	98.8
1530	98	44	41	98.4
1600	104	52	48	97.4
1630	128	51	46	98.7
1700	100	64	42	97.9
1730	110	70	45	97.5
1800	113	52	44	98.6
1830	106	54	40	97.3
1900	114	50	41	97.7
1930	98	46	49	98.1
2000	124	60	42	97.3



Systolic Blood Pressure

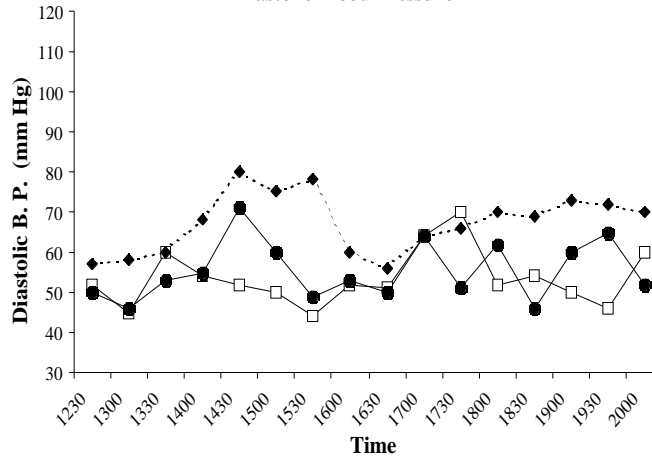


SESSION TWO

Dose = 0.25 mg/kg MDMA 16.6 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	96	57	41	98.0
1300	90	58	46	97.9
1330	108	60	41	97.8
1400	120	68	41	97.2
1430	130	80	42	96.8
1500	96	75	44	97.5
1530	114	78	37	96.9
1600	99	60	39	97.6
1630	96	56	45	98.5
1700	114	64	46	98.7
1730	100	66	42	98.4
1800	110	70	44	98.7
1830	101	69	39	98.8
1900	100	73	50	99.1
1930	114	72	51	98.0
2000	110	70	47	98.7

Diastolic Blood Pressure

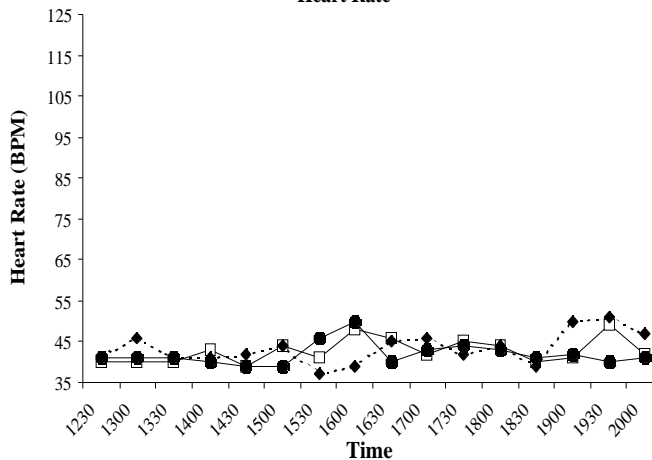


SESSION THREE

Dose = 0.50 mg/kg MDMA 33.2 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	106	50	41	98.4
1300	93	46	41	99.3
1330	114	53	41	98.9
1400	115	55	40	99.8
1430	117	71	39	98.6
1500	115	60	39	99.3
1530	123	49	46	99.9
1600	122	53	50	99.0
1630	115	50	40	98.4
1700	105	64	43	100.3
1730	115	51	44	100.1
1800	116	62	43	99.2
1830	100	46	41	100.0
1900	126	60	42	99.3
1930	117	65	40	99.3
2000	103	52	41	95.8

Heart Rate



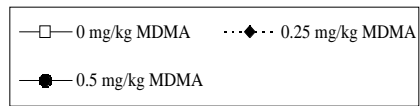
Weight = 66.4 kg

SAFETY DATA FROM SUBJECT 2: 41-Year-old Male

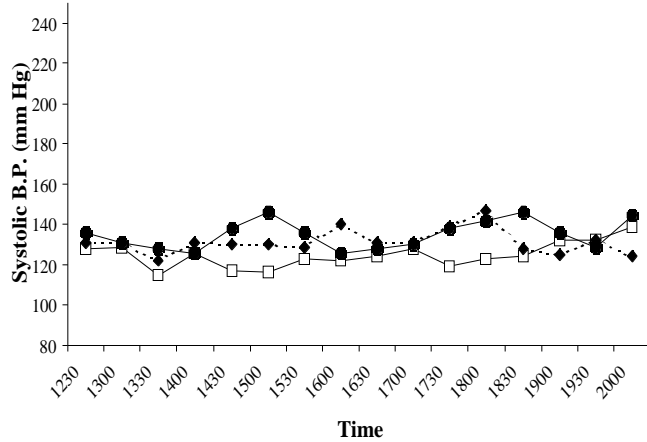
SESSION ONE

Dose = 0.00 mg/kg MDMA

TIME	SYS	DIAS	H.R.	TEMP
1230	128	67	63	98.6
1300	129	68	57	97.4
1330	115	63	57	97.5
1400	126	62	58	98.2
1430	117	63	54	97.2
1500	116	62	51	97.3
1530	123	81	57	96.8
1600	122	70	60	97.5
1630	124	69	56	97.9
1700	128	69	58	97.9
1730	119	67	57	97.3
1800	123	70	57	97.3
1830	124	67	58	97.6
1900	132	74	55	98.2
1930	132	74	55	98.2
2000	139	77	77	96.9



Systolic Blood Pressure

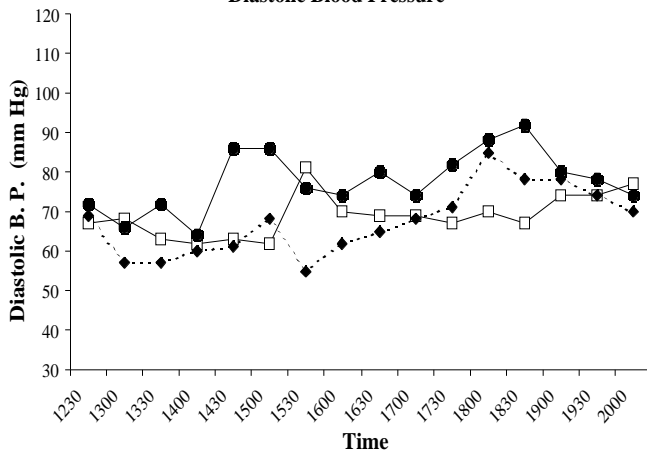


SESSION TWO

Dose = 0.25 mg/kg MDMA 28.2 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	131	69	75	98.9
1300	131	57	67	98.4
1330	122	57	68	98.6
1400	131	60	66	98.3
1430	130	61	62	98.2
1500	130	68	68	98.2
1530	129	55	66	98.7
1600	140	62	65	98.1
1630	131	65	59	97.4
1700	131	68	61	97.8
1730	139	71	62	98.7
1800	147	85	62	92.9
1830	128	78	60	96.6
1900	125	78	64	97.4
1930	132	74	59	95.1
2000	124	70	63	96.7

Diastolic Blood Pressure

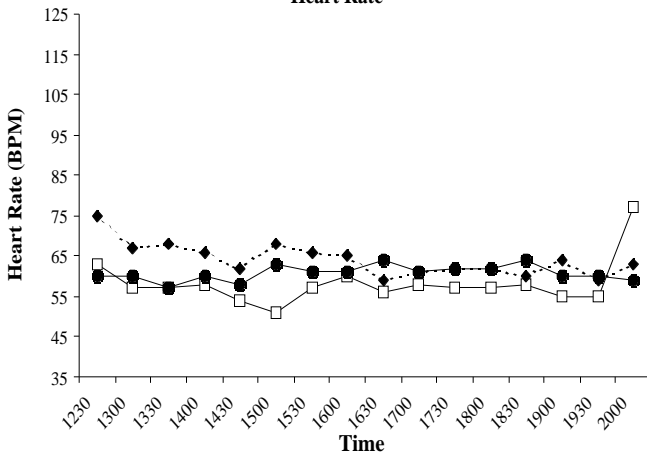


SESSION THREE

Dose = 0.50 mg/kg MDMA 56.3 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	136	72	60	98.6
1300	131	66	60	98.1
1330	128	72	57	97.9
1400	126	64	60	97.9
1430	138	86	58	98.2
1500	146	86	63	98.1
1530	136	76	61	98.1
1600	126	74	61	98.1
1630	128	80	64	98.6
1700	130	74	61	97.8
1730	138	82	62	96.7
1800	142	88	62	97.6
1830	146	92	64	98.5
1900	136	80	60	98.6
1930	129	78	60	98.4
2000	145	74	59	98.4

Heart Rate



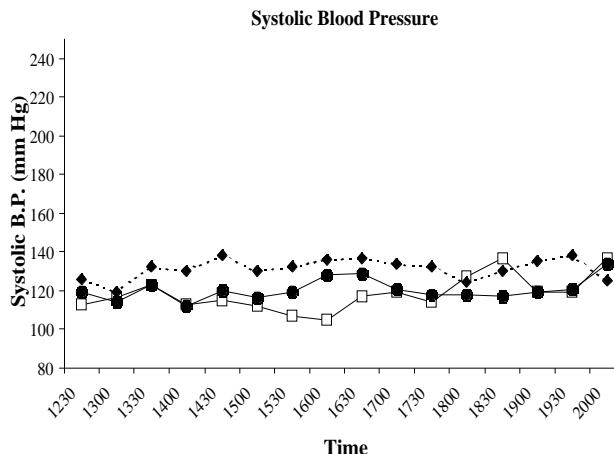
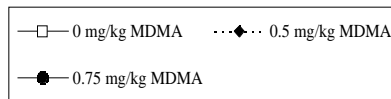
Weight = 112.6 kg

SAFETY DATA FROM SUBJECT 3: 48-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

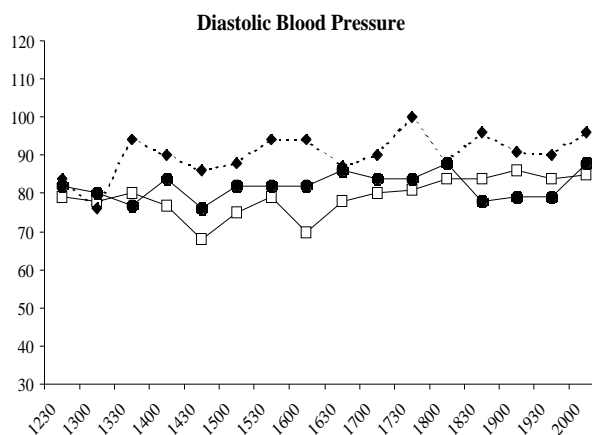
TIME	SYS	DIAS	H.R.	TEMP
1230	113	79	77	97.8
1300	116	78	81	97.7
1330	123	80	81	98.4
1400	113	77	79	98.4
1430	115	68	81	98.5
1500	112	75	85	98.3
1530	107	79	81	97.1
1600	105	70	79	98.1
1630	117	78	81	97.8
1700	119	80	81	97.9
1730	114	81	73	98.0
1800	127	84	79	98.6
1830	137	84	81	97.9
1900	119	86	79	98.1
1930	119	84	81	98.5
2000	137	85	87	98.9



SESSION TWO

Dose = 0.50 mg/kg MDMA 46.1 mg

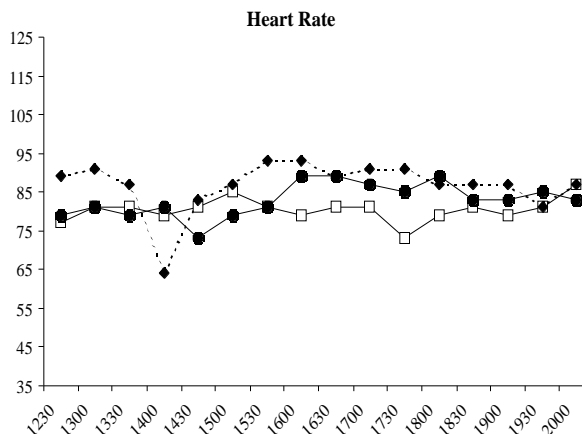
TIME	SYS	DIAS	H.R.	TEMP
1230	126	84	89	98.3
1300	119	76	91	97.4
1330	132	94	87	98.0
1400	130	90	64	98.3
1430	138	86	83	98.1
1500	130	88	87	98.6
1530	132	94	93	98.4
1600	136	94	93	99.2
1630	137	87	89	98.4
1700	134	90	91	98.0
1730	132	100	91	98.4
1800	124	88	87	97.6
1830	130	96	87	97.9
1900	135	91	87	97.8
1930	138	90	81	97.6
2000	125	96	87	98.4



SESSION THREE

Dose = 0.75 mg/kg MDMA 69.2 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	119	82	79	97.7
1300	114	80	81	97.7
1330	123	77	79	97.7
1400	112	84	81	97.6
1430	120	76	73	97.8
1500	116	82	79	97.8
1530	119	82	81	97.6
1600	128	82	89	98.1
1630	129	86	89	98.6
1700	121	84	87	97.9
1730	118	84	85	98.1
1800	118	88	89	98.3
1830	117	78	83	98.8
1900	119	79	83	99.3
1930	121	79	85	97.4
2000	134	88	83	98.4



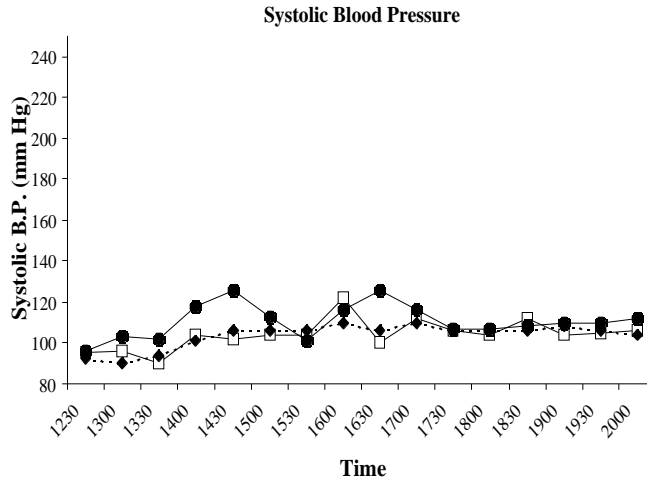
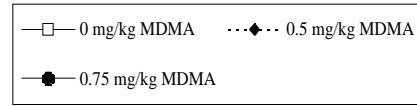
Weight = 92.2 kg

SAFETY DATA FROM SUBJECT 4: 24-Year-old Female

SESSION ONE

Dose = 0.00 mg/kg MDMA

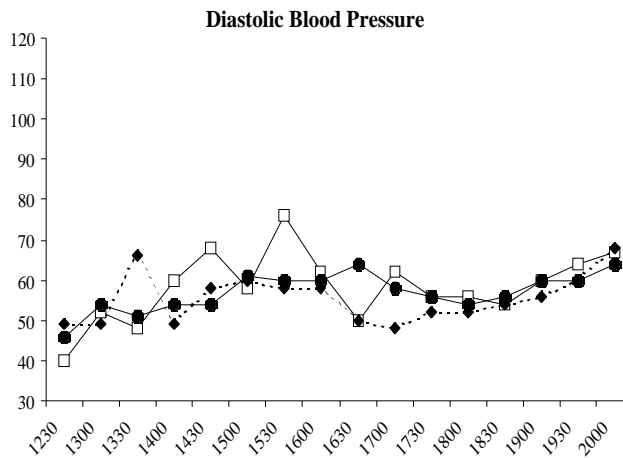
TIME	SYS	DIAS	H.R.	TEMP
1230	95	40	59	98.7
1300	96	52	57	98.4
1330	90	48	64	98.5
1400	104	60	62	98.7
1430	102	68	61	97.4
1500	104	58	56	98.5
1530	104	76	70	98.3
1600	122	62	70	98.3
1630	100	50	56	99.0
1700	112	62	53	98.4
1730	106	56	52	98.4
1800	104	56	52	98.4
1830	112	54	54	98.7
1900	104	60	60	98.4
1930	105	64	51	98.8
2000	106	67	53	98.1



