3,4-Methylenedioxymethamphetamine (MDMA): A Review of the English-Language Scientific and Medical Literature

Matthew Baggott, B.A. (matt@baggott.net)
Lisa Jerome, Ph.D. (ljerome@bigplanet.com)
Reid Stuart, M.A.

August 1, 2001

Introduction

This document is a review of English-language scientific and medical reports on MDMA/ecstasy. This literature review was commissioned by the Multidisciplinary Association for Psychedelic Studies (MAPS). The goal of this review is to act as a resource for researchers, regulatory agencies, and other interested parties. It is hoped that this review will aid in designing and conducting clinical MDMA research in a manner that reduces risks to volunteers and carefully balances potential benefits against these risks.

This document is divided into five chapters, each summarizing an area of MDMA research: clinical studies; information on illicit users, neurotoxicity research in animals; neurotoxicity research in humans; and adverse events in illicit users. Appendix A contains structured abstracts for all available clinical MDMA studies. Appendix B contains structured abstracts for all available neurotoxicity studies in ecstasy users. Findings from each chapter are summarized below. The document is incomplete in that a planned chapter on the acute neurochemical effects and behavioral pharmacology of MDMA is not included. This chapter is of little relevance to risk assessment and it was considered better to release this document now then to wait for the chapter's completion.

At this time, 1044 MDMA-related papers have been identified using Medline, PsychInfo, and examination of the bibliographies of MDMA-related papers. The most recent search of Medline was conducted on 5/14/2001. It is anticipated that updates of this literature review will be made at regular intervals. We attempted to define "scientific and medical literature" sufficiently broadly so as to avoid excluding any MDMA papers that would be useful for designing and conducting clinical MDMA studies. Although this literature review focuses on papers published in peer-reviewed journals, publications that were not peer-reviewed are discussed if they contain data that are not otherwise available. In addition, several researchers have kindly supplied manuscripts or findings that have not yet been published. These data are also discussed.

Much of the data on MDMA toxicity in humans involves illicit "ecstasy", not all of which is pure MDMA. In this review, we include any cases that may have involved MDMA, and only exclude so-called ecstasy cases in which subsequent analysis excluded the presence of MDMA. Even in cases where MDMA was confirmed, impurities or other drugs may have been present. Throughout this report, the term "ecstasy" is used instead of "MDMA" whenever the identity of the consumed drug is in question.

As a companion project to this literature review, we are obtaining and digitizing all published scientific and medical papers on MDMA. As of this time, 1083 papers have been obtained and digitally formatted. This number is larger than 1044 (the number of published scientific papers on MDMA that we have identified) because additional relevant documents have been scanned. These include a patent, testimony from the MDMA Scheduling Hearings, and articles on MDA. Digitized documents are being collected on a CD that will be submitted to the FDA. In addition, MAPS hopes to make

all digitized documents available on the MAPS website (http://www.maps.org/wwwpb/index). We have not yet been able to obtain approximately 90 published MDMA-related papers, mostly from European journals. Based on the abstracts of these papers, it is not anticipated that the conclusions of the present report will be substantially changed by the contents of these currently unavailable papers.

Readers who are familiar with the history of MDMA-assisted psychotherapy or who have personal knowledge of MDMA's effects may be surprised or even dismayed by the focus of this review. This focus reflects that of the scientific and medical literature, which has been primarily concerned with the potential toxicity of MDMA. Until proper clinical trials are carried out, this situation is not likely to change. Most of the discussion about MDMA's reportedly therapeutic effects has taken place in the lay literature. Although we note these discussions in passing, it was not appropriate to give them detailed treatment in this review. The reader may wish to bear in mind the conservative biases of the medico-scientific literature when reading this document.

