2012

Exploring MDMA and its therapeutic potential

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EXPLORING MDMA AND ITS THERAPEUTIC POTENTIAL

by:

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A thesis submitted in partial fulfillment of the requirements

for the Honors In the Major Program in Psychology

in the College of Sciences

at the University of Central Florida

Orlando, Florida

Spring Term 2012

Thesis Chair: Dr. Richard Gilson

Abstract

The clinical application of MDMA has long been an issue of great interest for doctors, counselors, researchers, and users alike. Originally synthesized by a pharmaceutical company and subsequently tested on military personnel, the drug was then used by many clinicians and physicians prior to the DEA's strict regulation of the drug, which began in the mid 1980s (Mithoefer et al, 2010). The DEA has classified MDMA a "Schedule 1" drug, which means that it among the most controlled substances, a fact which has hindered the progress of research. For a detailed explanation of the DEA's scheduling of controlled substances, please refer to appendix A. Exception was made to this restriction, however, in 2003 when the US government permitted one organization, the Multidisciplinary Association for Psychedelic Studies ("MAPS," for short), to conduct studies wherein the drug was to be administered to human participants in a clinically controlled experimental environment – a setting which allows for many of the most prevalent confounds found in MDMA research to be minimized and, in some cases, eliminated (Mithoefer et al., 2007; Mithoefer et al, 2010; MAPS.org, 2012). Though MAPS' studies are only just beginning, they have already had promising results in treating protracted cases of PTSD. These recent developments in MDMA research and the results of the subsequent studies have piqued the interest of academics and advocates alike as well as motive numerous other organizations to lend their support to the MAPS organization. This literature review aims to provide an overview of past and present paradigms within the body of MDMA research in order to provide an informational framework within which the recent works regarding the drug's therapeutic merit can be adequately examined.

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Introduction

"It can put holes in your brain." On average, that seems to be the extent of the general public understands when it comes to the risks of 3,4-methylenedioxymethamphetamine (MDMA) use. That simple idea, however pithy in ad campaigns, is a massive oversimplification of the complex psychophysiological effects induced by the designer drug known as "ecstasy." MDMA is an illicit, empathogenic (or entactogenic) drug with amphetamine properties that creates extremely acute euphoric states and periods of intoxication marked by powerful emotional reactions (Maisto, 2011). It should be noted that the term "Ecstasy" was he informal term previously used to refer MDMA, but given ever-increasing impurity of the illicit form of this substance, a distinction shall be made for the purposes of this thesis: "3,4-methylenedioxy-methamphetamine" or "MDMA" shall be used to refer to the pure, unadulterated substance while the term "ecstasy" shall be used only while referring its illicit counterpart. Additionally, it should be noted that the substances "5-Methyl-3,4-methylenedioxy- amphetamine" and "3,4-Methylenedioxyamphetamine" are very similar to MDMA, but are not the focus of the literature discussed herein either. At any time when there is no specific indication using these terms, it shall be assumed that the intended subject is the pure substance MDMA, as that is the chief topic herein.

This drug and the intense phenomenological experience it induces have gained wide appeal among recreational substance users. The popularity of ecstasy has continued to rise despite the efforts of the DEA and other law enforcement agencies to control its manufacture, distribution, and use. Currently, MDMA is one of the most popular recreational drug in North America as well as most other western societies and continues to attract younger and younger

users with each passing year (Dumont et al., 2006). In recent years, it has been reported that twenty percent of eighth graders and nearly half of all twelfth graders are able to easily access the substance. This information is particularly concerning in light of recent research which shows that MDMA is especially harmful and addictive to the developing brain. However, adolescents the world over continue to use it despite the common conception that it causes severe brain damage (Maisto, 2011). This popularity is a public health issue as MDMA causes an extremely complex set of physiological processes which can result in serious and potentially intractable consequences. The known side effects of the drug are extensive and include cerebral edema, neurotoxic brain damage, and acute depletion neurochemicals which are critical for psychological health. The array of physical changes resulting from MDMA use can manifest themselves as various symptoms including depression, sexual dysfunction, and persistent memory impairment (Surilla et al, 2009). Despite MDMA's chemical galvanization of the midbrain, many first-time users are not drawn into frequent use of the drug. Addiction does occur in some users, however, due to MDMA's heavy stimulation of the brain's mesolimbic reward system and for those users the risks are often permanent or fatal. These consequences, however, are not immediately apparent except in the case of overdose, which lead some users to underestimate the grave nature of MDMA-mediated neural injury. It is also important to note that the majority of ecstasy users also abuse a variety of other substances. Polydrug abuse is a very salient factor among MDMA users and within MDMA research alike. It is very typical for users to begin using the substance well after developing addictive patterns of behavior which may imply that they are predisposed to addiction and may already be experiencing pathological activity within the midbrain (Purdy et al, 2001).

Though MDMA was first synthesized over a century ago, research regarding its effects has been very popular throughout the last couple of decades. There are several reasons for this. First and foremost, there have been some very interesting and promising studies published recently which are aimed at therapeutic use of the drug (these shall be discussed in detail herein). Additionally, the population of users from which to sample is diverse and every-growing and the drug mediates some complex and somewhat enigmatic effects. It is becoming more and more beneficial to understand these effects owing to the aforementioned popularity of the substance and its potential for clinical use. Finally, MDMA research has been considerably hindered because of the DEA's strict regulation of the substance since the mid 1980s. However, this regulation has revised slightly and that has given a select few researches within the field new and intruiging ground to cover (Holland, 2010; Maisto, 2011).