SESSION TWO

Dose = 0.50 mg/kg MDMA 29.6 mg

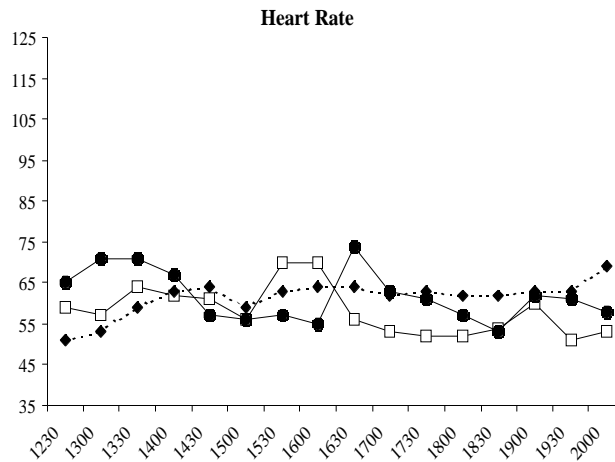
TIME	SYS	DIAS	H.R.	TEMP
1230	92	49	51	97.2
1300	90	49	53	97.3
1330	94	66	59	97.9
1400	101	49	63	98.1
1430	106	58	64	96.7
1500	106	60	59	98.1
1530	106	58	63	97.0
1600	110	58	64	97.9
1630	106	50	64	98.5
1700	110	48	62	97.9
1730	106	52	63	98.4
1800	106	52	62	98.3
1830	106	54	62	98.9
1900	108	56	63	98.4
1930	106	60	63	98.3
2000	104	68	69	98.5



SESSION THREE

Dose = 0.75 mg/kg MDMA 44.4 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	96	46	65	98.1
1300	103	54	71	98.3
1330	102	51	71	97.8
1400	118	54	67	98.6
1430	126	54	57	96.9
1500	113	61	56	97.6
1530	101	60	57	97.7
1600	116	60	55	97.6
1630	126	64	74	98.3
1700	116	58	63	98.6
1730	107	56	61	98.2
1800	107	54	57	98.1
1830	108	56	53	98.1
1900	110	60	62	98.1
1930	110	60	61	99.0
2000	112	64	58	98.3



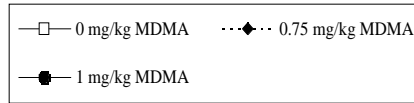
Weight = 59.2 kg

SAFETY DATA FROM SUBJECT 5: 34-Year-old Male

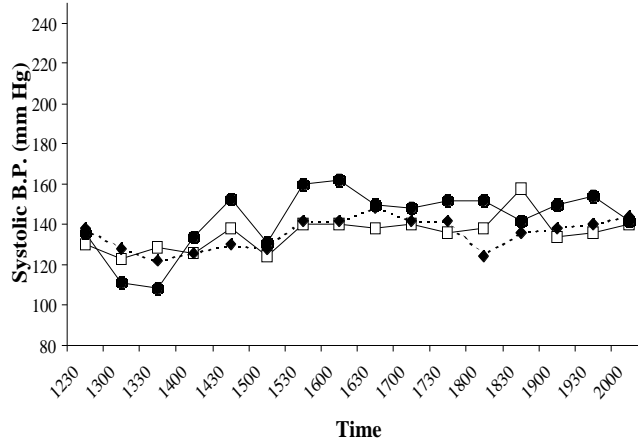
SESSION ONE

Dose = 0.00 mg/kg MDMA

TIME	SYS	DIAS	H.R.	TEMP
1230	130	72	56	96.6
1300	123	72	53	98.0
1330	129	80	55	97.5
1400	126	80	60	97.3
1430	138	82	63	97.4
1500	124	72	62	97.8
1530	140	82	63	98.6
1600	140	84	55	98.1
1630	138	78	56	98.4
1700	140	84	54	98.4
1730	136	84	53	98.2
1800	138	90	56	98.4
1830	158	88	56	98.1
1900	134	82	64	98.6
1930	136	80	55	98.3
2000	140	74	58	98.8



Systolic Blood Pressure

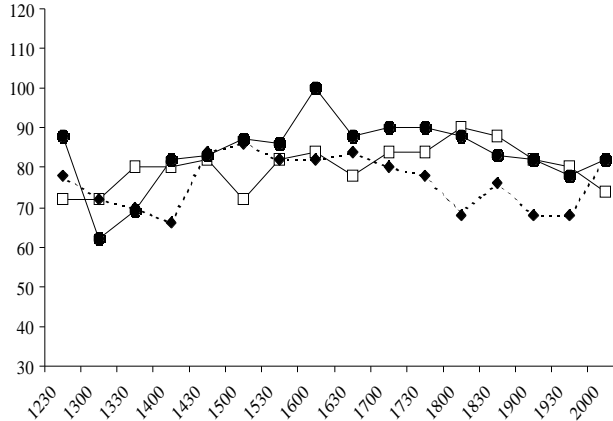


SESSION TWO

Dose = 0.75 mg/kg MDMA 55.5 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	138	78	59	97.4
1300	128	72	61	97.9
1330	122	70	63	98.4
1400	126	66	56	97.8
1430	130	84	59	97.8
1500	128	86	60	97.5
1530	142	82	66	97.8
1600	142	82	65	98.3
1630	148	84	62	98.3
1700	142	80	64	98.2
1730	142	78	59	98.8
1800	124	68	60	98.6
1830	136	76	61	98.7
1900	138	68	61	98.5
1930	140	68	60	98.6
2000	144	82	65	98.1

Diastolic Blood Pressure

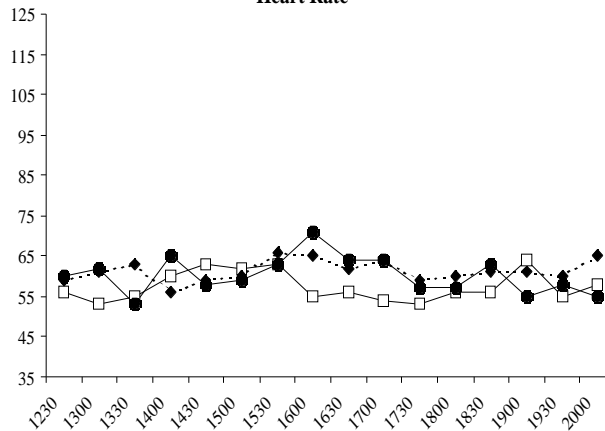


SESSION THREE

Dose = 1.00 mg/kg MDMA 74.0 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	136	88	60	98.4
1300	111	62	62	98.1
1330	108	69	53	98.0
1400	134	82	65	95.2
1430	153	83	58	96.5
1500	131	87	59	97.1
1530	160	86	63	98.4
1600	162	100	71	96.4
1630	150	88	64	98.8
1700	148	90	64	97.5
1730	152	90	57	95.0
1800	152	88	57	99.0
1830	142	83	63	98.1
1900	150	82	55	98.7
1930	154	78	58	98.4
2000	142	82	55	98.2

Heart Rate



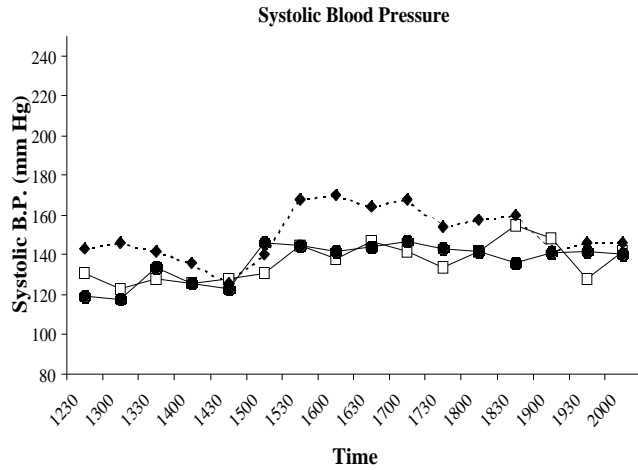
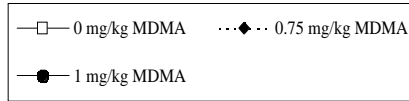
Weight = 74.0 kg

SAFETY DATA FROM SUBJECT 6: 52-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

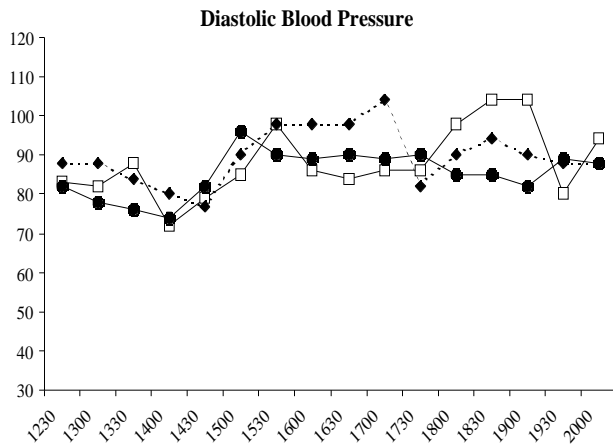
TIME	SYS	DIAS	H.R.	TEMP
1230	131	83	53	97.0
1300	123	82	53	97.4
1330	128	88	55	97.2
1400	126	72	62	97.6
1430	128	79	54	97.1
1500	131	85	56	97.3
1530	145	98	62	97.4
1600	138	86	54	97.6
1630	147	84	59	97.5
1700	142	86	55	98.1
1730	134	86	57	98.0
1800	142	98	65	98.1
1830	155	104	60	98.4
1900	148	104	58	97.9
1930	128	80	52	98.2
2000	142	94	52	98.7



SESSION TWO

Dose = 0.75 mg/kg MDMA 60.0 mg

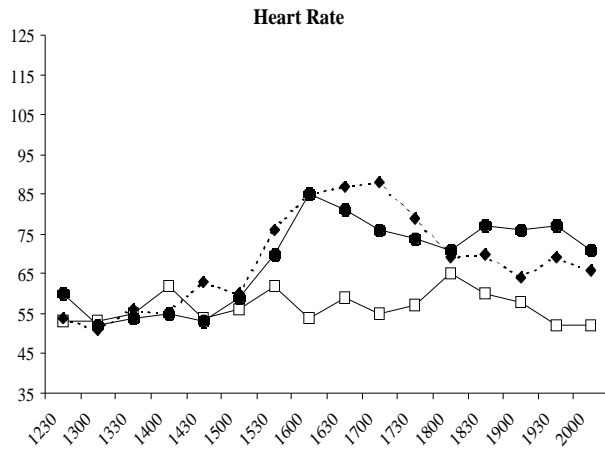
TIME	SYS	DIAS	H.R.	TEMP
1230	143	88	54	97.5
1300	146	88	51	97.2
1330	142	84	56	97.7
1400	136	80	55	97.4
1430	126	77	63	97.5
1500	140	90	60	97.5
1530	168	98	76	97.9
1600	170	98	85	98.1
1630	164	98	87	98.0
1700	168	104	88	98.6
1730	154	82	79	98.5
1800	158	90	69	99.1
1830	160	94	70	98.9
1900	142	90	64	98.6
1930	146	88	69	98.7
2000	146	88	66	98.8



SESSION THREE

Dose = 1.00 mg/kg MDMA 80.0 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	119	82	60	97.1
1300	118	78	52	97.3
1330	134	76	54	97.2
1400	126	74	55	97.3
1430	123	82	53	97.3
1500	146	96	59	97.3
1530	145	90	70	97.5
1600	142	89	85	97.4
1630	144	90	81	97.7
1700	147	89	76	97.8
1730	143	90	74	98.1
1800	142	85	71	98.5
1830	136	85	77	98.8
1900	141	82	76	98.6
1930	142	89	77	98.8
2000	140	88	71	98.4



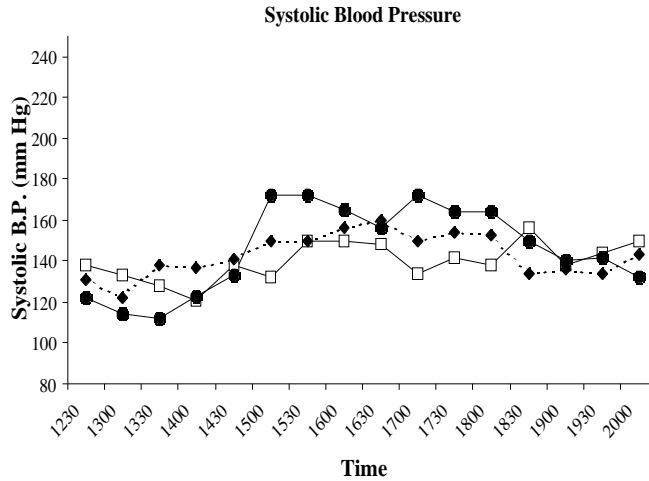
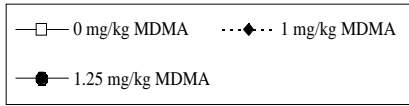
Weight = 80.0 kg

SAFETY DATA FROM SUBJECT 7: 33-Year-old Female

SESSION ONE

Dose = 0.00 mg/kg MDMA

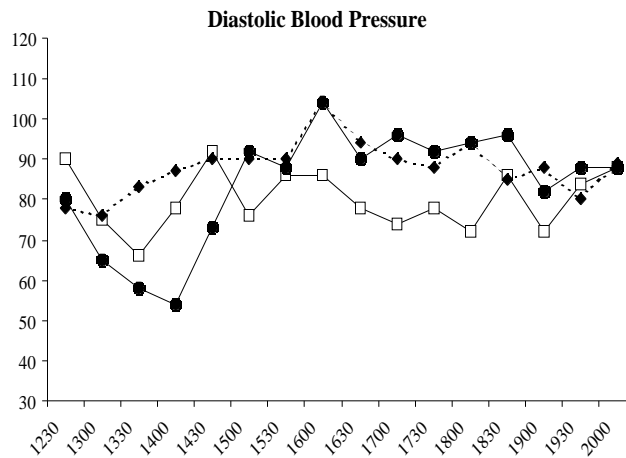
TIME	SYS	DIAS	H.R.	TEMP
1230	138	90	83	98.7
1300	133	75	73	98.3
1330	128	66	81	98.4
1400	121	78	81	98.1
1430	138	92	83	98.5
1500	132	76	74	98.3
1530	150	86	79	99.1
1600	150	86	85	98.7
1630	148	78	81	98.7
1700	134	74	76	98.2
1730	142	78	77	98.5
1800	138	72	70	98.1
1830	156	86	70	98.7
1900	138	72	87	98.2
1930	144	84	79	99.0
2000	150	88	79	99.1



SESSION TWO

Dose = 1.00 mg/kg MDMA 88.0 mg

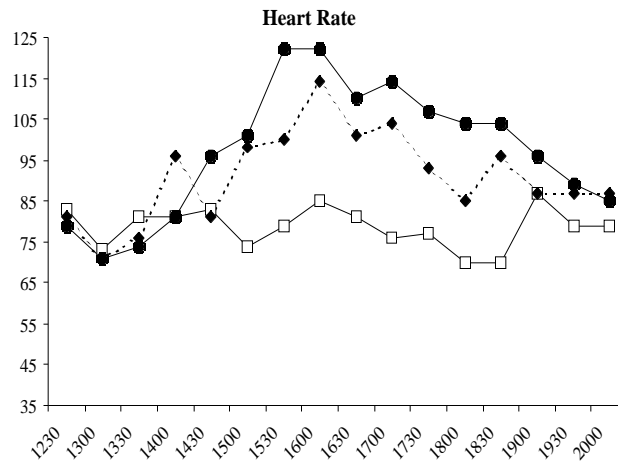
TIME	SYS	DIAS	H.R.	TEMP
1230	131	78	81	99.1
1300	122	76	71	98.8
1330	138	83	76	98.8
1400	137	87	96	98.8
1430	141	90	81	98.3
1500	150	90	98	98.5
1530	150	90	100	98.8
1600	156	104	114	99.7
1630	160	94	101	99.4
1700	150	90	104	99.6
1730	154	88	93	99.9
1800	153	94	85	99.4
1830	134	85	96	99.0
1900	136	88	87	98.6
1930	134	80	87	99.4
2000	143	89	87	98.7