The primary author of this review, Matthew Baggott, received a B.A. in Philosophy from the University of Chicago and has engaged in psychopharmacology research for over a decade. He assisted in behavioral neurotoxicity research at the University of Chicago and, more recently, investigated the clinical psychopharmacology of illicit drugs (including MDMA) at the University of California, San Francisco. Lisa Jerome earned a doctorate in psychology from the University of Maryland-College Park in 1999. She co-authored most chapters and was additionally responsible for statistical analysis. Reid Stuart contributed to Chapter 5 and was invaluable in editing the entire manuscript. He received a M.A. in psychology with a specialization in addiction studies from the Graduate School of Professional Psychology at John F. Kennedy University in Orinda, CA.

Research and editorial assistance by Michael Bauer, Kate Chapman, Earth & Fire Erowid, Ben Hidalgo, Zachary Plaut, Graham Scanlon, and Emily Schiller is gratefully acknowledged.

Conclusions and Summary

Matthew Baggott, B.A., Lisa Jerome, Ph.D., and Reid Stuart, M.A.

Conclusions

In reviewing the literature, the authors particularly focused on issues relating to clinical MDMA research. Before summarizing the individual chapters of this document, we will comment on the risks posed to participants in clinical MDMA research. A broad body of research confirms that MDMA can be safely administered in a clinical setting. As of this time, 33 papers have been published describing the effects of MDMA in at least ten independent samples of volunteers. In addition, numerous animal studies, including a FDA-required 28-day toxicity study in dogs and rats, have characterized the potential of MDMA to produce toxicity. Millions of individuals have self-administered ecstasy in uncontrolled settings and rare instances of serious toxicity have been documented in the medical literature. The conclusion that clinical MDMA research can be conducted with low risks is therefore supported by considerable evidence. However, clinical research should proceed cautiously because serious acute adverse reactions, though rare, are possible and the risks of neurotoxicity are incompletely understood.

The risks of neurotoxicity require special consideration. This is because it is not known what dose would produce neurotoxicity in a clinical setting and the consequences of neurotoxicity are poorly understood. If neurotoxicity occurred in a clinical study, it currently appears unlikely that it would produce clinically significant impairment. This is because even multiple exposures to illicit ecstasy in uncontrolled settings are associated with differences that are clinically subtle. Nevertheless, the relative lack of known consequences of MDMA neurotoxicity is not conclusive evidence that neurotoxicity has no consequences of import. Therefore, the potential benefits of carrying out MDMA research must be weighed against the partially unknown risks of neurotoxicity with each proposed protocol. MDMA exposure should be limited to the lowest dose and number of exposures required for the research goals. Whenever practicable, volunteers should be monitored for possible neurotoxicity.

The primary purpose of this review is to aid researchers. However, some of the findings are relevant to illicit users. The probability of a serious acute adverse event after ecstasy use is low, but the consequences of such an event can include serious illness or death. Outcome often depends on receiving prompt medical care, which may not be available in illicit settings. Although it may be possible to minimize ecstasy-related risks, these risks cannot be entirely eliminated and should be carefully considered by prospective users. There is evidence of neurotoxicity in some repeated users and pharmacokinetic estimates suggest there may be a narrow margin of safety between pharmacologically active and neurotoxic doses. Since the amount contained within each dose of illicit ecstasy varies, the cumulative likelihood that an individual will be exposed to a neurotoxic dose increases with each exposure. The possibility of neurotoxicity should therefore be taken seriously by repeated illicit users. In addition, warm ambient temperatures and co-administration of some other drugs, such as psychedelics/hallucinogens, may increase

extent of neurotoxicity. Although the consequences of this neurotoxicity appear to be clinically subtle and do not noticeably affect functioning in everyday life, research in this area is inadequate and any long-term consequences have not been studied.