Discovering the true nature of how MDMA interacts with the body can lead to new technologies and methods to help treat overdoses, disorders in abstinent users, any even lead to protective measures for current users—not that the recreational use of such a potentially dangerous drug should be encouraged. Neuroscience is continually evolving just as the field of pharmacological research is, and research regarding MDMA recently stood at a sort of crossroads as human studies, like those pertaining to the drug's therapeutic value, were only approved by the US government around eight years ago. Prior to this, progress in the field was heavily hindered by restrictions on experimental design. The past decade of MDMA research has developed in many interesting directions and there is a wealth of valuable information upon which to build.

The primary goals of this literature review are to first examine the current paradigms and findings within the body of MDMA research and literature in order to provide an adequate basis of understanding and then to examine the recent studies regarding MDMA's therapeutic potential with special emphasis being placed upon the works of the MAPS organization. Finally, recommendations for future MDMA research shall be postulated based upon the materials reviewed herein. Literature for this review was gathered from psychological, medical, and other scientific, peer-reviewed journals and database such as PsychInfo, MEDLINE, Access Medicine, various textbooks and other sources.

History of MDMA

MDMA was originally synthesized in 1912 by German chemist Anton Kollish while working for Merck Pharmaceuticals, a company which proceeded to file for a patent and finally began animal studies in 1927. Merck then went on to test the drug's potential as a stimulant but decided to shelve the project after several failed attempts and problematic outcomes (Holland, 2010). Many years later, in the mid 1950s, the US Military briefly conducted experiments with the substance and the documentation regarding these studies was declassified in 1969. Shortly after the Military's experimentation, Merck continued researching MDMA as a potential stimulant. Though there is no conclusive evidence of it, it is believed by some that the company conducted human studies in the late nineteen-fifties. Following more failed attempts, Merck once again discontinues work with the substance (Holland, 2010).

Several years after this, in 1965, famous Chemist Alexander T. Shulgin was given a sample of MDMA by an undisclosed colleague and friend. Shulgin proceeded to sample the drug himself and was astounded by its effects (Romero, 1995; Martinez, 2003; Maisto, 2011). He is quoted as saying that he "felt absolutely clean inside," and felt "nothing but pure euphoria." He went on to say "I have never before felt so great, or believed this to be possible. The cleanliness, clarity, and marvelous feeling of solid inner strength continued through the rest of the day, evening, and into the next day. I am overcome by the profundity of the experience." In reflection, he described the drug's effects as being somewhere between those of lysergic acid diethylamide (LSD) and amphetamine (speed) and stated simply "I still haven't found anything like it to this day ." Perhaps motivated by his initial experience with the drug, Shulgin later synthesized MDMA while working for Dow Pharmaceuticals believing it to have psychoactive

potential. He suggested that the drug's therapeutic applications should be heavily considered and tested (Romero, 1995; Martinez, 2003; Holland, 2010).

Some years after this, in the mid-to-late seventies, Shulgin, still convinced that MDMA has some use in a clinical context, gave his friend, Psychologist Leo Zeff, a sample of the drug. Zeff's interest in the substance was piqued immediately, so much so that he postponed his retirement in order to test MDMA as a therapeutic tool (Martinez, 2003; Holland, 2010; Maisto, 2011). Zeff was pleased with the drug's effects and proceeded to distribute sample of the drug to many of his colleagues and encouraged them to test its clinical merits as well. It is estimated that this led to the informal formation of a network of roughly 4,000 mental health professionals who were testing the drug with patients (Holland, 2010; Maisto, 2011).

Unfortunately, however, the drug was not being used exclusively for professional reasons; more and more people began using the drug recreationally, though at this time it was on a very limited scale. Nearly a decade after Leo Zeff had received his first sample of MDMA from Shulgin, in 1984, recreational use of the drug had gained more momentum and around this time the slang term "ecstasy" was coined by Michael Clegg—a term which was undoubtedly derived from the intense euphoric state that Shulgin described (Martinez, 2003; Holland, 2010). Clegg, who was at one time a seminary student, took full advantage of the drug's growing popularity and (then) undetermined legal status. He became possibly the nation's first major MDMA distributor and dealer in Texas, taking orders by phone via a toll-free phone number and fulfilling these order though the postal service. It is estimated that at the peak of his business he was selling as many as 500,000 pills or doses of MDMA per month in the greater Dallas area (Martinez, 2003; Holland, 2010). Though this makes for an interesting story, Clegg's actions

were detrimental to mental health professionals who were attempting to use the drug as a therapeutic tool as recreational use of the drug attracted the attention of the US government and Drug Enforcement Agency (DEA) (Maisto, 2011; MAPS.prg, 2012). In 1985, the DEA, reacting to the growing attention MDMA was gaining throughout the country, attempted to immediately classify the drug as a schedule 1 narcotic, meaning that the use or possession of the drug would be strictly prohibited (Mithoefer et al, 2010; Maisto, 2011; MAPS.org, 2012).