SESSION THREE

Dose = 1.25 mg/kg MDMA 110.0 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	122	80	79	98.2
1300	114	65	71	98.5
1330	112	58	74	98.3
1400	123	54	81	98.2
1430	133	73	96	98.3
1500	172	92	101	98.1
1530	172	88	122	99.1
1600	165	104	122	99.2
1630	156	90	110	98.6
1700	172	96	114	98.9
1730	164	92	107	98.5
1800	164	94	104	99.0
1830	150	96	104	98.4
1900	140	82	96	98.8
1930	142	88	89	98.4
2000	132	88	85	98.5



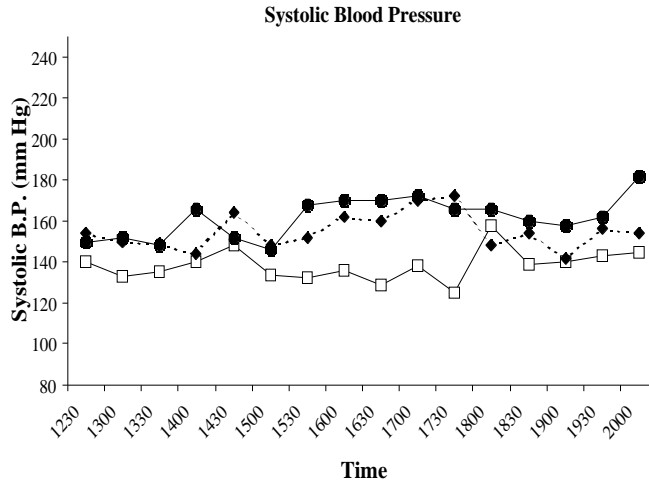
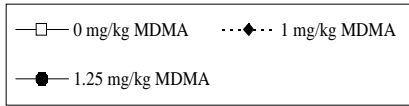
Weight = 88.0 kg

SAFETY DATA FROM SUBJECT 8: 43-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

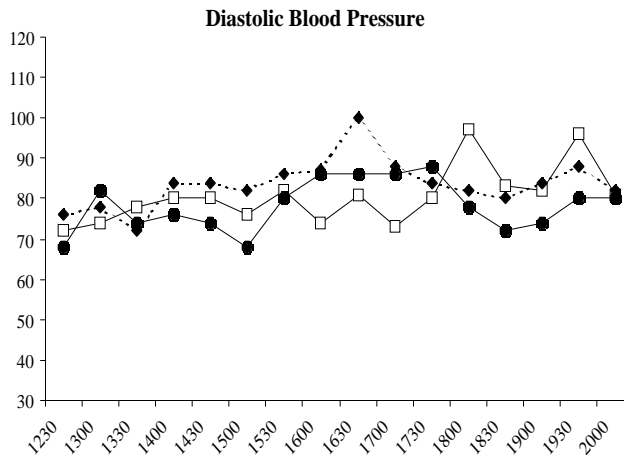
TIME	SYS	DIAS	H.R.	TEMP
1230	140	72	60	97.2
1300	133	74	61	97.7
1330	135	78	59	97.7
1400	140	80	60	97.2
1430	148	80	56	98.0
1500	134	76	54	97.7
1530	132	82	57	97.9
1600	136	74	53	98.4
1630	129	81	53	98.4
1700	138	73	53	97.9
1730	125	80	52	97.5
1800	158	97	54	97.1
1830	139	83	50	97.5
1900	140	82	51	97.6
1930	143	96	54	97.3
2000	145	81	50	98.0



SESSION TWO

Dose = 1.00 mg/kg MDMA 99.0 mg

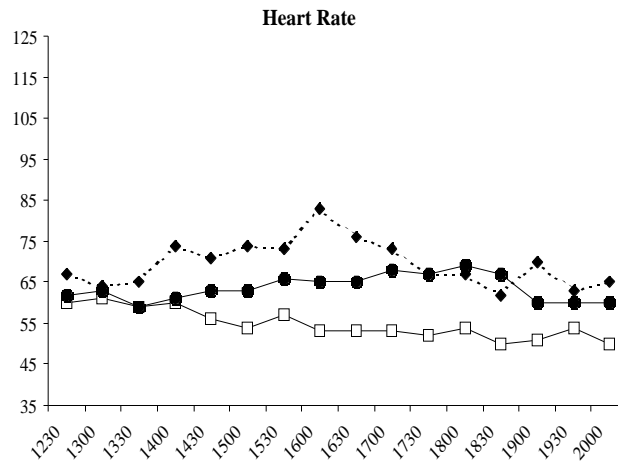
TIME	SYS	DIAS	H.R.	TEMP
1230	154	76	67	97.5
1300	150	78	64	97.7
1330	149	72	65	98.3
1400	144	84	74	97.0
1430	164	84	71	98.4
1500	148	82	74	98.0
1530	152	86	73	98.4
1600	162	87	83	97.3
1630	160	100	76	98.2
1700	170	88	73	99.0
1730	172	84	67	98.5
1800	148	82	67	97.7
1830	154	80	62	97.4
1900	142	84	70	98.4
1930	156	88	63	97.3
2000	154	82	65	97.6



SESSION THREE

Dose = 1.25 mg/kg MDMA 123.8 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	150	68	62	97.1
1300	152	82	63	97.3
1330	148	74	59	97.4
1400	166	76	61	98.1
1430	152	74	63	98.1
1500	146	68	63	97.6
1530	168	80	66	97.7
1600	170	86	65	98.3
1630	170	86	65	98.1
1700	172	86	68	98.4
1730	166	88	67	98.5
1800	166	78	69	97.7
1830	160	72	67	98.8
1900	158	74	60	98.2
1930	162	80	60	97.9
2000	182	80	60	98.0



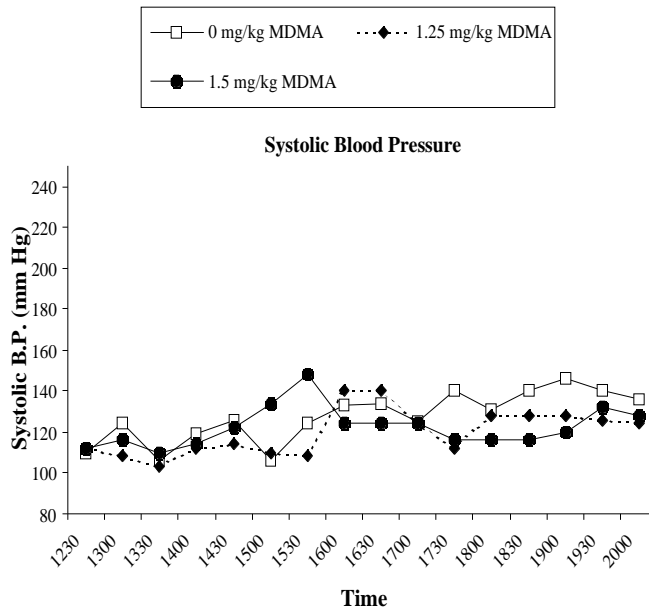
Weight = 99.0 kg

SAFETY DATA FROM SUBJECT 9: 50-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

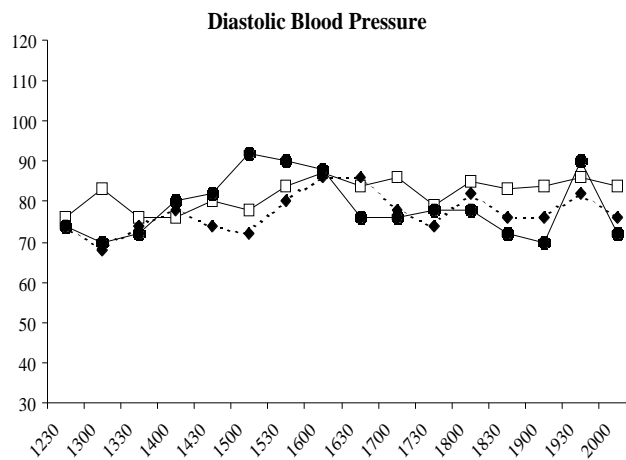
TIME	SYS	DIAS	H.R.	TEMP
1230	110	76	58	96.6
1300	124	83	56	96.1
1330	106	76	56	97.0
1400	119	76	55	96.8
1430	126	80	53	94.9
1500	106	78	57	97.0
1530	124	84	58	96.7
1600	133	87	65	96.5
1630	134	84	65	97.3
1700	125	86	61	97.2
1730	140	79	64	97.2
1800	131	85	58	96.9
1830	140	83	64	97.4
1900	146	84	59	97.9
1930	140	86	56	97.6
2000	136	84	63	97.1



SESSION TWO

Dose = 1.25 mg/kg MDMA 94.3 mg

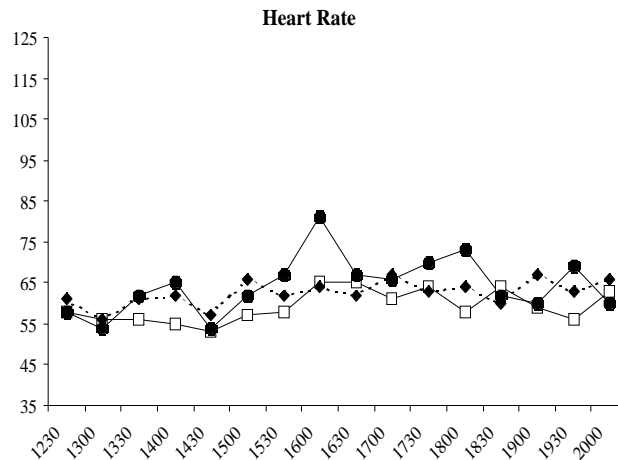
TIME	SYS	DIAS	H.R.	TEMP
1230	112	74	61	97.1
1300	108	68	56	97.3
1330	103	74	61	96.6
1400	112	78	62	97.8
1430	114	74	57	97.2
1500	110	72	66	96.1
1530	108	80	62	97.2
1600	140	86	64	97.1
1630	140	86	62	97.0
1700	124	78	67	95.6
1730	112	74	63	96.9
1800	128	82	64	96.0
1830	128	76	60	97.3
1900	128	76	67	95.6
1930	126	82	63	95.9
2000	124	76	66	96.0



SESSION THREE

Dose = 1.50 mg/kg MDMA 113.1 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	112	74	58	97.2
1300	116	70	54	96.2
1330	110	72	62	97.2
1400	114	80	65	97.2
1430	122	82	54	96.8
1500	134	92	62	96.7
1530	148	90	67	96.9
1600	124	88	81	96.9
1630	124	76	67	98.0
1700	124	76	66	98.3
1730	116	78	70	98.1
1800	116	78	73	97.8
1830	116	72	62	97.8
1900	120	70	60	97.9
1930	132	90	69	97.6
2000	128	72	60	97.1



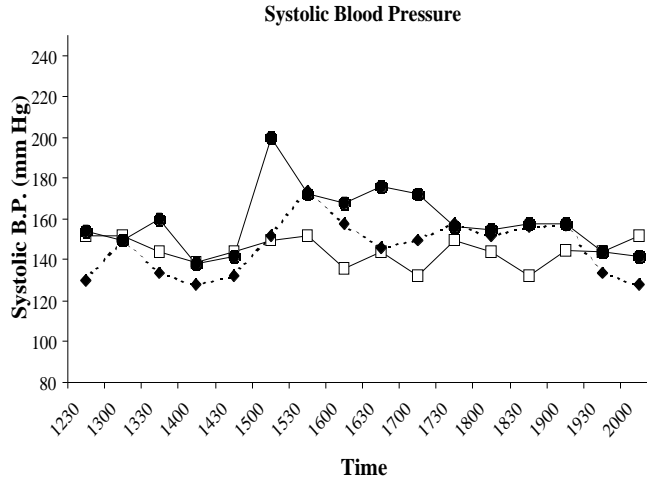
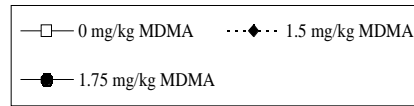
Weight = 75.4 kg

SAFETY DATA FROM SUBJECT 10: 24-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

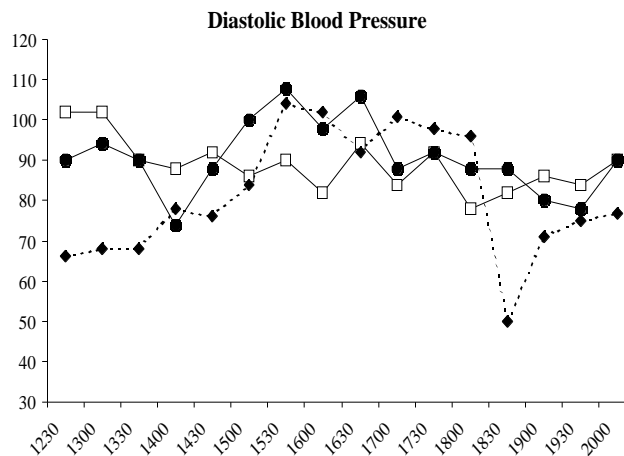
TIME	SYS	DIAS	H.R.	TEMP
1230	152	102	79	97.6
1300	152	102	79	97.6
1330	144	90	70	97.7
1400	139	88	71	97.2
1430	144	92	65	96.4
1500	150	86	65	96.5
1530	152	90	69	97.5
1600	136	82	66	97.0
1630	144	94	64	96.6
1700	132	84	64	96.6
1730	150	92	67	96.3
1800	144	78	60	96.6
1830	132	82	66	95.9
1900	145	86	70	97.4
1930	144	84	69	97.2
2000	152	90	70	97.7



SESSION TWO

Dose = 1.50 mg/kg MDMA 175.5 mg

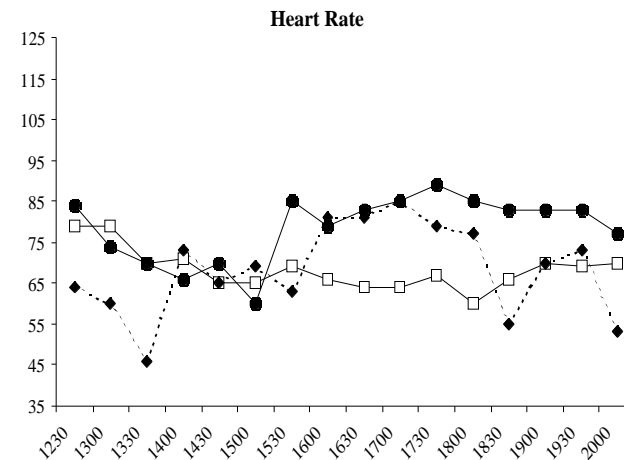
TIME	SYS	DIAS	H.R.	TEMP
1230	130	66	64	96.9
1300	150	68	60	97.0
1330	134	68	46	97.0
1400	128	78	73	97.2
1430	132	76	65	96.7
1500	152	84	69	96.8
1530	174	104	63	97.9
1600	158	102	81	98.1
1630	146	92	81	97.7
1700	150	101	85	98.1
1730	158	98	79	97.4
1800	152	96	77	98.1
1830	156	50	55	98.7
1900	157	71	70	98.5
1930	134	75	73	98.1
2000	128	77	53	98.1