Summary of Chapter 2: Clinical MDMA Studies

The second chapter of this document summarizes available information on clinical studies in which MDMA was administered. Three research groups in the United States and three more in Europe have conducted controlled clinical studies with MDMA. Thirty-three publications have documented the effects of MDMA in at least ten independent groups of volunteers. Pharmacokinetics and physiological, neuroendocrine, psychological, neurocognitive, cerebrofunctional, and immunological effects of MDMA have been reported. Studies have also used pharmacological probes to investigate the neurochemical mechanisms that produce the psychological and physiological effects of MDMA. In addition, several reports have been published describing clinical work carried out before MDMA became a controlled substance. Detailed descriptions of individual studies are available in Appendix A. There has been no reported evidence of serious or lasting toxicity to volunteers in these studies or to patients in MDMA-assisted psychotherapy

MDMA has been administered in controlled clinical studies using doses of up to 2.5 mg/kg, with most studies employing doses equivalent to 1.5 to 1.7 mg/kg MDMA. Earlier, uncontrolled studies and reports employed higher doses (e.g., up to 4.18 mg/kg in Downing 1986), but collected few and somewhat inconsistent data on drug effects.

The intoxication produced by MDMA in recent clinical studies is consistent with earlier reports of an easily controlled state characterized by euphoria, increased well being, increased sociability, and decreased anxiety. These effects are also consistent with the hypothesis that MDMA represents a novel class of pharmacological agent although further research is needed. Participants reportedly experience modest alterations in perception of surroundings and pleasurable loosening of ego boundaries. Subjective effects are accompanied by robust sympathomimetic cardiovascular effects. Acute increases in circulating cortisol, prolactin, ACTH, and antidiuretic hormone occur.

MDMA has been generally well tolerated, with hypertensive episodes being the most important acute adverse effect noted. Other commonly reported side effects include decreased appetite, jaw clenching, and impaired balance/gait. The acute effects of MDMA peak between one and three hours after drug administration and have largely resolved by six hours after drug administration. Documented effects persisting beyond this point include altered immune functioning, probably lasting about two days, and altered cerebral blood flow, lasting at least several weeks. Some volunteers also report feelings of lethargy and other symptoms for several days after MDMA exposure.

Serotonin release seems to be integral to many of the psychological and physiological effects of MDMA, but $5HT_2$ receptors and dopamine release have also been shown to be involved in producing specific MDMA effects.

MDMA has nonlinear pharmacokinetics with decreased non-renal clearance occurring at higher doses, probably due to inhibition of one metabolic pathway, cytochrome P-450 (CYP) isozyme 2D6. Pharmacological studies suggest that CYP 2D6 may be inactivated by MDMA and may therefore have a limited role in MDMA metabolism. Other enzymes playing a role in MDMA metabolism include CYP 2B6, 1A2, and 3A4.

Summary of Chapter 3: Demographics and Self-Reported Effects of Illicit Ecstasy Use

The third chapter discusses surveys that examine the demographics of ecstasy use and the effects of ecstasy as retrospectively described by illicit ecstasy users. Findings from these retrospective studies are compared with findings from clinical studies. Throughout this report, the term "ecstasy" is used instead of "MDMA" whenever the identity of the consumed drug is in question.

Surveys of ecstasy users are useful for documenting patterns of drug use and common effects of ecstasy in uncontrolled settings. Yet they are limited by both the questions researchers ask and the participants, who may not have experienced the full range of rewarding and adverse drug effects. Therefore, the therapeutic potential of MDMA is better documented in reports of its use in psychotherapy, as described in Chapter 2. Similarly, adverse effects of ecstasy are more adequately documented in the case reports and studies described in Chapters 5 and 6.

Ecstasy use is highest among individuals between the ages of 16 and 25, with the drug most strongly associated with dance and "rave" sub-cultures. However, ecstasy use is not limited to one age group or sub-culture. In the United States, prevalence of ecstasy use in the last year was estimated to be 3.1% for eighth graders, and 8.2% for 12 graders in 2000, and estimated to be 5.5% for college students, and 3.6% for young adults (ages 19-28) in 1999.