Michael Clegg was likely not pleased by this news, but more importantly, countless clinicians, physicians, and researchers alike expressed objection to this action, claiming the government must first allow the properties and characteristics of the drug to be adequately explored—that the evaluation of the substance must be allowed its due process. These individuals, united in their objection to the DEA's actions, formed an informal committee to argue on behalf of MDMA's therapeutic values and request due process in the scheduling of the substance. Many physicians and clinicians claimed to have successfully used of the drug with patients to great benefit and, in turn, many patients extolled the beneficial nature of their MDMA-assisted clinical experiences (Holland, 2010; Mithoefer et al, 2010; Maisto, 2011). This conflict led the DEA to hold a summit to determined how scheduling of the drug should be handled. Later that same year (1985), the hearings commenced under the supervision of judge Francis Young as appointed by the DEA. They stretched on for many months and often dissolved into bitter arguments and great tensions between those advocating for and those opposed to allowing mental health professionals to continue testing the drug in controlled environments. Finally, in May of the following year (1986), judge Young decides, after much deliberation, to classify the substance as a Schedule 3 narcotic. This meant that MDMA could be

used as a prescription drug and had been deemed acceptable for use under the supervision of medical professionals. The DEA, however, was not pleased with this outcome and very quickly overturned it, implying that judge Young was bias and that his decision was incorrect; they proceed to immediate categorize the drug as a Schedule 1 substance. Groups advocating the use of MDMA were greatly angered by this action and considered it to be unjust, fervently objecting the ruling (Maisto, 2011). Finally, in 1988, the DEA is ordered to reevaluate their previous decision. During this time, there is a short period during which MDMA was once again legal. This reevaluation, however, amounts to little more than nothing as the DEA promptly determines that they were correct in their initial approach to the substance's regulation and MDMA is once again deemed a Schedule 1 controlled substance (Holland, 2010; Mithoefer et al, 2010).

Though the DEA's ruling was resolute this time, the popularity of MDMA continued to steadily grow from this time to present day; efforts by law enforcement to stymie the recreational use of the drug had little effect. Many years later, in March of 2001, the US government (against the recommendations of many prominent figures from the scientific community) placed harsh legal penalties on MDMA possession—more severe, in fact, than those placed upon heroin or any other controlled substance (Maisto, 2011). Contrarily, the US government also approved human testing of MDMA for the treatment of PTSD just a couple of short years later. Only one organization, however, was able to garner governmental permission to administer the substance to human participants: the Multidisciplinary Association for Psychedelics Studies" (MAPS.org, 2012). This is a pivotal point in the history of MDMA as it allows the continuation of a collective body of work that had been dormant for over a decade, since the initial heated debate and swift action of the DEA. The works of the MAPS organization and their investigation into

the therapeutic potential of MDMA will be explored thoroughly herein. It is first paramount to have basic understanding of the body of work that preceded these recent endeavors. Though previous works were somewhat hindered in their research design, they produced interesting and valuable information nonetheless.

Physiological Effects

Introduction

Understanding the physiological mechanisms by which MDMA acts on the body and brain are of the utmost importance. New research initiatives aimed at utilizing MDMA for therapeutic applications shall be built upon currently paradigms and shall seek to exploit the physiological effects of the drug to enhance the efficacy of psychotherapy. Additionally, recreational use of MDMA is widely regarded as a public health issue because of its widespread popularity and potential for harm. Prior to examining the physiological implications of MDMA, however, it should be noted, again, that the scientific literature discussed herein pertains to the effects of pure Methylenedioxymethamphetamine (MDMA) and not the related designer drugs nor the street drug referred to as "Ecstasy." Though that term was initially used to address pure MDMA, the illicit incarnation of the drug is regularly contaminated with various other drugs and adulterating agents. The street drug Ecstasy now essentially refers to a designer drug cocktail which may or may not include MDMA or MDA (Green, 2004).

MDMA is typically produced in tablet form and ingested orally by users. When administered in this way, the drug is rapidly absorbed into the bloodstream, is detectable within human plasma within 30 minutes, and reaches its peak serum levels between 60 and 120 minutes post administration, depending on other physiological variables (Gamma et al., 2000; Dumont et al., 2006). The drug has a half life of 6 to 8 hours and causes substantial increases in cortical blood flow in the window of time approaching and following its peak effects (Gamma et al., 2000). As serum levels increase, the psychoactive effects which users are typically seeking begin to manifest themselves. However, given MDMA's moderate half life, plasma levels of the

drug remain elevated well after these effects have subsided; it is during this post-peak effect time that the objective impairment mediated by MDMA persists in the absence of the more salient subjective effects (Gamma et al., 2000). The onset, severity, and resolution of the physiological changes are directly correlated to the plasma concentration of the drug and its metabolites. Unfortunately, however, the correlation coefficient of this relationship is not significant enough for researchers to use plasma concentrations as a means of predicting a subject's physiological or psychological state (Kolbrich et al., 2008).

MDMA has the ability to elicit a host of physical changes in the human body including pupil dilation, elevated cortisol levels, changes in respiration rate, changes in blood-oxygen levels, and hyperthermia—a very important characteristic of the drug which will be explored more thoroughly herein (Dumont, 2006; Kolbrich et al., 2006). A recent, large-scale literature review targeting the subjective effects of MDMA found that the most salient somatic changes included nausea, vomiting, bruxism, muscle tension and aches, headaches (typically subsequent to peak effects), sweating, numbness, changes in body temperature, fatigue, mild to moderate dizziness, dry mouth, decreased appetite, and increased energy levels. These effects were found to vary substantially with respect to elapsed time post administration, magnitude of the dose, and gender, to a lesser extent (Baylen and Rosenberg, 2006). The most consistent short-term physiological effects of MDMA include primarily increases in heart rate and blood pressure, hypertension, and mild to moderate hyperthermia (Hoffman and Froemke, 2007). The drug also causes hyperactivity, increased locomotion, and psychomotor stimulation, all of which help to explain why users frequently enjoy music and dancing while intoxicated (Feduccia et al, 2008). This long list of effects is mediated by MDMA's modulation of the body's dopaminergic,

noradrenergic, and serotonergic neurological pathways (Maisto, 2011). Though there are seemingly endless subtopics within the topic of MDMA's physiological effects, for the sake of this review the relevant material shall be divided into the following subsections: mechanism of action and addiction, hyperthermia and thermogenic properties, cardiovascular issues and the blood-brain-barrier, neurotoxicity and neurogenesis, circadian rhythms and sleep-wake cycles, and finally metabolic issues along with a few miscellaneous points of interest.