SESSION THREE

Dose = 1.75 mg/kg MDMA 204.8 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	154	90	84	96.5
1300	150	94	74	97.0
1330	160	90	70	96.9
1400	138	74	66	97.6
1430	142	88	70	97.9
1500	200	100	60	97.9
1530	172	108	85	97.7
1600	168	98	79	96.1
1630	176	106	83	97.2
1700	172	88	85	98.1
1730	156	92	89	98.7
1800	155	88	85	98.4
1830	158	88	83	98.4
1900	158	80	83	98.2
1930	144	78	83	97.3
2000	142	90	77	98.2



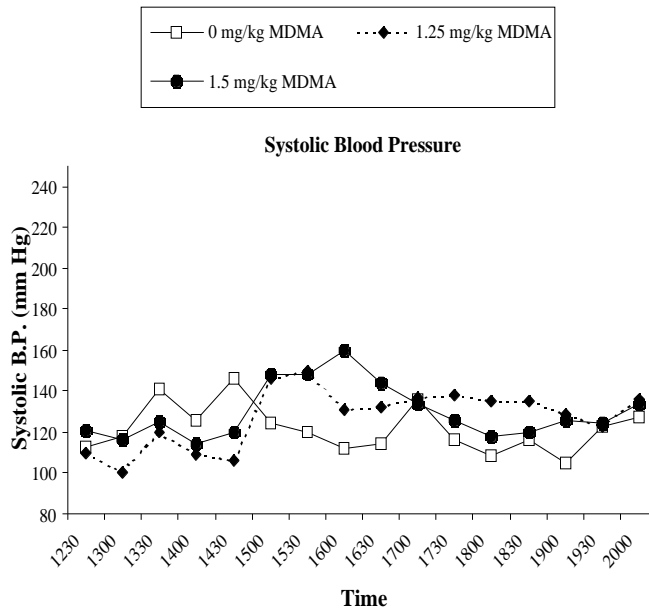
Weight = 117.0 kg

SAFETY DATA FROM SUBJECT 11: 27-Year-old Female

SESSION ONE

Dose = 0.00 mg/kg MDMA

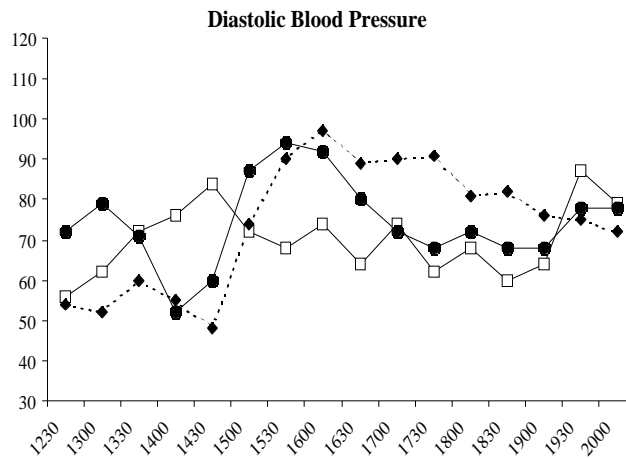
TIME	SYS	DIAS	H.R.	TEMP
1230	113	56	55	98.0
1300	118	62	55	98.3
1330	141	72	76	98.3
1400	126	76	71	97.1
1430	146	84	74	96.2
1500	124	72	61	98.7
1530	120	68	59	98.0
1600	112	74	58	99.1
1630	114	64	54	98.2
1700	136	74	56	98.0
1730	116	62	52	97.4
1800	108	68	63	98.5
1830	116	60	55	98.6
1900	105	64	56	98.3
1930	123	87	61	98.1
2000	127	79	55	98.7



SESSION TWO

Dose = 1.25 mg/kg MDMA 112.5 mg

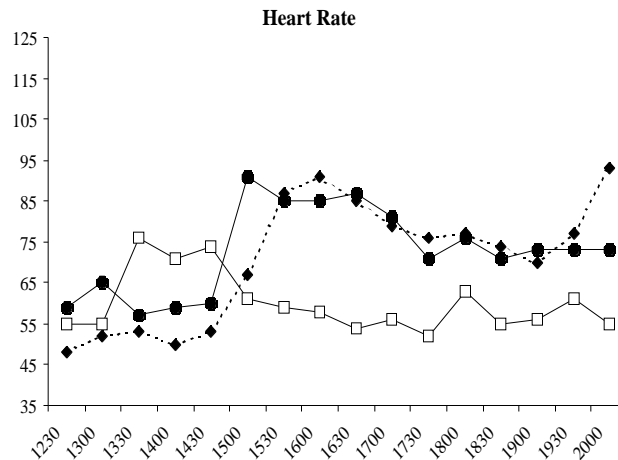
TIME	SYS	DIAS	H.R.	TEMP
1230	110	54	48	98.6
1300	100	52	52	97.9
1330	120	60	53	97.4
1400	109	55	50	96.6
1430	106	48	53	98.5
1500	146	74	67	98.7
1530	150	90	87	96.0
1600	131	97	91	97.5
1630	132	89	85	99.1
1700	137	90	79	98.7
1730	138	91	76	98.5
1800	135	81	77	99.2
1830	135	82	74	99.0
1900	129	76	70	98.6
1930	123	75	77	98.8
2000	136	72	93	99.0



SESSION THREE

Dose = 1.50 mg/kg MDMA 135.0 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	121	72	59	95.6
1300	116	79	65	98.0
1330	125	71	57	98.7
1400	114	52	59	98.9
1430	120	60	60	98.9
1500	148	87	91	98.0
1530	148	94	85	98.6
1600	160	92	85	99.4
1630	144	80	87	99.7
1700	134	72	81	99.4
1730	126	68	71	99.3
1800	118	72	76	95.6
1830	120	68	71	99.1
1900	126	68	73	98.8
1930	124	78	73	99.2
2000	134	78	73	98.8



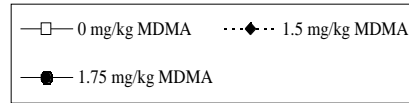
Weight = 90.0 kg

SAFETY DATA FROM SUBJECT 12: 42-Year-old Male

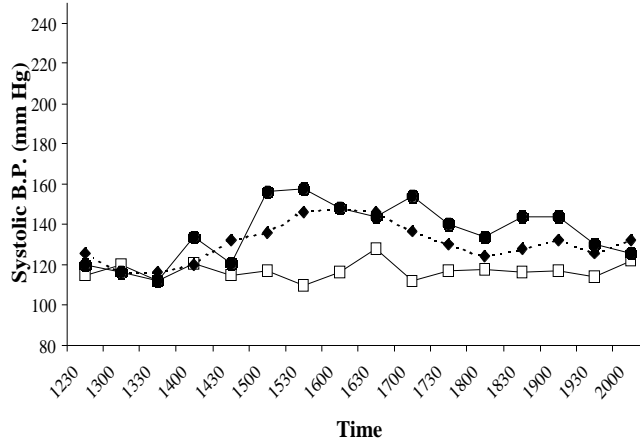
SESSION ONE

Dose = 0.00 mg/kg MDMA

TIME	SYS	DIAS	H.R.	TEMP
1230	115	62	70	97.9
1300	120	70	66	98.1
1330	112	70	62	97.5
1400	121	76	69	97.7
1430	115	60	69	97.8
1500	117	72	64	97.8
1530	110	58	60	97.0
1600	116	74	61	96.4
1630	128	80	56	96.1
1700	112	78	63	96.0
1730	117	76	64	97.7
1800	118	70	66	97.6
1830	116	74	65	98.5
1900	117	82	62	95.5
1930	114	76	59	96.0
2000	122	76	66	96.9



Systolic Blood Pressure

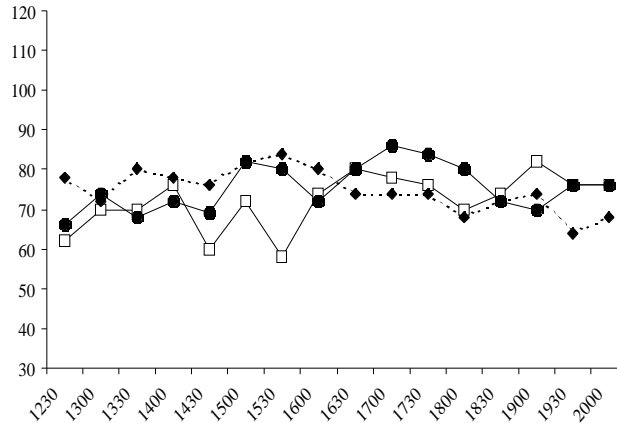


SESSION TWO

Dose = 1.50 mg/kg MDMA 115.5 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	126	78	63	96.5
1300	116	72	63	96.5
1330	116	80	65	98.7
1400	120	78	78	98.7
1430	132	76	67	98.6
1500	136	82	73	98.1
1530	146	84	71	98.1
1600	148	80	71	98.6
1630	146	74	77	97.9
1700	137	74	81	99.0
1730	130	74	93	99.2
1800	124	68	79	98.9
1830	128	72	76	98.8
1900	132	74	77	97.1
1930	126	64	76	98.4
2000	132	68	70	98.2

Diastolic Blood Pressure

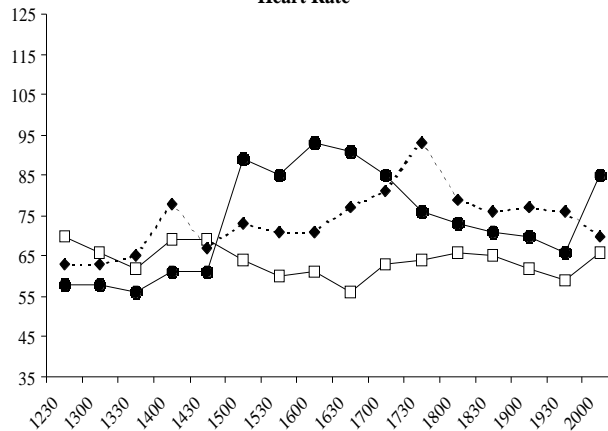


SESSION THREE

Dose = 1.75 mg/kg MDMA 134.8 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	120	66	58	96.0
1300	116	74	58	96.2
1330	112	68	56	96.0
1400	134	72	61	97.3
1430	121	69	61	97.6
1500	156	82	89	96.4
1530	158	80	85	98.3
1600	148	72	93	97.7
1630	144	80	91	97.8
1700	154	86	85	99.4
1730	140	84	76	97.6
1800	134	80	73	98.9
1830	144	72	71	98.8
1900	144	70	70	98.8
1930	130	76	66	98.7
2000	126	76	85	98.1

Heart Rate



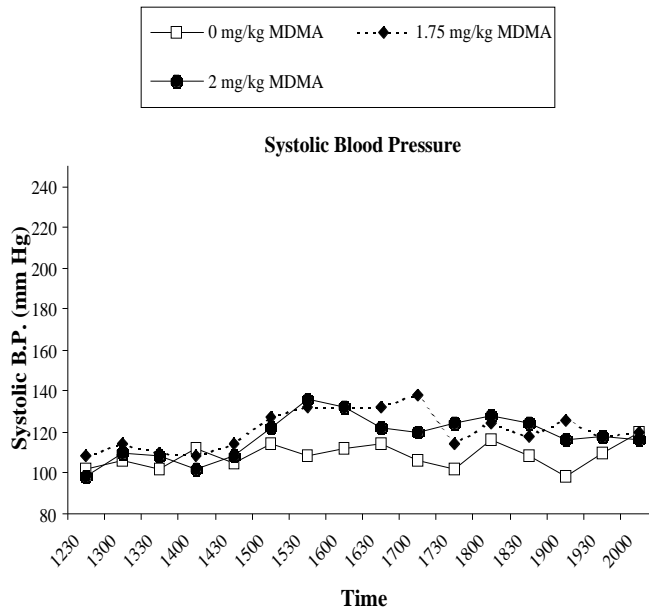
Weight = 77.0 kg

SAFETY DATA FROM SUBJECT 13: 35-Year-old Female

SESSION ONE

Dose = 0.00 mg/kg MDMA

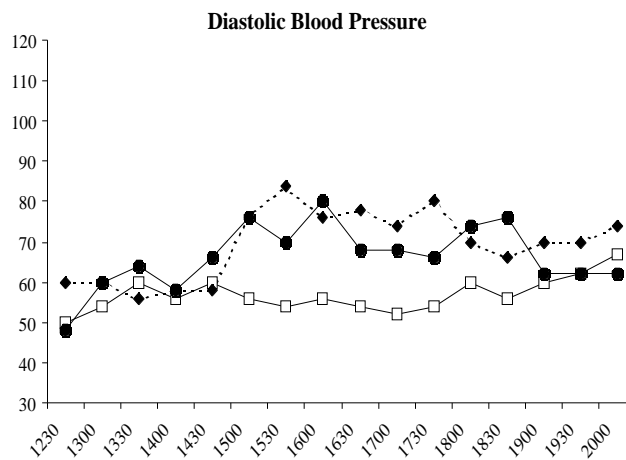
TIME	SYS	DIAS	H.R.	TEMP
1230	102	50	70	98.5
1300	106	54	66	97.6
1330	102	60	69	98.0
1400	112	56	73	98.0
1430	105	60	64	96.5
1500	114	56	61	98.2
1530	108	54	74	99.0
1600	112	56	67	98.6
1630	114	54	65	99.1
1700	106	52	74	98.4
1730	102	54	67	98.4
1800	116	60	66	98.5
1830	108	56	65	98.6
1900	98	60	64	98.7
1930	110	62	69	99.2
2000	120	67	70	98.7



SESSION TWO

Dose = 1.75 mg/kg MDMA 97.0 mg

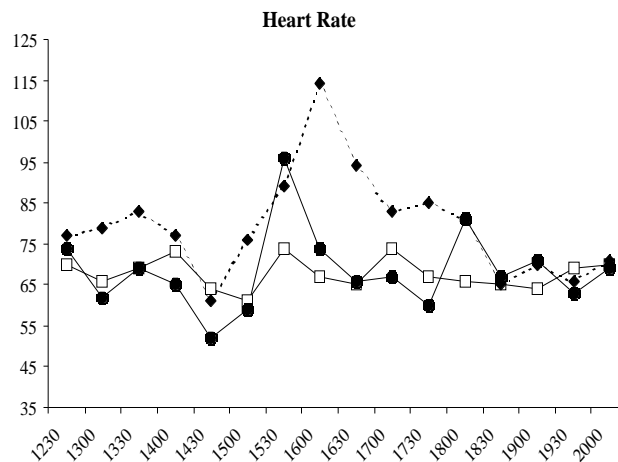
TIME	SYS	DIAS	H.R.	TEMP
1230	108	60	77	98.8
1300	114	60	79	98.8
1330	110	56	83	98.2
1400	108	58	77	98.0
1430	114	58	61	97.7
1500	127	76	76	98.1
1530	132	84	89	98.5
1600	132	76	114	98.7
1630	132	78	94	98.2
1700	138	74	83	98.1
1730	114	80	85	98.2
1800	124	70	81	98.8
1830	118	66	65	98.8
1900	126	70	70	98.7
1930	118	70	66	98.6
2000	120	74	71	98.8



SESSION THREE

Dose = 2.00 mg/kg MDMA 110.8 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	98	48	74	98.8
1300	110	60	62	97.7
1330	108	64	69	97.8
1400	102	58	65	97.8
1430	108	66	52	96.3
1500	122	76	59	97.6
1530	136	70	96	98.1
1600	132	80	74	98.5
1630	122	68	66	99.0
1700	120	68	67	98.8
1730	124	66	60	98.4
1800	128	74	81	97.7
1830	124	76	67	98.6
1900	116	62	71	99.2
1930	118	62	63	99.1
2000	116	62	69	98.1