In surveys of ecstasy users, commonly reported effects of ecstasy are generally consistent with effects seen in clinical MDMA studies, as described in Chapter 2. However in some surveys, users of illicit ecstasy reported ecstasy-induced hallucinations and increases in sexual arousal, two effects either not reported or contradicted by descriptions appearing in other reports. Differences between clinical studies and retrospective surveys are probably due to a variety of factors, including differences in measurement techniques, differences in respondents' understanding of terms used in measures, and the varying identity, potency, and purity of illicit ecstasy. Comparisons of the effects of ecstasy, amphetamines, and psychedelics/hallucinogens by experienced users support the hypothesis that MDMA has novel psychopharmacological effects.

Few of the reports reviewed in this chapter assessed possible long-term effects of ecstasy use and only a minority of volunteers in these reports described long-term benefits or difficulties. Most users of illicit ecstasy report decreased drug effects (short-term tolerance) when one dose of ecstasy is rapidly followed by another. However, lasting

decrease of drug effects (long-term tolerance) has not been confirmed by all studies asking respondents about this phenomenon.

Summary of Chapter 4: Neurotoxicity Research in Animals

Numerous studies have examined nonhuman animals and tissue cultures for evidence of MDMA-induced neurotoxicity. These studies are important because they allow controlled investigation of toxic changes that may occur in humans. These studies can be divided into three areas of neurochemical investigation: (1) monoaminergic neurotoxicity; (2) non-monoaminergic neurotoxicity; and (3) *in vitro* decreases in neural cell viability. The possible damage identified in each of these areas cannot always be equated. Nonetheless, any study of functioning in intact MDMA-exposed animals implicitly investigates all types of neurotoxicity.

High or repeated-dose MDMA regimens can produce long-term changes in indices of monoaminergic and axonal functioning in animals. Increasing evidence indicates that these changes are at least partially the result of damage. The magnitude of these changes varies with dose, species, and route of administration. Rodent studies have shown that changes in the core temperature of animals can increase or decrease MDMA neurotoxicity, although this finding has not been confirmed in primates. While some recovery does occur, a study in squirrel monkeys suggests that there may be permanent changes in axonal distribution. Oxidative stress appears to play an important role in MDMA neurotoxicity, but the exact mechanisms are poorly understood. The sustained acute pharmacological effects of MDMA may exhaust neuronal energy sources and antioxidant defenses, leading to damage. Metabolites of MDMA are another possible source of oxidative stress. The risks of monoaminergic neurotoxicity in humans are controversial and are discussed in the next chapter.

Research has also uncovered MDMA-induced non-monoaminergic neurotoxicity in rats. Measures of neural cell injury indicate that MDMA, like methamphetamine, can damage non-monoaminergic cell bodies in the somatosensory cortex. Another area of research uses cultured cell lines and has suggested that sustained exposure to MDMA can decrease neural cell viability and trigger programmed cell death. These neural cell changes have only been detected after high MDMA exposures that are unlikely to occur in clinical settings.

Few behavioral correlates of neurotoxic MDMA exposure have been found in drug-free nonhuman animals, despite dramatic serotonergic changes, alterations in neurofunctioning, and changes in response to drugs. Changes in MDMA-exposed animals include thermoregulatory impairment, decreased locomotor activity, and neurocognitive impairment. Lasting thermoregulatory impairment has been demonstrated in MDMA-exposed animals by two research groups. Rats exposed to a neurotoxic MDMA regimen showed reductions in diurnal and nocturnal locomotor activity at 7 to 14 days after drug treatment. Two studies have suggested that neurotoxic MDMA exposure may cause neurocognitive impairment in rats. The first study used adult animals and the second study used newborn rats. In contrast, at least 9 other studies failed to find evidence of neurocognitive impairment in MDMA-exposed animals. These

studies indicate that neurotoxic MDMA exposures can cause behavioral changes. These changes have been difficult to detect and it is not known whether they are temporary or permanent.