Mechanisms of Action and Addiction

Owing to its relatively short history and its wide array of effects on the body, MDMA has been formally classified in a number of ways and the appropriate way to classify it is still debated today. It has been referred to as an indirect monoamine agonist, a methylated amphetamine, a psychostimulant with hallucinogenic properties, a hallucinogen with stimulant properties, a phenethylamine with a potent emotional profile, and, more recently, an "entactogen" or "empathogen" (Parrott, 2001; Carlson, 2010; Maisto, 2011). In fact, the latter terms are relatively new additions to the taxonomy of pharmacological substances which are specifically used to describe substances such as MDMA with a pronounced and unique emotional profile; the distinct psychosocial and physiological effects of these drugs necessitated, as many researchers felt, a new classification (Morgan, 2000). However, all of these names and classes are accurate in their own respectl MDMA is chemically similar to amphetamine and, like amphetamines, it causes widespread exocytosis dopamine and norepinephrine throughout brain in addition to reversing the function of the associated transporter proteins. In other words, vesicles containing dopamine and norepinephrine release their contents into the extracellular

spaces in mass throughout the brain rapidly triggering receptors while simultaneously the body's remaining mechanism for restoring the balance—the aforementioned transporter proteins—are rendered ineffective (Carlson, 2010; Maisto, 2011) .

Though cateocholamines play their roles in mediating MDMA's effects, the most salient and characterisitic effects of the drug (such as the emotional and social effects) are suspected to be mediated by the neurotransmitter serotonin, which is responsible for the regulation of mood, appetite, sexual function, and sleep cycles (Baumann et al., 2000). It is through the action of serotonin (and dopamine, to a lesser extent), that MDMA heavily stimulates the median forebrain bundle (MFB), a large tract in the brain which interconnects the essential substructures of the limbic system and midbrain. This tract is the primary infrastructure of the mesolimbic reward system and connects the Nucleus Accumbens (the brain's "addiction center") to the Ventral Tegmental Area and the Hypothalamus (Purdy et al, 2001). The Hypothalamus and pituitary gland are key components of the Hypothalamic-Pituitary-Adrenal (HPA) axis, the functional connection between the body's nervous and endocrine systems. This connection is heavily stimulated by MDMA through the drug's excitation of the median forebrain bundle and, by extension, the supraoptic and paraventricular nuclei of the hypothalamus (Kirsch et al, 2005; Zak et al, 2005; Domes et al 2007). This physiological relationship between MDMA and the HPA axis is the basis for MDMA's ability to elevate levels of the hormones oxytocin and prolactin-all very important factors which contribute to the drug's unique "entactogenic" effects (Domes et al., 2007; Kirsch et al., 2005; Zak et al, 2005). It is believed that elevated levels of oxytocin (often referred to as the "cuddle" or "love" hormone) cause the overt physical affection, increased socialability, and gregariousness expressed by users (Dumont et al., 2006).

Furthermore, high levels of oxytocin suppress function of the amygdala which is believed to mediate the pronounced feelings of trust and emotional engagement that MDMA users experience. These factors, specifically, are of particular interest regarding MDMA's therapeutic potential (Kisrch et al., 2005; Kosfeld et al., 2005). Additionally, elevated levels of prolactin are believed to be responsible for the "post-orgasmic like" sense of relaxation, elation, as well as the physical and emotional receptivity reported by users (Passie et al., 2005).

By acting on the midbrain and limbic systems, MDMA also has the potential to trigger neural activity conducive of learning, conditioning, and addiction. Stimulation of the median forebrain bundle has been found to produce profound reinforcing effects, a characteristic which makes it a core mechanism in the development of addiction and certain types of conditioning (Purdy et al., 2001). Like all drugs of abuse, many users find, upon repeating use of the drug that the more desirable effects subside very quickly and are replaced with anxiety and subdued emotions despite very positive expectancies. This transition occurs particularly fast with MDMA owing to the acute depletion of the aforementioned neurotransmitters (as well as their precursor substances) which occurs following use of the drug, creating a sort of transient refractory period during which the drug is much less effective (Martinez, 2003). Since the drug's desired effects are mediated by these neurochemicals and they only gradually return to their normal levels following MDMA use, repeated doses are both less effective and potentially more dangerous for users. In the case of other habit-forming substances and activities, it is believed that dopaminergic neural adaptations within the mesolimbic reward system cause this addictive behavior and it is likely that similar changes explain this behavior in MDMA users, though research which aims to expound upon this relationship is currently being conducted

(Schneck, 2010). There are also studies being done which aim to define MDMA's potential for neurotoxic damage, specifically with the drug's serotonin-mediated affects. It has been found that adolescent exposure to MDMA results in a greater likelihood for abuse of the drug later in life (Ribiero et al., 2011). Schneck (2010) has postulated that the serotonergic abnormalities resulting from MDMA exposure potentiate sensitivity to the dopaminergic changes associated with addiction, even long after cessation. Assuming this is true, it is very possibly that MDMA-mediated neural damage may increase one's future propensity for addiction with other substances (or behaviors) of abuse (Schneck, 2010). Finally, there is believed to be a connection between the activities users typically engage in (such as dancing) and the formation of addiction, which represents a sort-of cyclical relationship between the drug's inherent effects and the behavioral manifestation of these effects (Feduccia et al, 2008).