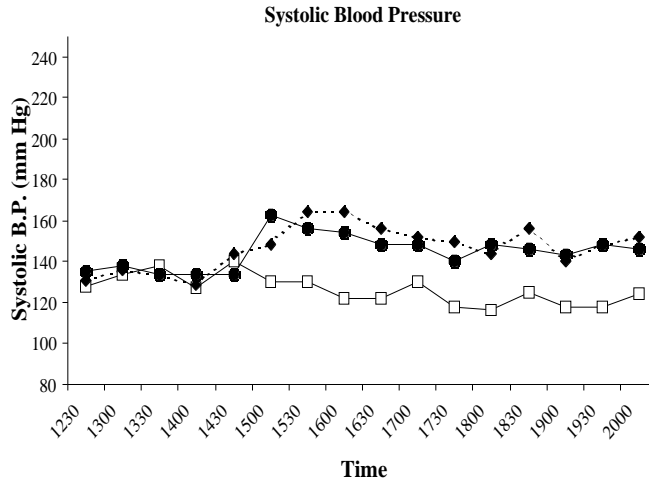
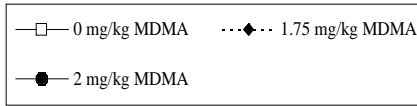
Weight = 55.4 kg

SAFETY DATA FROM SUBJECT 14: 48-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

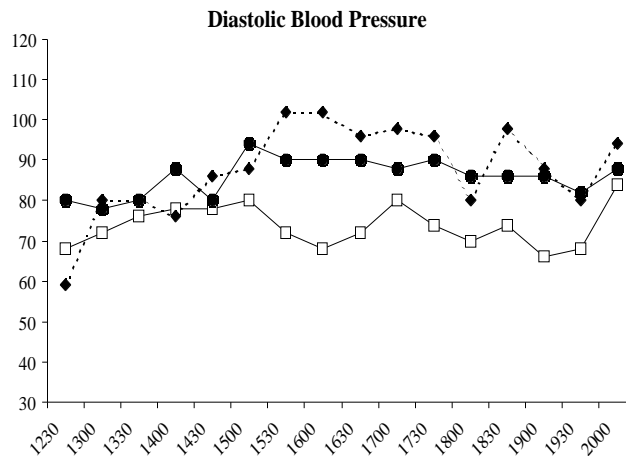
TIME	SYS	DIAS	H.R.	TEMP
1230	128	68	52	98.0
1300	134	72	50	97.7
1330	138	76	50	97.6
1400	127	78	54	97.0
1430	140	78	50	97.3
1500	130	80	49	98.2
1530	130	72	53	98.4
1600	122	68	49	98.2
1630	122	72	50	98.2
1700	130	80	60	97.3
1730	118	74	52	97.9
1800	116	70	53	97.9
1830	125	74	52	98.6
1900	118	66	49	97.9
1930	118	68	48	97.7
2000	124	84	50	97.9



SESSION TWO

Dose = 1.75 mg/kg MDMA 125.3 mg

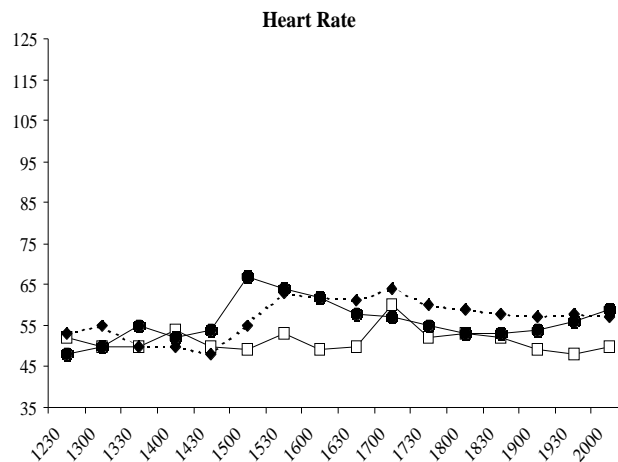
TIME	SYS	DIAS	H.R.	TEMP
1230	131	59	53	98.0
1300	136	80	55	98.4
1330	134	80	50	98.2
1400	129	76	50	97.6
1430	144	86	48	97.7
1500	148	88	55	98.1
1530	164	102	63	98.2
1600	164	102	62	98.6
1630	156	96	61	98.8
1700	152	98	64	99.0
1730	150	96	60	98.9
1800	144	80	59	98.1
1830	156	98	58	98.2
1900	140	88	57	98.3
1930	148	80	58	98.5
2000	152	94	57	99.6



SESSION THREE

Dose = 2.00 mg/kg MDMA 143.2 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	135	80	48	97.6
1300	138	78	50	97.4
1330	134	80	55	97.2
1400	134	88	52	97.7
1430	134	80	54	96.6
1500	163	94	67	97.1
1530	156	90	64	97.1
1600	154	90	62	97.7
1630	148	90	58	98.1
1700	148	88	57	98.2
1730	140	90	55	98.2
1800	148	86	53	98.2
1830	146	86	53	97.5
1900	143	86	54	97.6
1930	148	82	56	98.2
2000	146	88	59	97.8



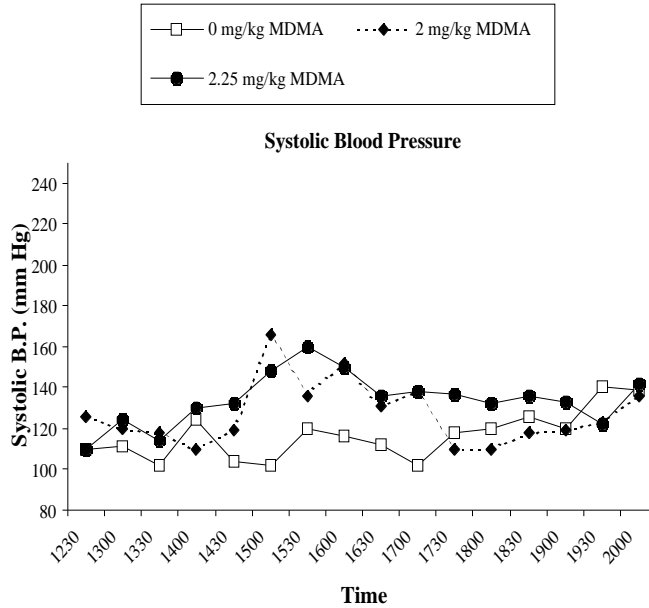
Weight = 71.6 kg

SAFETY DATA FROM SUBJECT 15: 21-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

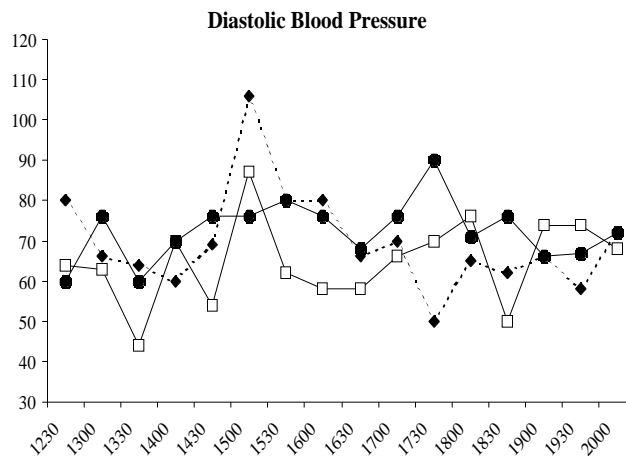
TIME	SYS	DIAS	H.R.	TEMP
1230	110	64	53	97.0
1300	111	63	54	96.6
1330	102	44	52	96.5
1400	124	70	66	96.0
1430	104	54	48	96.2
1500	102	87	53	97.3
1530	120	62	47	97.1
1600	116	58	44	97.8
1630	112	58	44	97.5
1700	102	66	50	97.5
1730	118	70	52	97.8
1800	120	76	55	97.8
1830	126	50	48	97.8
1900	120	74	45	98.2
1930	140	74	57	98.5
2000	139	68	54	98.1



SESSION TWO

Dose = 2.00 mg/kg MDMA 156.0 mg

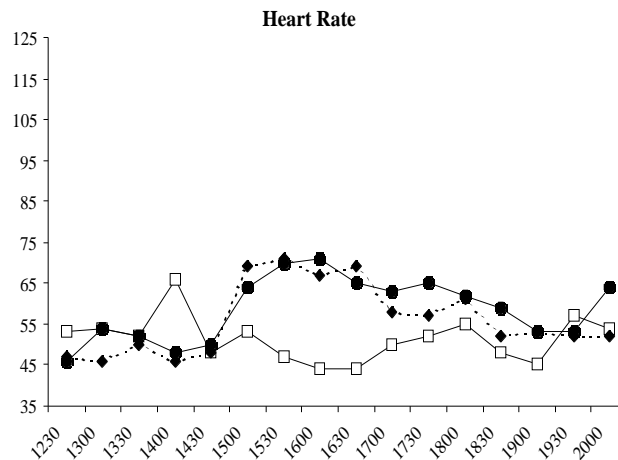
TIME	SYS	DIAS	H.R.	TEMP
1230	126	80	47	96.8
1300	120	66	46	96.5
1330	118	64	50	96.1
1400	110	60	46	96.2
1430	119	69	48	96.5
1500	166	106	69	96.2
1530	136	80	71	96.5
1600	152	80	67	97.9
1630	131	66	69	97.2
1700	138	70	58	98.0
1730	110	50	57	98.3
1800	110	65	61	98.1
1830	118	62	52	98.2
1900	119	66	53	97.8
1930	123	58	52	98.2
2000	136	72	52	97.7



SESSION THREE

Dose = 2.25 mg/kg MDMA 175.5 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	110	60	46	96.9
1300	124	76	54	96.5
1330	114	60	52	96.8
1400	130	70	48	96.6
1430	132	76	50	96.6
1500	148	76	64	96.0
1530	160	80	70	97.3
1600	150	76	71	97.8
1630	136	68	65	97.2
1700	138	76	63	97.3
1730	137	90	65	97.5
1800	132	71	62	97.4
1830	136	76	59	97.7
1900	133	66	53	97.3
1930	122	67	53	97.7
2000	142	72	64	98.3



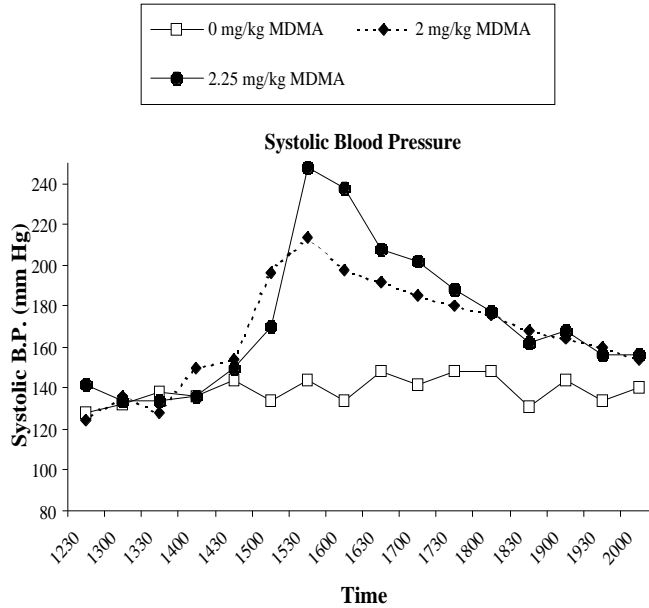
Weight = 78.0 kg

SAFETY DATA FROM SUBJECT 16: 61-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

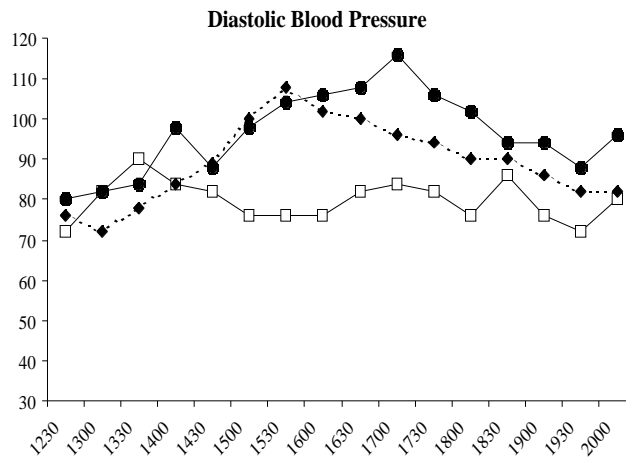
TIME	SYS	DIAS	H.R.	TEMP
1230	128	72	60	98.1
1300	132	82	53	97.9
1330	138	90	58	96.0
1400	136	84	69	97.2
1430	144	82	59	96.3
1500	134	76	66	96.2
1530	144	76	61	95.9
1600	134	76	61	96.9
1630	148	82	64	96.7
1700	142	84	64	96.4
1730	148	82	59	96.2
1800	148	76	59	96.4
1830	131	86	61	97.5
1900	144	76	65	98.1
1930	134	72	60	97.1
2000	140	80	64	97.1



SESSION TWO

Dose = 2.00 mg/kg MDMA 144.0 mg

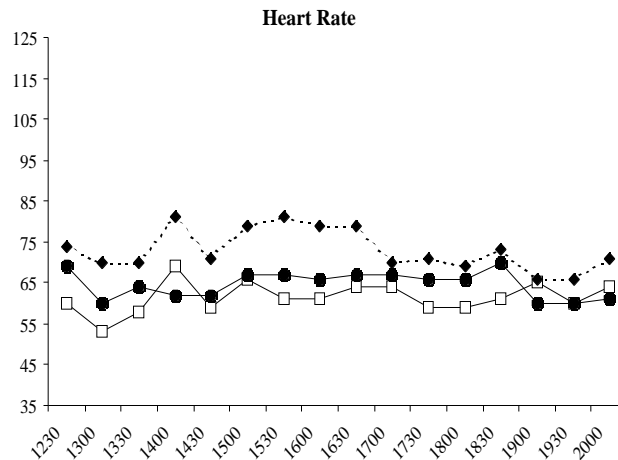
TIME	SYS	DIAS	H.R.	TEMP
1230	124	76	74	95.2
1300	136	72	70	96.8
1330	128	78	70	97.0
1400	150	84	81	97.3
1430	154	89	71	97.0
1500	196	100	79	97.6
1530	214	108	81	99.0
1600	198	102	79	99.2
1630	192	100	79	99.5
1700	185	96	70	98.7
1730	180	94	71	98.4
1800	176	90	69	98.2
1830	168	90	73	98.3
1900	164	86	66	98.5
1930	160	82	66	98.2
2000	154	82	71	98.8



SESSION THREE

Dose = 2.25 mg/kg MDMA 162.0 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	142	80	69	98.4
1300	134	82	60	97.5
1330	134	84	64	98.0
1400	136	98	62	97.6
1430	150	88	62	96.9
1500	170	98	67	97.4
1530	248	104	67	98.3
1600	238	106	66	98.8
1630	208	108	67	99.0
1700	202	116	67	98.0
1730	188	106	66	98.8
1800	177	102	66	98.4
1830	162	94	70	98.6
1900	168	94	60	98.0
1930	156	88	60	98.4
2000	156	96	61	98.3