Summary of Chapter 5: Neurotoxicity Research in Humans

The fifth chapter reviews the studies that explore the possibility of neurotoxicity in ecstasy users. Studies of illicit ecstasy users are useful in assessing risk because they identify possible areas of toxicity and identify the possible severity of toxic changes. Studies of ecstasy users are limited because it is not always possible to distinguish the effects of MDMA exposure from other factors with confidence and many questions have not been adequately studied. This chapter attempts to interpret findings in a manner that produces a conservative risk assessment.

Most research on ecstasy users can be categorized into two areas of study: neurofunctional measures and neurocognitive measures. In this document, "neurofunctional" is loosely used to indicate measures of how the brain is working and measures of the concentration or density of neurochemicals. "Neurocognitive measures" refers to performance on standardized tests of mental abilities. Research on ecstasy users supports associations between MDMA exposure and alterations in both neurofunctional and neurocognitive measures. Measures that do not cleanly fit either of these categories include those examining mood and personality in ecstasy users. These measures are also reviewed, even though they are difficult to interpret and have questionable relevance for neurotoxicity risk assessment.

Reported neurofunctional differences between ecstasy users and nonusers include concentration of a serotonin metabolite in cerebrospinal fluid (CSF 5HIAA levels), serotonin transporter (SERT) density, $5HT_{2A}$ receptor density, neuroendocrine response to serotonergic drugs, EEG measures, altered sleep architecture, cerebral myo-inositol concentration, cerebral glucose utilization, and cerebral blood flow/volume. There is insufficient evidence to assess the permanence or reversibility of most reported neurofunctional differences.

Statistically significant correlations have been reported between ecstasy exposure and specific neurofunctional measures, such as CSF 5HIAA levels, SERT density, global brain volume, myo-inositol increases, $5HT_{2A}$ receptor density, and EEG alterations. The most conservative interpretation of these correlations is to regard them as evidence that ecstasy exposure caused the neurofunctional differences. A less conservative interpretation would be that differences in these neurofunctional measures predate ecstasy exposure and indicate a tendency to use ecstasy. The authors find this interpretation to be implausible.

In some cases, there are questions as to whether these changes can be considered evidence of serotonergic neurotoxicity rather than responses to the nontoxic pharmacological effects of MDMA. To distinguish between neurotoxicity and responses to pharmacological effects of MDMA, it is helpful to consider (1) animal data on the

effects of MDMA and other serotonergic neurotoxins and (2) human data on the effects of drugs that are not serotonergic neurotoxins, particularly stimulants. When these additional data are considered, some neurofunctional differences can conservatively be regarded as evidence of serotonergic neurotoxicity in users, because they are documented in animals after neurotoxic regimens of MDMA and other serotonergic neurotoxins. These differences include decreases in serotonin transporter and CSF 5HIAA.

Nonetheless, most neurofunctional differences are not clear evidence of selective serotonergic neurotoxicity. Some, such as increased alpha and beta EEG and altered sleep architecture, occur in users of stimulant drugs that do not cause serotonergic neurotoxicity. Others, such as cerebral blood flow/volume and cerebral glucose utilization, are altered in the opposite direction in ecstasy users compared to neurotoxin-exposed animals. Still others, such as increased $5HT_{2A}$ receptor density, have not been seen in animals exposed to serotonergic neurotoxins. These reported differences are of unknown significance.

Neurocognitive performance studies suggest that, under some conditions or patterns of use, ecstasy exposure can decrease performance in some measures of neurocognitive functioning into the lower range of what is considered clinically normal. There is no conclusive evidence that a specific domain of cognitive functioning is impaired in ecstasy users, although some have suggested that a category of mental abilities called "executive function" that includes the ability to plan ahead may be specifically altered. Measures of verbal memory have most consistently detected differences between ecstasy users and nonusers, but many other measures have also sometimes detected differences.

We do not know the relationship between these neurocognitive changes and serotonergic neurotoxicity. Decreased neurocognitive performance can occur in users of other drugs of abuse, such as cocaine or marijuana. Only 2 of at least 11 studies have found evidence of long-term impairment in the neurocognitive performance of animals exposed to neurotoxic MDMA regimens. This suggests that serotonergic neurotoxicity might occur in the absence of neurocognitive performance changes and that neurocognitive performance changes in ecstasy users may or may not be caused by serotonergic neurotoxicity.