Hyperthermia and Thermogenic Effects

One of the most well documented and potentially harmful effects that MDMA has on the human body is the elevation of core body temperature (Sharma, 2008). Relatively speaking, MDMA is not responsible for a large number of deaths each year (approximately fifty each year in the United States), but in nearly all fatal cases of MDMA use hyperthermia plays a central role (Rogers et al., 2009). MDMA's thermogenic properties, like many of its properties, have been found to be mediated by serotonergic activity (particularly receptors 5-HT_{1A} and $5HT_{3B}$) and have been found to be dose-dependent in that higher doses result in more severe hyperthermia (Sprague et al., 2003; Ying-Jui et al., 2004). It has also been found that MDMA alters the expression and function of various proteins involved γ–Aminobutyric acid

(GABA)-dependent neurotransmission which is suspected to be involved in more acute case of MDMA-mediated hyperthermia (Simantov, 2004). Peak body temperature is reached approximately one hour after ingestion and can be sustained for several hours at a time, particularly when use of the drug is coupled with physical activity, as MDMA use very frequently is (Soto-Montenegro, 2007; Sharma, 2008; Feduccia et al., 2008; Kolbrich et al., 2008). The aerobic activity typically associated with use of the drug causes a significant increase in oxygen consumption, which elevates the danger posed by the aforementioned hyperthermia (Freedman et al., 2005). Additionally, these factors are frequently exacerbated by dehydration as users commonly neglect to properly hydrate or rest when fatigued (Kolbrich et al., 2008; Sharma, 2008). Furthermore, MDMA-induced hyperthermia has been found to be closely linked with certain aspects of the endocrine system as well as activity in the autonomic nervous system, which is normally responsible for maintaining core body temperature (Sprague et al., 2003). This is concurrent with the finding that MDMA has the ability to impede normal perspiration, another bodily function mediated by the autonomic nervous system and related to the body's heat-response. It is likely that this autonomic dysregulation plays a central role in MDMA-mediated hyperthermia (Freedman et al, 2005).

All of these factors can combine and result in a profound, prolonged hyperthermia which can, in turn, result in heat stroke or, in extreme cases, seizure or death. Even in the event that the user does not suffer immediately observable consequences, MDMA-mediated hyperthermia still typically results in various forms of brain damage. Additionally, acute hyperthermia results in the release of heat-shock proteins (HSP), endogenous, functional substances the body releases to responds to acute heat and stress. This heat-shock response can result in cortical edema and

widespread cellular stress throughout the nervous system (Sharma, 2008). This response can also place strain upon the vascular structures of the brain-damage which, over time, can interfere with the proper functioning of the blood-brain-barrier (BBB), an immensely important line of biological defense for the brain (Soro-Montenegro, 2007; Sharma, 2008).

As previously stated, the hyperthermic potential of MDMA has been very well documented and researched. Within this subset of research, however, there is a debate, or sorts, as to the relevance of ambient temperatures. Some researchers in the field, such as Parrott (2001) as well as Kolbrich and colleagues (2008), believe that high ambient temperatures exacerbate the drug-induced hyperthermia described above. Kolbrich et al. (2008) found that users with prior exposure to MDMA experienced clinically significant elevations in body temperature and went on to suggest that these changes were directly related to participants' physical activity and environmental conditions (primarily ambient temperature). To determine the magnitude and nature of this correlation, however, more research will be required. Another study conducted around this time concurs that ambient temperatures do contribute to changes in core body temperature and that, furthermore, changes in body temperature were clinically negligible when subjects were placed in environments at "room" temperature (Jaehne and Irvine, 2008). Contrarily, there are other studies which indicate that ambient temperatures are of little concern (Parrott, 2001). One of these studies observed that subjects on MDMA appeared to be much less sensitive than control subjects to changes in external temperatures (Freedman et al., 2005). Jaehne and Irvine (2008) go on to postulate that, though previous studies produced mixed results, their study provides evidence that human subjects may develop a tolerance to MDMA-

mediated thermal dysregulation. More research will be needed to bring this issue to a definitive conclusion.

Regardless of the specific mechanisms and the involvement of ambient temperatures, MDMA-mediated hyperthermia is a serious risk to the health of users. As such, several researchers have investigated means and methods by which this risk can be controlled or marginalized. One such study sought to do this by utilizing two pharmacological agents: Prozosin, a selective serotonin reuptake inhibitor (SSRI) and Cyanpindolol, a partial serotonin antagonist (targeted at 5-HT1A receptors) and β-1adrenoreceptor (ADRB1) antagonist. This experiment discovered that pretreatment with a combination of the two drugs resulted in a complete abolishment of MDMA-induced hyperthermia (Sprague et al., 2003). Sprague and colleagues (2003) went on to specify that Prozosin was linked to reductions in rectal temperature while Cyanpindolol was linked with reductions in skeletal temperature. Another, more recent study conducted by Rodsiri (2009) utilized less aggressive interventional methods. In this experiment, subjects were kept on a tyrosine-free diet prior to administration so as to limit the body's potential for synthesizing dopamine. This resulted in an attenuated thermogenic response in subjects which indicates that one, MDMA-mediated hyperthermia may be heavily reliant upon dopamine (or tyrosine) and two, that there may dietary measures users can take prior to use of the drug in order to reduce their risk of harmful over-heating while under the drug's effects. It should be noted, however, that the subjects from this experiment also experienced more substantial striatal depletion of dopamine, even weeks following experimentation/administration, which, provided the hyperthermia was not severe, may be of greater concern (Rodsiri, 2009). This could mean that inhibiting MDMA-mediated hyperthermia actually increases other types of