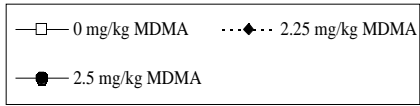
Weight = 72.0 kg

SAFETY DATA FROM SUBJECT 17: 34-Year-old Female

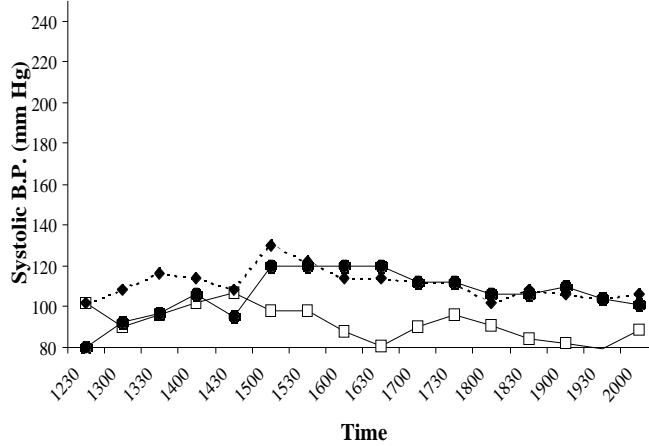
SESSION ONE

Dose = 0.00 mg/kg MDMA

TIME	SYS	DIAS	H.R.	TEMP
1230	102	58	57	98.2
1300	90	52	63	99.0
1330	96	56	65	99.0
1400	102	66	66	99.0
1430	107	62	60	98.8
1500	98	60	59	99.0
1530	98	60	57	98.8
1600	88	56	57	98.7
1630	81	41	54	98.9
1700	90	53	52	98.8
1730	96	56	56	98.7
1800	91	53	48	98.6
1830	84	52	53	98.7
1900	82	44	54	98.7
1930	79	50	59	98.5
2000	89	60	66	98.7



Systolic Blood Pressure

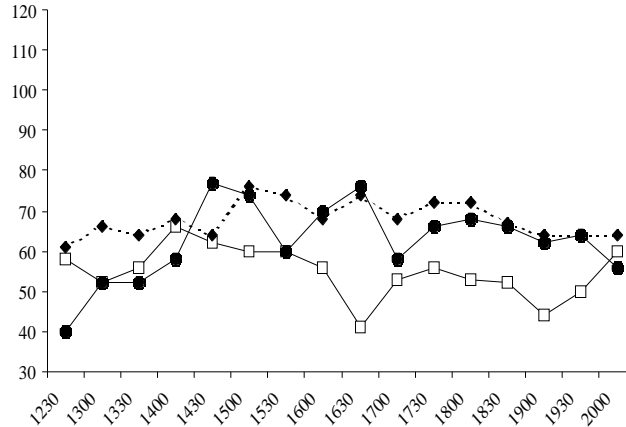


SESSION TWO

Dose = 2.25 mg/kg MDMA 137.3 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	102	61	61	98.3
1300	108	66	66	97.6
1330	116	64	77	98.9
1400	114	68	83	98.1
1430	108	64	63	98.6
1500	130	76	87	99.0
1530	122	74	89	99.0
1600	114	68	79	99.5
1630	114	74	87	98.5
1700	112	68	87	99.2
1730	112	72	67	98.6
1800	102	72	66	98.5
1830	108	67	63	98.4
1900	106	64	63	97.8
1930	104	64	74	97.7
2000	106	64	69	98.2

Diastolic Blood Pressure

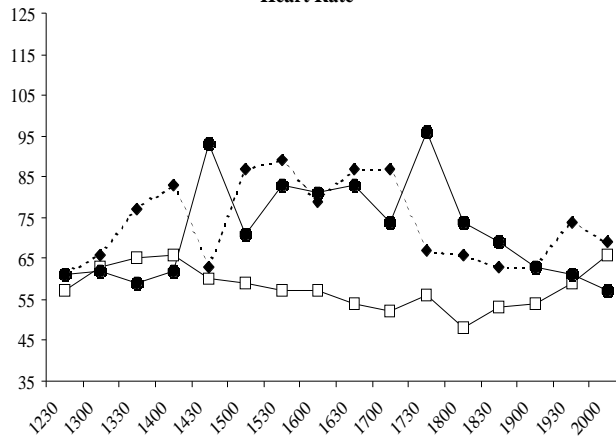


SESSION THREE

Dose = 2.50 mg/kg MDMA 152.5 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	80	40	61	99.0
1300	92	52	62	98.7
1330	97	52	59	98.9
1400	106	58	62	99.1
1430	95	77	93	98.3
1500	120	74	71	98.9
1530	120	60	83	99.0
1600	120	70	81	98.2
1630	120	76	83	98.9
1700	112	58	74	97.7
1730	112	66	96	98.8
1800	106	68	74	98.4
1830	106	66	69	98.2
1900	110	62	63	98.5
1930	104	64	61	98.3
2000	101	56	57	98.3

Heart Rate



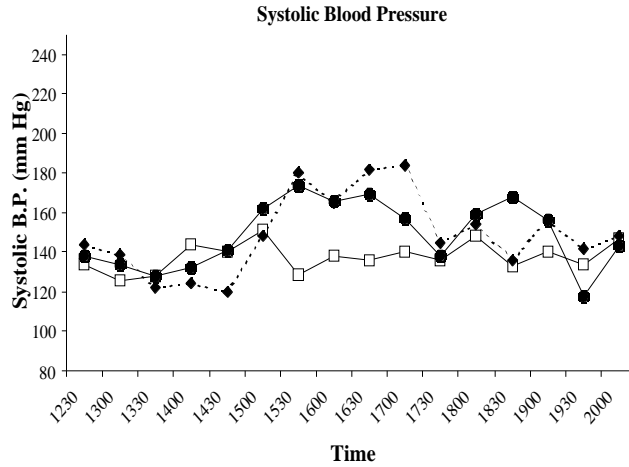
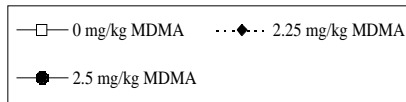
Weight = 61.0 kg

SAFETY DATA FROM SUBJECT 18: 21-Year-old Male

SESSION ONE

Dose = 0.00 mg/kg MDMA

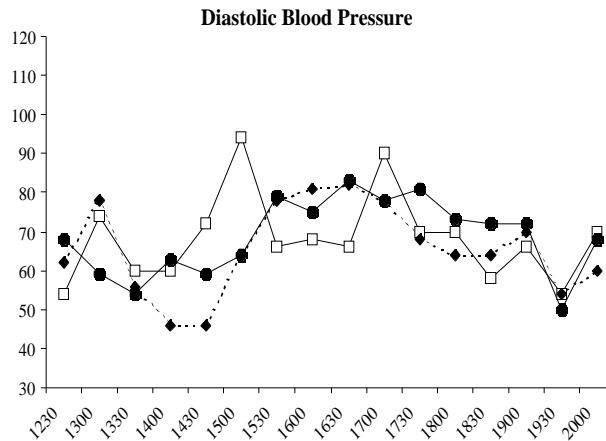
TIME	SYS	DIAS	H.R.	TEMP
1230	134	54	54	98.0
1300	126	74	48	98.0
1330	128	60	53	98.0
1400	144	60	59	97.8
1430	140	72	54	98.4
1500	151	94	61	98.6
1530	129	66	50	98.3
1600	138	68	50	98.5
1630	136	66	52	98.5
1700	140	90	53	98.7
1730	136	70	50	98.2
1800	148	70	60	98.1
1830	133	58	54	98.4
1900	140	66	50	98.0
1930	134	54	52	97.7
2000	147	70	53	98.5



SESSION TWO

Dose = 2.25 mg/kg MDMA 172.8 mg

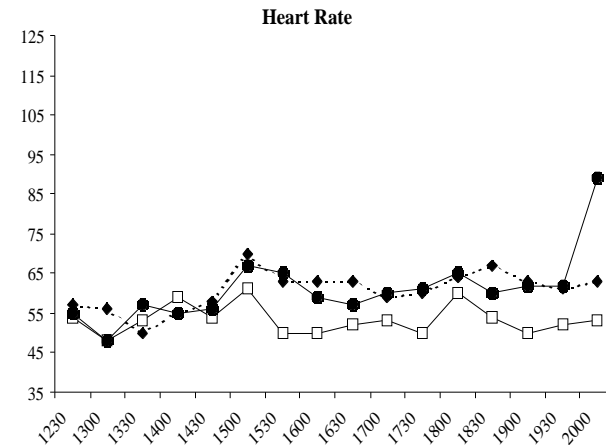
TIME	SYS	DIAS	H.R.	TEMP
1230	144	62	57	98.1
1300	139	78	56	98.5
1330	122	56	50	97.6
1400	124	46	55	98.4
1430	120	46	58	98.5
1500	148	64	70	97.1
1530	180	78	63	97.7
1600	165	81	63	98.7
1630	182	82	63	99.0
1700	184	78	59	97.8
1730	145	68	60	99.0
1800	154	64	64	98.8
1830	136	64	67	98.2
1900	156	70	63	98.3
1930	142	54	61	98.1
2000	148	60	63	98.4



SESSION THREE

Dose = 2.50 mg/kg MDMA 192.0 mg

TIME	SYS	DIAS	H.R.	TEMP
1230	138	68	55	98.4
1300	134	59	48	98.3
1330	128	54	57	97.9
1400	132	63	55	98.8
1430	141	59	56	97.5
1500	162	64	67	98.3
1530	174	79	65	98.9
1600	166	75	59	98.3
1630	169	83	57	98.3
1700	157	78	60	98.5
1730	138	81	61	99.0
1800	159	73	65	98.6
1830	168	72	60	98.6
1900	156	72	62	98.4
1930	118	50	62	98.6
2000	143	68	89	98.7



Weight = 76.8

References

- Adamson S (1985) Through the gateway of the heart: Accounts of experiences with MDMA and other empathogenic substances. Four Trees Publications, San Francisco, CA.
- Aghajanian GK, Lieberman JA (2001) Response. *Neuropsychopharmacology* 24: 335-336, http://www.maps.org/publications/2001_aghajanian_1.pdf.
- American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). APA, Washington.
- Arnsten AF (1998) The biology of being frazzled. *Science* 280: 1711-2.
- Battaglia G, Yeh SY, De Souza EB (1988) MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. *Pharmacol Biochem Behav* 29: 269-74, http://www.maps.org/publications/1988_battaglia_2.pdf.
- Beitia G, Cobreros A, Sainz L, Cenarruzabeitia E (2000) Ecstasy-induced toxicity in rat liver. *Liver* 20: 8-15, http://www.maps.org/publications/2000_beitia_1.pdf.
- Blake DD, Owens MD, & Keane TM (1990). Increasing group attendance on a psychiatric unit: an alternating treatments design comparison. *J Behav Ther Exp Psychiatry*, 21: 15-20.
- Bolla KI, McCann UD, Ricaurte GA (1998) Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* 51: 1532-7, http://www.maps.org/publications/1998_bolla_1.pdf.
- Bonny HL, Savary LM (1990) Music and Your Mind. Station Hill, Tarrytown, New York.
- Boone, KB, Chang, L., Grob, CS, Poland, RE (Unpublished, In Preparation). Neuropsychological effects of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy).
- Brady JF, Di Stefano EW, Cho AK (1986) Spectral and inhibitory interactions of (+/-)-3,4-methylenedioxyamphetamine (MDA) and (+/-)-3,4-methylenedioxyamphetamine (MDMA) with rat hepatic microsomes. *Life Sci* 39: 1457-64, http://www.maps.org/publications/1986_brady_1.pdf.
- Brady KT, Sonne S, & Lydiard, RB (1994). Valproate treatment of comorbid panic disorder and affective disorders in two alcoholic patients (Letter). *J Clin Psychopharmacol*, 14(1),.
- Brady K, Killeen T, Saladin M, Dansky B, & Becker S (1994). Comorbid substance abuse and posttraumatic stress disorder: characteristics of women in treatment. *American Journal of Addiction*, 3, 160-164.
- Brady, KT, Charney, DS, Davidson, JRT. (2000) Current Issues in the Management of Posttraumatic Stress Disorder. Medical Education Resources, Littleton, CO.
- Bremner JD, Innis RB, Ng CK et al. (1997) PET measurement of central metabolic correlates of yohimbine administration in posttraumatic stress disorder. *Biol Psychiatry* 54: 246-256.
- Bremner JD, Staib LH, Kaloupek D, et al. (1999) Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. *Biol Psychiatry* 45:806-816 .

- Breslau N (1998) Epidemiology of Trauma and Posttraumatic Stress Disorder. In Yelda R (Ed.) Psychological Trauma. American Psychiatric Association, Washington: 1-29.
- Brunner D, Hen R (1997) Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. *Ann N Y Acad Sci* 836: 81-105.
- Cami J, Farre M, Mas M, Roset PN, Poudevida S, Mas A, San L, de la Torre R (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. *J Clin Psychopharmacol* 20: 455-66, http://www.maps.org/publications/2000_cami_1.pdf.
- Carvalho M, Carvalho F, Bastos ML (2001) Is hyperthermia the triggering factor for hepatotoxicity induced by 3,4- methylenedioxymethamphetamine (ecstasy)? An in vitro study using freshly isolated mouse hepatocytes. *Arch Toxicol* 74: 789-93, http://www.maps.org/publications/2001_carvalho_1.pdf.
- Chang L, Grob CS, Ernst T, Itti L, Mishkin FS, Jose-Melchor R, Poland RE (2000) Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow: a co-registered SPECT and MRI study. *Psychiatry Res* 98: 15-28, http://www.maps.org/publications/2000_chang_1.pdf.
- Cho AK, Hiramatsu M, Distefano EW, Chang AS, Jenden DJ (1990) Stereochemical differences in the metabolism of 3,4-methylenedioxymethamphetamine in vivo and in vitro: a pharmacokinetic analysis. *Drug Metab Dispos* 18: 686-91, http://www.maps.org/publications/1990_cho_1.pdf.
- Chu T, Kumagai Y, DiStefano EW, Cho AK (1996) Disposition of methylenedioxymethamphetamine and three metabolites in the brains of different rat strains and their possible roles in acute serotonin depletion. *Biochem Pharmacol* 51: 789-96, http://www.maps.org/publications/1996_chu_1.pdf.
- Clark CR, Geffen GM, Geffen LB (1987) Catecholamines and attention. II: Pharmacological studies in normal humans. *Neurosci Biobehav Rev* 11: 353-64.
- Commins DL, Vosmer G, Virus RM, Woolverton WL, Schuster CR, Seiden LS (1987) Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther* 241: 338-45, http://www.maps.org/publications/1987_commins_1.pdf.
- Connor TJ, Kelly JP, Leonard BE (2000a) An assessment of the acute effects of the serotonin releasers methylenedioxymethamphetamine, methylenedioxyamphetamine and fenfluramine on immunity in rats. *Immunopharmacology* 46: 223-35, http://www.maps.org/publications/2000_connor_1.pdf.
- Connor TJ, Kelly JP, McGee M, Leonard BE (2000b) Methylenedioxymethamphetamine (MDMA; Ecstasy) suppresses IL-1beta and TNF-alpha secretion following an in vivo lipopolysaccharide challenge. *Life Sci* 67: 1601-12, http://www.maps.org/publications/2000_connor_2.pdf.
- Connor TJ, McNamara MG, Finn D, Currid A, O'Malley M, Redmond AM, Kelly JP, Leonard BE (1998) Acute 3,4-methylenedioxymethamphetamine(MDMA) administration produces a rapid and sustained suppression of immune function in the rat. *Immunopharmacology* 38: 253-60, http://www.maps.org/publications/1998_connor_1.pdf.