There are not yet sufficient data to conclude whether these neurocognitive differences would lessen after the discontinuation of frequent ecstasy exposure. One study and one analysis described in this document found evidence of recovery, while another study and a second analysis in this document found no evidence of recovery. The issue of recovery is worrisome because even small changes in illicit users could be important if they were permanent.

It is possible that impairment will manifest as users age. Some hypothesize that serotonergic neurotoxicity could lead to depression and anxiety disorders as individuals' serotonergic systems undergo age-related decreases in functioning. Although age-related decreases in serotonergic functioning appear relatively modest compared to those seen in the dopaminergic system, age-related changes in the brain are not sufficiently understood

to make predictions about the possible long-term consequences of serotonergic neurotoxicity with any confidence.

Furthermore, there is currently no direct evidence on this issue. There are no published studies with rodents or other animals with short lifespans suggesting MDMA exposure causes significant toxicity that only becomes apparent in the aged animal. There are also no published studies or other evidence of problems developing in humans. MDMA has been widely used for over 20 years and similar drugs with similar capacity for long-term serotonergic changes (e.g., 3,4-methylenedioxyamphetamine, MDA) have been used since the 1960s without evidence of dramatic age-related toxicity. Methamphetamine, which produces both long-term serotonergic and dopaminergic changes, has been used clinically for over 60 years without reported incidents of neurocognitive deficits appearing with age. This lack of evidence of problems developing with age is reassuring, but not conclusive. Until appropriate studies are conducted, lack of evidence of problems cannot be taken as evidence of lack of problems.

Overall, it is very likely that repeated ecstasy exposure causes neurofunctional changes in some illicit users. It is also very likely that some of these changes are due to serotonergic neurotoxicity. Nevertheless, the reported differences between matched groups of ecstasy users and nonusers are clinically subtle and can, so far, only be detected with sensitive neurofunctional and neurocognitive measures. Studies of illicit ecstasy users give no indication that one or two exposures to MDMA in a clinical setting would produce significant or lasting toxicity. Preliminary data from clinical MDMA studies support this conclusion. However, the risks and benefits of proposed MDMA studies must be assessed on an individual basis.

Summary of Chapter 6: Adverse Events in Illicit Users

The final chapter is a summary of the literature on medical emergencies and adverse events related to MDMA/ecstasy. Published analyses suggest that most ecstasy pills contain MDMA. However, many other drugs have been detected in these pills, and some pills sold as ecstasy do not contain any MDMA. This chapter does not discuss cases involving drugs sold as ecstasy that were determined to contain no MDMA. Because serious adverse events are rare after illicit ecstasy exposure, they are even less likely in clinical settings. Nonetheless, this chapter may be useful for assessing and minimizing the risks of acute toxicity in clinical studies.

In 1999, there were 2,848 emergency department (ED) cases involving ecstasy in the United States. 78% of these cases also involved other drugs, most commonly alcohol. Most ecstasy-related ED cases occurred in young adults (age 18 to 25), as would be expected given the demographics of ecstasy use in the United States. Given the distribution of ecstasy use among young adults, it can be estimated that 2.9 to 3.6 in 10,000 ecstasy exposures in young adults resulted in an ED visit. A survey of 329 Australian ecstasy users suggests that this estimate is realistic. In this Australian survey, the equivalent of at least 11 ED visits in 10,000 ecstasy exposures occurred. Deaths relating to ecstasy use are poorly documented in the US. Gore (1999) estimated that 0.21

ecstasy-related deaths per 10,000 illicit users occurred annually in England from 1995-96 and 0.87 ecstasy-related deaths per 10,000 illicit users occurred annually in Scotland from 1995-97. Of course, the probability of an ED visit or death after ecstasy use is not evenly distributed among users. Possible risk factors for ecstasy-related medical emergencies or fatalities are discussed at a later point.