MDMA-mediated damage. So, there is definitely a need for further investigation, but these preliminary results are intriguing. Finally, another such experiment, by Rusyniak and colleagues (2008) found that pretreatment injections of muscimol (a powerful, partial GABA agonist which acts primarily on the $GABA_A$ receptor) into the dorsomedial hypothalamus resulted in less significant elevations of core body temperature versus control subjects (Rusyniak et al., 2008).

Cardiovascular Issues and the Blood-Brain-Barrier

As previously stated, the blood-brain-barrier (BBB) is a critical line of defense for the brain. The term refers to the set of physiological mechanisms, such as the function of astrocytes in relation to endothelial cells, which separates the brain from normal inter-vascular diffusion such as occurs in the rest of the body. Even in moderate doses, it has been shown that MDMA causes irregular permeability and vascular instability within the BBB. One study which demonstrates this nature of this instability utilized intravenous contrast material and imaging technology to observe cerebral blood flow in subjects treated with MDMA. In doing so, it was clearly observed that the dye flowed outside of the cerebral blood vessels and into several brain areas, including the cerebellum, hippocampus, thalamus, hypothalamus, and various cortical areas, in a manner which was inconsistent with proper function of the BBB (Sharma, 2008). This could indicate that MDMA disrupts neural homeostasis on a very basic level. The same study also detected irregular changes in ion content within these areas; specifically, sodium (Na^+), potassium (K^+), and chlorine (Cl^-), were all elevated above normal levels and these ions are all paramount in normal neurological function. Additionally, abnormal configurations and formations of glial cells were detected in these areas (Sharma, 2008). This breakdown of the

barrier's integrity is also demonstrated in the observation of abnormal albumin immunoreactiviy and the irregular activation of astrocytes. These detrimental effects, though sufficiently separate from MDMA's thermogenic profile, is heavily inter-related with it. For instance, the aforementioned hyperthermia-mediated edema and prolonged cellular stress are key aspects of MDMA's effect on the BBB (Sharma, 2008).

MDMA's affects on the brain's vascular system notwithstanding, the substance also initiates an assortment of more systemic cardiovascular changes; many of which are closely related with the previous discussed thermogenic changes given the large role the cardiovascular system plays in bodily thermoregulatory processes (Freedman et al., 2005; Jaehne and Irvine, 2008; Ramaekers, 2009). Relatively speaking, however, much less emphasis has been placed on investigating the full nature of MDMA's cardiovascular affects as opposed to the large amount of attention is typically placed on its neurological properties (Jaehne and Irvine, 2008). Like its pharmacological relative, amphetamine, MDMA causes an elevation in pulse and blood pressure, changes which have been found to be dose-dependent such that greater doses result in greater elevations of these parameters (Freedman et al, 2005; Kolbrich et al., 2008; Ramaekers, 2009). Specifically, one study observed that at moderate doses, MDMA alone (factors such as physical activity and environmental interference were controlled for as much as possible) elevated systolic pressure up to a maximum of 171mm Hg and diastolic pressure up to a maximum of 102mm Hg, with peak pressures being observed between one and two hours post-administration (Kolbrich et al., 2008). In more severe cases, these elevations can be perpetuated to the point of acute tachycardia and hypertension in more severe cases (Rusyniak et al., 2008). It has been shown that a single dose can cause mild transient tachycardia and moderate elevations in mean

arterial blood pressure while repeated doses can lead to more substantial elevations in mean arterial blood pressure and can result in a biphasic pulse. Moreover, extended dosing (3 doses per week) produced the greatest elevation in pulse and blood pressure during the first week while more moderate elevations were observed during subsequent weeks (Jaehne and Irvine, 2008). In terms of the neurochemicals involved in these cardiovascular effects, serotonin, as usual, is believe to be the primary underlying neurotransmitter associated with the cerebrovascular changes, while a combination of serotonin, dopamine, and norepinephrine is likely to be responsible for the more systemic cardiovascular changes (van Donkelaar et al., 2010). More recent research indicates that the hypothalamus's role in thermoregulation (as well as the relationship between thermoregulation and cardiovascular function) are important components of MDMA's interaction with the cardiovascular system. Further study will help explain not only MDMA's effects on these systems, but also provide more information regarding the interaction of these systems.