- Cozzi NV, Sievert MK, Shulgin AT, Jacob P, 3rd, Ruoho AE (1999) Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. *Eur J Pharmacol* 381: 63-9, http://www.maps.org/publications/1999_cozzi_1.pdf.
- Crifasi J, Long C (1996) Traffic fatality related to the use of methylenedioxymethamphetamine. *J Forensic Sci* 41: 1082-4, http://www.maps.org/publications/1996_crifasi_1.pdf.
- de Boer D, Tan LP, Gorter P, van de Wal RM, Kettenes-van den Bosch JJ, de Bruijn EA, Maes RA (1997) Gas chromatographic/mass spectrometric assay for profiling the enantiomers of 3,4-methylenedioxymethamphetamine and its chiral metabolites using positive chemical ionization ion trap mass spectrometry. *J Mass Spectrom* 32: 1236-46, http://www.maps.org/publications/1997_deboer_1.pdf.
- de la Torre R, Farre M, Ortuno J, Mas M, Brenneisen R, Roset PN, Segura J, Cami J (2000a) Non-linear pharmacokinetics of MDMA ('ecstasy') in humans. *Br J Clin Pharmacol* 49: 104-9, http://www.maps.org/publications/2000_delatorre_1.pdf.
- de la Torre R, Farre M, Roset PN, Hernandez Lopez C, Mas M, Ortuno J, Menoyo E, Pizarro N, Segura J, Cami J (2000b) Pharmacology of MDMA in humans. *Ann N Y Acad Sci* 914: 225-37, http://www.maps.org/publications/2000_delatorre_2.pdf.
- Delaforge M, Jaouen M, Bouille G (1999) Inhibitory metabolite complex formation of methylenedioxymethamphetamine with rat and human cytochrome p450: particular involvement of CYP 2D. *Environmental Toxicology and Pharmacology* 7: 7:153-158, http://www.maps.org/publications/1999_delaforge_1.pdf.
- Doblin R (1995) MDMA Research Update: Phases 1 and 2: The Phase 2 PTSD Study. [Online], . Available: [2000, Aug. 20]. Newsletter of the Multidisciplinary Association for Psychedelic Studies 6: online at <http://www.maps.org/newsletters/v06n2/06202mdm.html>.
- Downing J (1986) The psychological and physiological effects of MDMA on normal volunteers. *J Psychoactive Drugs* 18: 335-40, http://www.maps.org/publications/1986_downing_1.pdf.
- Downing JJ (1985) Testimony of Joseph J. Downing, M.D. In the Matter of MDMA Scheduling. Docket No. 84-48. (United States Department of Justice, Drug Enforcement Administration).
- Drake RE, & Wallach MA (1989). Substance abuse among the chronic mentally ill. *Hosp Community Psychiatry*, 40(10), 1041-6.
- Fallon JK, Kicman AT, Henry JA, Milligan PJ, Cowan DA, Hutt AJ (1999) Stereospecific analysis and enantiomeric disposition of 3, 4-methylenedioxymethamphetamine (Ecstasy) in humans [published erratum appears in *Clin Chem* 1999 Sep;45(9):1585]. *Clin Chem* 45: 1058-69, http://www.maps.org/publications/1999_fallon_1.pdf.
- Faustman, WO & White, PA (1989). Diagnostic and psychopharmacological treatment characteristics of 536 inpatients with posttraumatic stress disorder. *J Nerv Ment Dis*, 177(3), 154-9.
- First MB, Spitzer R, Gibbon M, & Williams J (1994). Structured clinical interview for Axis I DSM-IV disorders. Patient Edition (SCID-I/P, vs 2.0).
- Fischer C, Hatzidimitriou G, Wlos J, Katz J, Ricaurte G (1995) Reorganization of ascending 5-HT axon projections in animals previously exposed to the

- recreational drug (+/-)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy").
J Neurosci 15: 5476-85, http://www.maps.org/publications/1995_fischer_1.pdf.
- Fitzgerald JL, Reid JJ (1990) Effects of methylenedioxymethamphetamine on the release of monoamines from rat brain slices. *Eur J Pharmacol* 191: 217-20, http://www.maps.org/publications/1990_fitzgerald_1.pdf.
- Fitzgerald RL, Blanke RV, Poklis A (1990) Stereoselective pharmacokinetics of 3,4-methylenedioxymethamphetamine in the rat. *Chirality* 2: 241-8, http://www.maps.org/publications/1990_fitzgerald_2.pdf.
- Gamma A, Buck A, Berthold T, Liechti ME, Vollenweider FX (2000) 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [¹⁸F]mefenorex-PET in healthy humans. *Neuropsychopharmacology* 23: 388-95, http://www.maps.org/publications/2000_gamma_1.pdf.
- Gamma A, Buck A, Berthold T, Vollenweider FX (2001) No difference in brain activation during cognitive performance between Ecstasy (MDMA) users and controls: a [¹⁸F]mefenorex-PET study. *Journal of Clinical Psychopharmacology* 21: 66-71, http://www.maps.org/publications/2001_gamma_1.pdf.
- Gamma, A. (2000) Does Ecstasy Cause Memory Deficits? A Review of Studies of Memory Function in Ecstasy Users, report posted on MAPS website, <http://www.maps.org/research/mdma/mdmamemory.html>.
- Garrett ER, Seyda K, Marroum P (1991) High performance liquid chromatographic assays of the illicit designer drug "Ecstasy", a modified amphetamine, with applications to stability, partitioning and plasma protein binding. *Acta Pharm Nord* 3: 9-14, http://www.maps.org/publications/1991_garrett_1.pdf.
- Gasser P (1994) Psycholytic Therapy with MDMA and LSD in Switzerland. *MAPS Newsletter* 5: 3-7, <http://www.maps.org/news-letters/v05n3/05303psy.html>.
- Gijssman HJ, Verkes RJ, van Gerven JM, Cohen AF (1999) MDMA study. *Neuropsychopharmacology* 21: 597, http://www.maps.org/publications/1999_gijssman_1.pdf.
- Gollamudi R, Ali SF, Lipe G, Newport G, Webb P, Lopez M, Leakey JE, Kolta M, Slikker W, Jr. (1989) Influence of inducers and inhibitors on the metabolism in vitro and neurochemical effects in vivo of MDMA. *Neurotoxicology* 10: 455-66, http://www.maps.org/publications/1989_gollamudi_1.pdf.
- Gouzoulis-Mayfrank, E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HJ, Fimm B, Sass H (2000) Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *J Neurol Neurosurg Psychiatry* 68: 719-25 http://www.maps.org/publications/2000_gouzoulis_1.pdf
- Graeff FG, Guimaraes FS, De Andrade TG, Deakin JF (1996) Role of 5-HT in stress, anxiety, and depression. *Pharmacol Biochem Behav* 54: 129-41.
- Greer G, & Tolbert, R. (1985) Using MDMA in psychotherapy. *Advances: Journal of the Institute for the Advancement of Health* 2: 57-59.
- Greer G, Tolbert RA (1986) Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs* 18: 319-27, http://www.maps.org/publications/1986_greer_1.pdf.

- Greer GR, Tolbert R (1998) A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs* 30: 371-9,
http://www.maps.org/publications/1998_greer_1.pdf.
- Griffiths RR, Ator NA, Lukas SE, Lamb, RJ, & Brady JV (1984). Benzodiazepines: drug discrimination and physiological dependence. *NIDA Res Monogr*, 49, 163-4.
- Grillon C, Southwick SM, Charney DS, (1996) The psychobiological basis of posttraumatic stress disorder. *Mol Psychiatry* 1:278-297.
- Grinspoon L, Bakalar JB (1986) Can drugs be used to enhance the psychotherapeutic process? *Am J Psychother* 40: 393-404,
http://www.maps.org/publications/1986_grinspoon_1.pdf.
- Grob CS, Poland RE, Chang L, Ernst T (1996) Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. *Behav Brain Res* 73: 103-7,
http://www.maps.org/publications/1996_grob_1.pdf.
- Grob CS, Poland RE, others (in preparation) Psychological, physiological and neuroendocrine effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") in healthy humans.
- Grof S (1980) *LSD Psychotherapy*. Hunter House, Alameda, CA.
- Grof S (2000) *The Psychology of the Future*. SUNY Press, Albany, NY.
- Gudelsky GA (1996) Effect of ascorbate and cysteine on the 3,4-methylenedioxymethamphetamine-induced depletion of brain serotonin. *J Neural Transm* 103: 1397-404, http://www.maps.org/publications/1996_gudelsky_2.pdf.
- Gudelsky GA, Nash JF (1996) Carrier-mediated release of serotonin by 3,4-methylenedioxymethamphetamine: implications for serotonin-dopamine interactions. *J Neurochem* 66: 243-9,
http://www.maps.org/publications/1996_gudelsky_1.pdf.
- Guimaraes FS, Del Bel EA, Padovan CM, Netto SM, de Almeida RT (1993) Hippocampal 5-HT receptors and consolidation of stressful memories. *Behav Brain Res* 58: 133-9.
- Haertzen, CA (1966). Development of scales based on patterns of drug effects, using the Addiction Research Center Inventory (ARCI). *Psychol Rep*, 18(1), 163-94.
- Harmon RJ, Riggs PD (1996) Clonidine for posttraumatic stress disorder in preschool children. *J Am Acad Child Adolesc Psychiatry* 35: 1247-9.
- Hatzidimitriou G, McCann UD, Ricaurte GA (1999) Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/-)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. *J Neurosci* 19: 5096-107,
http://www.maps.org/publications/1999_hatzidimitriou_1.pdf.
- Helmlin HJ, Bracher K, Bourquin D, Vonlanthen D, Brenneisen R (1996) Analysis of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS. *J Anal Toxicol* 20: 432-40,
http://www.maps.org/publications/1996_helmlin_1.pdf.
- Helmlin HJ, Brenneisen R (1992) Determination of psychotropic phenylalkylamine derivatives in biological matrices by high-performance liquid chromatography with photodiode-array detection. *J Chromatogr* 593: 87-94,
http://www.maps.org/publications/1992_helmlin_1.pdf.

- Henry JA, Fallon JK, Kicman AT, Hutt AJ, Cowan DA, Forsling M (1998) Low-dose MDMA ("ecstasy") induces vasopressin secretion. *Lancet* 351: 1784, http://www.maps.org/publications/1998_henry_1.pdf.
- Hensley D, Cody JT (1999) Simultaneous determination of amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), and methylenedioxyethylamphetamine (MDEA) enantiomers by GC-MS. *J Anal Toxicol* 23: 518-23, http://www.maps.org/publications/1999_hensley_1.pdf.
- Hiramatsu M, Cho AK (1990) Enantiomeric differences in the effects of 3,4-methylenedioxyamphetamine on extracellular monoamines and metabolites in the striatum of freely-moving rats: an in vivo microdialysis study. *Neuropharmacology* 29: 269-75, http://www.maps.org/publications/1990_hiramatsu_1.pdf.
- Hiramatsu M, Kumagai Y, Unger SE, Cho AK (1990) Metabolism of methylenedioxymethamphetamine: formation of dihydroxymethamphetamine and a quinone identified as its glutathione adduct. *J Pharmacol Exp Ther* 254: 521-7, http://www.maps.org/publications/1990_hiramatsu_2.pdf.
- Hiratsuka A, Chu TY, Distefano EW, Lin LY, Schmitz DA, Cho AK (1995) Inactivation of constitutive hepatic cytochromes P450 by phencyclidine in the rat. *Drug Metab Dispos* 23: 201-6, http://www.maps.org/publications/1995_hiratsuka_1.pdf.
- Holland J (Ed). (2001). *Ecstasy, a complete guide: A comprehensive look at the risks and benefits of MDMA* (Publication date: August, 2001). Rochester, VT: Inner Traditions.
- Horowitz M, Wilner N, & Alvarez W (1979). Impact of Event Scale: a measure of subjective stress. *Psychosom Med*, 41, 209-18.
- House RV, Thomas PT, Bhargava HN (1995) Selective modulation of immune function resulting from in vitro exposure to methylenedioxyamphetamine (Ecstasy). *Toxicology* 96: 59-69, http://www.maps.org/publications/1995_house_1.pdf.
- Johnson M, Letter AA, Merchant K, Hanson GR, Gibb JW (1988) Effects of 3,4-methylenedioxyamphetamine and 3,4-methylenedioxyamphetamine isomers on central serotonergic, dopaminergic and nigral neurotensin systems of the rat. *J Pharmacol Exp Ther* 244: 977-82, http://www.maps.org/publications/1988_johnson_1.pdf.
- Kankaanpaa A, Meririnne E, Lillsunde P, Seppala T (1998) The acute effects of amphetamine derivatives on extracellular serotonin and dopamine levels in rat nucleus accumbens. *Pharmacol Biochem Behav* 59: 1003-9, http://www.maps.org/publications/1998_kankaanpaa_1.pdf.
- Kessler RC, Sonnega A, Bromet EJ, Hughes M, Nelson CB, (1995) Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 52:1048-1060 .
- Kessler RC, Zhao S, Katz SJ, et al. (1999) Past-year use of outpatient services for psychiatric problems. The National Comorbidity Survey. *Am J Psychiatry* 156: 115-123.
- Kinzie JD, Leung P (1989) Clonidine in Cambodian patients with posttraumatic stress disorder. *J Nerv Ment Dis* 177: 546-50.

- Koch S, Galloway MP (1997) MDMA induced dopamine release in vivo: role of endogenous serotonin. *J Neural Transm* 104: 135-46, http://www.maps.org/publications/1997_koch_1.pdf.
- Kreth K, Kovar K, Schwab M, Zanger UM (2000) Identification of the human cytochromes P450 involved in the oxidative metabolism of "Ecstasy"-related designer drugs. *Biochem Pharmacol* 59: 1563-71, http://www.maps.org/publications/2000_kreth_1.pdf.
- Kumagai Y, Wickham KA, Schmitz DA, Cho AK (1991) Metabolism of methylenedioxyphenyl compounds by rabbit liver preparations. Participation of different cytochrome P450 isozymes in the demethylenation reaction. *Biochem Pharmacol* 42: 1061-7, http://www.maps.org/publications/1991_kumagai_1.pdf.
- Lanz M, Brenneisen R, Thormann W (1997) Enantioselective determination of 3,4-methylene-dioxymethamphetamine and two of its metabolites in human urine by cyclodextrin-modified capillary zone electrophoresis. *Electrophoresis* 18: 1035-43, http://www.maps.org/publications/1997_lanz_1.pdf.
- Lavelle A, Honner V, Docherty JR (1999) Investigation of the prejunctional alpha2-adrenoceptor mediated actions of MDMA in rat atrium and vas deferens. *Br J Pharmacol* 128: 975-80, http://www.maps.org/publications/1999_lavelle_1.pdf.
- Lester SJ, Baggott M, Welm S, Schiller NB, Jones RT, Foster E, Mendelson J (2000) Cardiovascular effects of 3,4-methylenedioxymethamphetamine. A double-blind, placebo-controlled trial. *Ann Intern Med* 133: 969-973, http://www.maps.org/publications/2001_lester_1.pdf.
- Lew, R, Sabol KE, Chou C, Vosmer GL, Richards J, Seiden LS (1996) Methylenedioxymethamphetamine-induced serotonin deficits are followed by partial recovery over a 52-week period. Part II: Radioligand binding and autoradiography studies. *J Pharmacol Exp Ther* 276: 855-65 http://www.maps.org/publications/1996_lew_1.pdf
- Lieberman JA, Aghajanian GK (1999) Caveat emptor: researcher beware. *Neuropsychopharmacology* 21: 471-3, http://www.maps.org/publications/1999_lieberman_1.pdf.
- Liechti ME, Baumann C, Gamma A, Vollenweider FX (2000a) Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology* 22: 513-21, http://www.maps.org/publications/2000_liechti_1.pdf.
- Liechti ME, Gamma A, Vollenweider FX (2001a) Gender differences in the subjective effects of MDMA. *Psychopharmacology*, 154: 161-168 http://www.maps.org/publications/2001_liechti_1.pdf.
- Liechti ME, Geyer MA, Hell D, Vollenweider FX (2001b) Effects of MDMA (Ecstasy) on pre-pulse inhibition and habituation of startle in humans after pretreatment with citalopam, haloperidol, or ketanserin. *Neuropsychopharmacology* 24: 240-252, http://www.maps.org/publications/2001_liechti_2.pdf.
- Liechti ME, Saur MR, Gamma A, Hell D, Vollenweider FX (2000b) Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT(2) antagonist ketanserin in healthy humans. *Neuropsychopharmacology* 23: 396-404, http://www.maps.org/publications/2000_liechti_2.pdf.