Serious adverse effects occurring after ecstasy use are documented in case reports in the medical literature. Before discussing these reports, it is worth considering that they may not indicate the true frequency of various adverse events. First, published case reports are probably often more severe than cases that go unpublished. Second, they probably under-represent adverse effects of ecstasy that do not require emergency treatment. Three reports – two from poison control centers and one from an emergency department (ED) – suggest that most ecstasy-related ED visits result from symptoms that are modest in severity. Signs and symptoms of ecstasy intoxication documented in these reports are similar to those of amphetamines.

We have obtained over 205 published case reports of adverse events in ecstasy users. Some of these reports describe severe forms of common side effects of ecstasy (difficulty urinating, dental problems), motor vehicle accidents, and other injuries due to intoxication. When these reports are excluded, 199 case reports remain. The most common categories of diagnosis are hyperthermia-related syndromes (24.6% of cases), psychiatric complications (22.1% of cases), hepatotoxicity (16.1% of cases), and hyponatremia (9.5% of cases). Other reported problems include cardiovascular and cerebrovascular, neurological, hematological, respiratory (pneumomediastinum and subcutaneous emphysema), ophthalmic, dermatological, teratological, and dental problems.

Ecstasy-related hyperthermia is described in adverse case reports. While most cases of ecstasy-related hyperthermia were known to have occurred in dance settings, some cases involved individuals who were apparently not involved in “risky” behavior (aside from ecstasy ingestion).

There are reports of hepatotoxicity (liver damage) in ecstasy users. Three *in vitro* studies have confirmed that pure MDMA can damage liver cells and one of these studies found that hyperthermia increases vulnerability to this damage. Although the MDMA concentrations used in these studies are high, they could be attained in individuals taking high doses or having impaired MDMA metabolism (due to pharmacological interactions with other drugs or previous liver damage).

Cases of ecstasy-related hyponatremia (low salt levels) have been reported. The pharmacological effects of MDMA appear to place the user at increased risk of hyponatremia. Consumption of large volumes of water that would normally be safe may lead to symptoms of “water intoxication” after ecstasy ingestion.

The possible dose-dependence of ecstasy toxicity is discussed. It is argued that dose is probably a risk factor for toxicity, but that other risk factors (some of them unknown) are

important and may mask the significance of dose. Probable risk factors include exercise, dehydration, over-hydration, and hot or humid settings. More frequent use or greater total lifetime dose may be risk factors for psychological problems. While rare, serious ecstasy toxicity cannot be predicted beforehand, and in many specific cases cannot be explained afterwards. Serious adverse reactions or even death can occur after modest amounts of ecstasy in the absence of known risk factors.

Finally, it is noted that a minority of users can be classified as dependent on ecstasy, using standard criteria.

Recommendations for Future Psychotherapy Research

With proper precautions, MDMA research should pose low risks to volunteers. Nonetheless, clinical MDMA research is likely to be accompanied by controversy for the next several years due to both scientific and extra-scientific reasons. Given this controversy, the authors of this document suggest to MAPS that a particularly cautious psychotherapy research program could begin with collecting evidence that doses in the vicinity of 125 mg have benefits to treatment-resistant patients before increasing MDMA exposure. Recommended doses around 125 mg were conservatively chosen because they have been widely used in research without evidence of toxicity and with preliminary evidence of non-neurotoxicity. Additionally, the pharmacokinetics of 125 mg have been well-characterized by the Spanish research team. Because higher doses have been administered with apparent safety, 125 mg provides a conservative margin of acute safety while producing sufficient pharmacological effects for research purposes.

Concluding Remark

The illicit use of ecstasy by millions of people is, by itself, a compelling reason to study MDMA. Reports that it is helpful in psychotherapy increase the importance of this research. In order to answer concerns and hopes involving MDMA, research must include studies in which MDMA is administered to carefully selected volunteers in controlled clinical settings.