Neurotoxicity

One of the most popular topics within the world of MDMA research has always been the drug's capacity for neurotoxic damage. This long-standing debate led one prominent researcher to say that "the consequences of MDMA neurotoxicity have defied ready characterization." (McCann et al., 2008). What this means is that, though countless studies have essentially concluded that it can cause neurotoxic damage, researchers have as of yet been unable to pinpoint the exact mechanisms by which these injuries occur or their full nature. As with nearly all types of investigation aimed at the drug, governmental restrictions placed on the drug have

stymied researched attempts resulting in a lack of data pertaining to human subjects (Guillot, 2005). It has been believed, for many years, that the drug caused severe neurotoxicity, likely linked to the abnormal and excessive serotonergic function. Several studies have emerged that indicate MDMA's ability to cause various encephalopathies, neuronal damage, and cellular damage (Nifosi, 2009; van Donkelaar et al., 2010; Darversh, 2005). Given the many physiological mechanism by which MDMA affects the body and brain, it stands to reason that there are many routes by which MDMA causes damage. In some respects, it is known how MDMA can cause neurological damage. For instance, it is known that hyperthermia can cause brain damage and it is known that MDMA can induce hyperthermia; therefore, it is of sound logic to say that the drug can indirectly damage neural tissues in this manner (Freedman et al., 2005). Others have examined human metabolic function and its relationship with MDMA neurotoxicity and have found that the administration method is of great relevance. One such study concluded that systemic metabolizing (such as results from oral administration) is required for the drug to reach its full neurotoxic potential (Erives et al., 2010). However, the most central and salient factor researchers focus on whilst investigating MDMA-mediated neurotoxicity and neural damage is serotonergic function. This stands to reason, as serotonin appears to mediate nearly all of the drug's most desirable, dangerous, and destructive effects.

As previously stated, MDMA causes large-scale exocytosis of serotonin and dopamine resulting in incredibly high synaptic levels of these neurotransmitters-particularly during the drug's peak effects. It has been suggested that this effect results in oxidative stress and explains the damage detected on axon terminals throughout the brain, but, again, these more detailed processes are not yet well understood (Darvesh, 2005; Nifosi, 2009). It could also be possible, as

some researchers believe, that the amplification of the adrenergic neurotransmitters directly damages nerve terminals via excitotoxicty. On similar notes, is it been suggested the aforementioned abnormal function of GABA (the brain's primary inhibitory neurotransmitter) and associated proteins could be a source of neurotoxicity (Simantov, 2004).

By and large, serotonin is the focus of investigations of MDMA-mediated neural damage and neurotoxicity. In several studies, it has been shown that following the large neurotransmitter release during intoxication, there are periods marked by depletion of tryptophan, tyrosine, serotonin, and dopamine as well as reduced binding potential for serotonin transporter proteins (van Donkelaar et al., 2010; Selvaraj S. et al., 2009). While these effects are not completely understood, it is clear that the severity of these periods is directly correlated with the magnitude and frequency of dosing (Darvesh, 2005). Conservative dosing, such as that used in clinical applications of the drug, often produces only mild, transient side effects while heavy abuse of the drug almost invariably leads to extended periods characterized by these malfunctions and, more importantly, their psychological manifestations (Guillot, 2005). Single, moderate doses apparently do not disturb the function of serotonin nor its transporter proteins, while moderate, infrequent doses, have been found to produce extreme changes in neurotransmitter function and toxic encephalopathy in various cerebral areas as was demonstrated by neuroimaging in very recent years (Guillot, 2005; Nifosi, 2009). Multiple doses (with varying consistency) have also been linked to dopamine levels being elevated in the frontal cortex and reduced in the striatum; an effect which was not observed after a single dose (Ludwig et al., 2008).

Neurogenesis

Until recent years, it was believed that hippocampal neurogenesis nearly or completely ceased as the brain reached its pinnacle of maturation. However, it is now understood that this process continues into adulthood, though the nature and extent of neurogenesis does change substantially (Maisto, 2011). Additionally, it has been found in more recent research that there is a link in hippocampal mass and propensity for depression. Specifically, depressed patients have been found to have small average hippocampal size. Neurogenesis and serotonergic function in and around the midbrain are believed to be very important factors in this observation, which, by extension, means that these issues are strongly related to MDMA's potential for neural damage (Maisto, 2011). For instance, the depression that many abstinent users suffer from is likely linked to MDMA-mediated changes in hippocampal neurogenesis and serotonergic function (Nifosi, 2009; Maisto, 2011). Particularly in cases of repeated or heavy use, MDMA has a residual effect on cell proliferation (mitosis) as can be observed in decreased levels of hippocampal neurogenesis following use (Nifosi, 2009; Maisto, 2011). The drug's effect on this process is another area of particular interest for researchers given the critical role that neurogenesis plays in long-term memory, learning, and neural plasticity (Catlow et al., 2010). The central nervous system can only produce new neurons in limited capacity, and this is an even more substantial concern for adults as neurogenesis becomes less substantial as the brain ages. Aside from interrupting cellular proliferation, MDMA has also been found to mediate large drops in the concentration of adenosine triphosphate (ATP), serotonin, and dopamine in the hippocampal area as well as the striatum (Darvesh, 2005). ATP, which plays a vital role in energy production and metabolic function, was found to be decreased by up to 30% in these

areas while serotonin and dopamine levels dropped between 55 and 70% in these areas (Darvesh, 2005). This impact on neurotransmitters as well as ATP may very well be implicated in, if not responsible for, the aforementioned hippocampal changes induced by MDMA.

Though this information does not bode well for current and abstinent users, there is much work to be done before a definitive understanding of these issues is reached. For example, Murphy et al. (2009) found that, though lasting neurochemical changes were observed in the hippocampal area, executive processes remained relatively unaffected and subjects had little difficulty shifting between mental processes. Admittedly, however, this study observed abnormally low neurotransmitter concentrations in the hippocampus even several days after moderate, controlled administration, which has been the general consensus regarding this topic (Murphy et al., 2009).