- Liechti ME, Vollenweider FX (2000a) Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans. *Eur Neuropsychopharmacol* 10: 289-95, http://www.maps.org/publications/2000_liechti_3.pdf.
- Liechti ME, Vollenweider FX (2000b) The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. *J Psychopharmacol* 14: 269-74, http://www.maps.org/publications/2000_liechti_4.pdf.
- Lim HK, Foltz RL (1988) In vivo and in vitro metabolism of 3,4-(methylenedioxy)methamphetamine in the rat: identification of metabolites using an ion trap detector. *Chem Res Toxicol* 1: 370-8, http://www.maps.org/publications/1988_lim_1.pdf.
- Lin HQ, Jackson DM, Atrens DM, Christie MJ, McGregor IS (1997) Serotonergic modulation of 3,4-methylenedioxymethamphetamine (MDMA)-elicited reduction of response rate but not rewarding threshold in accumbal self-stimulation. *Brain Res* 744: 351-7, http://www.maps.org/publications/1997_lin_1.pdf.
- Lin LY, Di Stefano EW, Schmitz DA, Hsu L, Ellis SW, Lennard MS, Tucker GT, Cho AK (1997) Oxidation of methamphetamine and methylenedioxymethamphetamine by CYP2D6. *Drug Metab Dispos* 25: 1059-64, http://www.maps.org/publications/1997_lin_2.pdf.
- Lin LY, Kumagai Y, Cho AK (1992) Enzymatic and chemical demethylenation of (methylenedioxy)amphetamine and (methylenedioxy)methamphetamine by rat brain microsomes. *Chem Res Toxicol* 5: 401-6, http://www.maps.org/publications/1992_lin_1.pdf.
- Ling M, Perry P, Tsuang M, (1981) Side effects of corticosteroid therapy. *Arch Gen Psychiatry* 38:471-477.
- Manchee GR, Eddershaw PJ, Ranshaw LE, Herriott D, Park GR, Bayliss MK, Tarbit MH (1996) The aliphatic oxidation of salmeterol to alpha-hydroxysalmeterol in human liver microsomes is catalyzed by CYP3A. *Drug Metab Dispos* 24: 555-9.
- Mas M, Farre M, de la Torre R, Roset PN, Ortuno J, Segura J, Cami J (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. *J Pharmacol Exp Ther* 290: 136-45, http://www.maps.org/publications/1999_mas_1.pdf.
- Matsushima K, Nagai T, Kamiyama S (1998) Optical isomer analysis of 3,4-methylenedioxyamphetamine analogues and their stereoselective disposition in rats. *J Anal Toxicol* 22: 33-9, http://www.maps.org/publications/1998_matsushima_1.pdf.
- Maurer HH, Bickeboeller-Friedrich J, Kraemer T, Peters FT (2000) Toxicokinetics and analytical toxicology of amphetamine-derived designer drugs ('Ecstasy'). *Toxicol Lett* 112-113: 133-42, http://www.maps.org/publications/2000_maurer_1.pdf.
- McCann UD, Ricaurte G (2001) Caveat Emptor: Editors Beware. *Neuropsychopharmacology* 24: 333-334, http://www.maps.org/publications/2001_mccann_1.pdf.
- McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA (1998) Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin

- neurons in human beings. *Lancet* 352: 1433-7,
http://www.maps.org/publications/1998_mccann_1.pdf.
- McElhatton PR, Bateman DN, Evans C, Pughe KR, Thomas SH (1999) Congenital anomalies after prenatal ecstasy exposure. *Lancet* 354: 1441-2,
http://www.maps.org/publications/1999_mcelhatton_1.pdf.
- McFarlane AC (1989) The aetiology of posttraumatic stress disorder morbidity: predisposing, precipitating and perpetuating factors. *Br J Psychiatry* 154: 221-228.
- Meltaer-Brody K, Hidalgo R, Connor KM, Davidson J. (2000) Posttraumatic Stress Disorder: Prevalence, Health Care Costs, and Pharmacologic Considerations. *Psychiatric Annals* 30 (12): 722-730.
- Metzner R (1988) The nature of the MDMA experience and its role in healing, psychotherapy and spiritual practice. *ReVision* 10 (4).
- Montgomery D & Wakelin J (2000) Post traumatic Stress Disorder: Guidelines for investigating efficacy of pharmacological intervention. *European Neuropsychopharmacology*. 10: 297-303.
- Moore KA, Mozayani A, Fierro MF, Poklis A (1996) Distribution of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) stereoisomers in a fatal poisoning. *Forensic Sci Int* 83: 111-9, http://www.maps.org/publications/1996_moore_1.pdf.
- Nagy LM, Morgan CAD, Southwick SM, & Charney DS (1993). Open prospective trial of fluoxetine for posttraumatic stress disorder. *J Clin Psychopharmacol*, 13, 107-13.
- Nash JF, Brodtkin J (1991) Microdialysis studies on 3,4-methylenedioxymethamphetamine-induced dopamine release: effect of dopamine uptake inhibitors. *J Pharmacol Exp Ther* 259: 820-5,
http://www.maps.org/publications/1991_nash_1.pdf.
- Nash JF, Roth BL, Brodtkin JD, Nichols DE, Gudelsky GA (1994) Effect of the R(-) and S(+) isomers of MDA and MDMA on phosphatidyl inositol turnover in cultured cells expressing 5-HT_{2A} or 5-HT_{2C} receptors. *Neurosci Lett* 177: 111-5,
http://www.maps.org/publications/1994_nash_1.pdf.
- Nichols, DE and Oberlender, R. (1990) Structure-activity relationships of MDMA and related compounds: A new class of psychoactive agents? In S.J. Peroutka (Ed.), *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA*. Holland, Kluwer.
- Nunes EV, Quitkin FM, & Klein DF (1989). Psychiatric diagnosis in cocaine abuse. *Psychiatry Res*, 28(1), 105-14.
- O'Hearn E, Battaglia G, De Souza EB, Kuhar MJ, Molliver ME (1988) Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of serotonergic axon terminals in forebrain: immunocytochemical evidence for neurotoxicity. *J Neurosci* 8: 2788-803,
http://www.maps.org/publications/1988_ohearn_1.pdf.
- Ortuno J, Pizarro N, Farre M, Mas M, Segura J, Cami J, Brenneisen R, de la Torre R (1999) Quantification of 3,4-methylenedioxymetamphetamine and its metabolites in plasma and urine by gas chromatography with nitrogen-phosphorus detection. *J*

- Chromatogr B Biomed Sci Appl 723: 221-32,
http://www.maps.org/publications/1999_ortuno_1.pdf.
- Pacifici R, Zuccaro P, Farre M, Pichini S, Di Carlo S, Roset PN, Hernandez Lopez C, Ortuno J, Segura J, Cami J, de la Torre R (2000) Immunomodulating activity of MDMA. *Ann N Y Acad Sci* 914: 215-24,
http://www.maps.org/publications/2000_pacifici_1.pdf.
- Pacifici R, Zuccaro P, Farre M, Pichini S, Di Carlo S, Roset PN, Ortuno J, Segura J, de la Torre R (1999) Immunomodulating properties of MDMA alone and in combination with alcohol: a pilot study. *Life Sci* 65: L309-16,
http://www.maps.org/publications/1999_pacifici_1.pdf.
- Pacifici R, Zuccaro P, Lopez CH, Pichini S, Di Carlo S, Farre M, Roset PN, Ortuno J, Segura J, Torre RL (2001) Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans. *J Pharmacol Exp Ther* 296: 207-15,
http://www.maps.org/publications/2001_pacifici_1.pdf.
- Palfreyman MG, Schmidt CJ, Sorensen SM, Dudley MW, Kehne JH, Moser P, Gittos MW, Carr AA (1993) Electrophysiological, biochemical and behavioral evidence for 5-HT₂ and 5-HT₃ mediated control of dopaminergic function. *Psychopharmacology (Berl)* 112: S60-7,
http://www.maps.org/publications/1993_palfreyman_1.pdf.
- Ramcharan S, Meenhorst PL, Otten JM, Koks CH, de Boer D, Maes RA, Beijnen JH (1998) Survival after massive ecstasy overdose. *J Toxicol Clin Toxicol* 36: 727-31, http://www.maps.org/publications/1998_ramcharan_1.pdf.
- Rauch SL, van der Kolk BA, Fisler RE, et al. (1996) A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script driven imagery. *Arch Gen Psychiatry*. 53: 380-387.
- Ritz MC, Kuhar MJ (1993) Psychostimulant drugs and a dopamine hypothesis regarding addiction: update on recent research. *Biochem Soc Symp* 59: 51-64.
- Robbins TW, Everitt BJ (2000) Central Norepinephrine Neurons and Behavior *Psychopharmacology, The Fourth Generation of Progress On-Line Edition*. The American College of Neuropsychopharmacology,
<http://www.acnp.org/G4/GN401000033/Default.htm>.
- Robertson AR (1997) Fluoxetine and involuntary recall of remote memories. *Aust N Z J Psychiatry* 31: 128-30.
- Rohrig TP, Prouty RW (1992) Tissue distribution of methylenedioxymethamphetamine. *J Anal Toxicol* 16: 52-3, http://www.maps.org/publications/1992_rohrig_1.pdf.
- Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, Partilla JS (2001) Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* 39: 32-41, http://www.maps.org/publications/2001_rothman_1.pdf.
- Rudnick G, Wall SC (1992) The molecular mechanism of "ecstasy" [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. *Proc Natl Acad Sci U S A* 89: 1817-21,
http://www.maps.org/publications/1992_rudnick_1.pdf.
- Sabol KE, Lew R, Richards JB, Vosmer GL, Seiden LS (1996) Methylenedioxymethamphetamine-induced serotonin deficits are followed by

- partial recovery over a 52-week period. Part I: Synaptosomal uptake and tissue concentrations. *J Pharmacol Exp Ther* 276: 846-854
http://www.maps.org/publications/1996_sabol.1.pdf
- Sapolsky R, Uno H, Rebert CS (1990) Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci.* 10: 2897-2902.
- Saunders N (1993) *E for Ecstasy*. Neal's Yard Desktop Publishing, London.
- Scheffel U, Szabo Z, Mathews WB, Finley PA, Dannals RF, Ravert HT, Szabo K, Yuan J, Ricaurte GA (1998) In vivo detection of short- and long-term MDMA neurotoxicity--a positron emission tomography study in the living baboon brain. *Synapse* 29: 183-92, http://www.maps.org/publications/1998_scheffel_1.pdf.
- Schmidt CJ, Fadayeel GM, Sullivan CK, Taylor VL (1992) 5-HT₂ receptors exert a state-dependent regulation of dopaminergic function: studies with MDL 100,907 and the amphetamine analogue, 3,4-methylenedioxymethamphetamine. *Eur J Pharmacol* 223: 65-74, http://www.maps.org/publications/1992_schmidt_2.pdf.
- Schuldiner S, Steiner-Mordoch S, Yelin R, Wall SC, Rudnick G (1993) Amphetamine derivatives interact with both plasma membrane and secretory vesicle biogenic amine transporters. *Mol Pharmacol* 44: 1227-31, http://www.maps.org/publications/1993_schuldiner_1.pdf.
- Shin LM, Kosslyn SM, McNally RJ, et al. (1997) Visual imagery and perception in posttraumatic stress disorder: a positron emission tomography investigation. *Arch Gen Psychiatry.* 54:233-237.
- Shulgin, AT. (1990) History of MDMA. In SJ Peroutka (Ed.) *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA*. Boston, MA, Kluwer Academic Publishers.
- Simantov R, Tauber M (1997) The abused drug MDMA (Ecstasy) induces programmed death of human serotonergic cells. *Faseb J* 11: 141-6, http://www.maps.org/publications/1997_simantov_1.pdf.
- Solomon SD & Davidson JRT (1997) Trauma: Prevalence, impairment, service use, and cost. *J Clin Psychiatry.* 58(suppl): 5-11.
- Stumm G, Schlegel J, Schafer T, Wurz C, Mennel HD, Krieg JC, Vedder H (1999) Amphetamines induce apoptosis and regulation of bcl-x splice variants in neocortical neurons. *Faseb J* 13: 1065-72, http://www.maps.org/publications/1999_stumm_1.pdf.
- Tucker GT, Lennard MS, Ellis SW, Woods HF, Cho AK, Lin LY, Hiratsuka A, Schmitz DA, Chu TY (1994) The demethylenation of methylenedioxymethamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6). *Biochem Pharmacol* 47: 1151-6, http://www.maps.org/publications/1994_tucker_1.pdf.
- Unkefer RF (1990) *Music Therapy in the Treatment of Adults with Mental Disorders: Theoretical Bases and Clinical Interventions*. Schirmer Books, New York.
- Van der Kolk BA (1997) The psychobiology of posttraumatic stress disorder. *Clin Psychiatry* 58(suppl):16-24.
- Varela-Rey M, Montiel-Duarte C, Beitia G, Cenarruzabeitia E, Iraburu MJ (1999) 3,4-methylenedioxymethamphetamine ("Ecstasy") stimulates the expression of alpha1(I) procollagen mRNA in hepatic stellate cells. *Biochem Biophys Res Commun* 259: 678-82.

- Varela-Rey M, Montiel-Duarte C, Beitia G, Cenarruzabeitia E, Iraburu MJ (1999) 3,4-methylenedioxymethamphetamine ("Ecstasy") stimulates the expression of alpha1(I) procollagen mRNA in hepatic stellate cells. *Biochem Biophys Res Commun* 259: 678-82, http://www.maps.org/publications/1999_varelarey_1.pdf.
- Vollenweider FX, Gamma A, Liechti M, Huber T (1998) Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. *Neuropsychopharmacology* 19: 241-51, http://www.maps.org/publications/1998_vollenweider_1.pdf.
- Vollenweider FX, Gamma A, Liechti M, Huber T (1999a) Is a single dose of MDMA harmless? *Neuropsychopharmacology* 21: 598-600, http://www.maps.org/publications/1999_vollenweider_1.pdf.
- Vollenweider, FX, Gucker, P., Schönbachler, R, Kamber, E, Vollenweider-Scherpenhuyzen, MFI, Schubiger, G, & Hell, D (2000). Effects of MDMA on 5-HT uptake sites using PET and [11C]-McN5652 in humans. Data presented at 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine [Deutsche Gesellschaft für psychiatrie, Psychotherapie und Nervenheilkunde] http://www.maps.org/publications/2000_Vollenweider_1.pdf.
- Vollenweider FX, Remensberger S, Hell D, Geyer MA (1999b) Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. *Psychopharmacology (Berl)* 143: 365-72, http://www.maps.org/publications/1999_vollenweider_2.pdf.
- Widmer S (1997) Listening into the heart of things: The awakening of love: On MDMA and LSD: The undesired psychotherapy. Basic Editions, Basic Editions.
- Wise RA & Bozarth MA (1985) Brain mechanisms of drug reward and euphoria. *Psychiatr Med* 3: 445-60.
- Wolfson PE (1986) Meetings at the edge with Adam: A man for all seasons? *Journal of Psychoactive Drugs* 18: 329-333, http://www.maps.org/publications/1986_wolfson_1.pdf.
- Wolkowitz OM, Reus VI, Weingartner H (1990) Cognitive effects of corticosteroids. *Am J Psychiatry*. 147: 1297-1303.
- Wu D, Otton SV, Inaba T, Kalow W, Sellers EM (1997) Interactions of amphetamine analogs with human liver CYP2D6. *Biochem Pharmacol* 53: 1605-12, http://www.maps.org/publications/1997_wu_1.pdf.
- Yamamoto BK, Nash JF, Gudelsky GA (1995) Modulation of methylenedioxymethamphetamine-induced striatal dopamine release by the interaction between serotonin and gamma-aminobutyric acid in the substantia nigra. *J Pharmacol Exp Ther* 273: 1063-70, http://www.maps.org/publications/1995_yamamoto_1.pdf.
- Zilberg NJ, Weiss DS, & Horowitz MJ (1982). Impact of Event Scale: a cross-validation study and some empirical evidence supporting a conceptual model of stress response syndromes. *J Consult Clin Psychol*, 50(3), 407-14.