Circadian Rhythms and Sleep-Wake Cycles

A review of acute subjective effects related to MDMA found that users frequently reported sleeplessness following use of the drug; this affect was found to be dose-dependent and to diminish with time (Baylen and Rosenberg, 2006). Obviously, users experience typical psychostimulant effects during intoxication, but the real concern is the inability to properly sleep in the days or even weeks and months following cessation (Schierenbeck et al., 2008). Many other studies have demonstrated that subjects and users experience subtle to serious cognitive deficits along with abnormal sleep architecture, insomnia, and suppressed or abnormal REM cycles (Hoffman and Froemke, 2007; Schierenbeck, 2008; McCann et al., 2009). Schierenbeck and colleagues (2008) demonstrated these disturbed sleep architectures via polysomnography

examination. Like other aspects of MDMA usr, impedance of sleep function has been found to be dose-dependent (Surilla et al., 2009; Ogeil, 2010). Ogeil (2010) found that a single dose induced irregular patterns of restlessness which persisted for up to two days post-administration. Specifically, subjects displayed extended duration of active sleep phases and variations in waking behavioral patterns. Light exposure was believed to play a role in this, but further testing revealed that these effects were consistent and independent of light exposure. Similarly, very conservative doses were found to impair the quality of stage 3 and 4 REM cycles during a double-blind, placebo-controlled trial (Surilla et al., 2009).

Surilla et al. (2009) postulated that, like many other characteristics of the drug, sleep disruption was likely related to serotonergic irregularities, given its critical role in the activation of sleep cycles. Surilla and colleagues (2009) concur that it is MDMA's affect on the monoamine neurotransmitters that result in irregular sleep and wake cycles, as well as interfere in daytime alertness, though this effect may be secondary to poor sleep quality. Specifically, animal testing has resulted in sustained serotonin disturbances have been observed in the raphe nucleus following administration, which may be linked to poor sleep quality and states of hyperarousal; additionally, metabolic function is potentially a source of these observations, though more testing is required (Freedman et al., 2005; Cowan et al., 2006). One related experiment observed subjects for a week straight to examine sleep quality, daytime alertness, and related cognitive function. This study found that sleep quality and duration was significantly impaired for up to five days following a single administration. Moreover, on days three through six following administration, subjects experienced clinically significant cognitive deficits. By

the seventh day of this study, sleep patterns and cognitive function had return to levels comparable to those in control subjects (Jones et al, 2008).

In addition to generally poor sleep quality, MDMA has recently been investigated as a potential cause for specific sleep pathology: obstructive sleep apnea (OSA). In recent years, both the prevalence of OSA and of MDMA use have been steadily increasing (McCann et al., 2009). McCann and colleagues (2009) believe that serotonin irregularities and associated neuronal damage is the number one mediator of OSA in abstinent MDMA users. Additionally, they believe that this relationship involves chemoreflex or possibly processes of arousal. Studies by these researchers have confirmed that previous MDMA use can aid in the prediction of OSA occurrence even more accurately that obesity-a leading risk factor for OSA. Total lifetime exposure to MDMA is directly correlated with occurrence of OSA and subjects who had previously used MDMA, but been drug-free for at least two weeks had the greatest occurrence of OSA and hypopnea compared to controls (McCann et al., 2009). McCann (2009) expounds upon these observations by saying that serotonergic neuronal dysfunction plays a large role in the pathophysiology of OSA and that previous MDMA users are at an elevated risk of developing OSA due to their greater likelihood of suffering from these neuronal deficits. See related commentary by Chamberlin and Saper (2009) for continuation of this discussion.

Metabolic and Other Physiological Issues

As previously discussed, MDMA induces profound hyperthermia, a factor believed to play a role in most, if not all, MDMA overdose deaths. Recent studies have found that these fatal cases are also contributed to by a metabolic condition known as hyponatraemia, which

involves abnormally low extracellular electrolyte levels, particularly sodium (Rogers et al., 2009). This condition may also explain the convulsions which are characteristic of MDMA overdose-convulsions also frequently occur prior to death in cases of overdose. Symptoms of hyponatraemia include confusion, headaches, fatigue, hallucinations, syncope, and convulsions (Ramaekers, 2009). Some of these symptoms (confusion, fatigue, hallucinations, and syncope) are common for users to experience while intoxicated, which means that these users may be experiencing early warning signs of this serious metabolic condition, exacerbating their risk. Hyponatraemia in MDMA users is likely related to the aforementioned hyperactivity, hyperthermia, and dehydration. MDMA also has the potential to induce significant hypoglycemia and it has been observed that it causes the dysregulation of energy production and alters glucose metabolizing within the motor cortex, limbic system, and somatosensory areas (Darvesh, 2005; Soro-Montenegro 2007). Soto-Montenegro (2007) conducted a study to examine these effects in relation to dosing patternsand found that single, moderate doses caused hyperactive glucose metabolizing in the cerebellum and hypoactive glucose metabolizing in the hippocampus, amygdale, and the auditory cortex. These observations could be related to MDMA's interactions with the mesolimbic reward system, hippocampal neurogenesis, and the interaction between behavioral conditioning and external stimulus. Furthermore, this study revealed that shortly after administration, blood glucose levels dropped significantly, possible due to the irregular, imbalanced shift in glucose metabolizing in the aforementioned areas (Soro-Montenegro, 2007). Multiple, repeated doses were found to cause the same effects. However, subsequent doses were found to cause incrementally less substantial changes in said metabolic activity. This is concurrent with other studies that indicate MDMA's effects are both largely

mediated by serotonin and induce a refractory period during which the brain's neurochemical homeostasis is gradually restored. In any case, these results also indicate that these metabolic changes are correlated to dosing patterns to some degree (Soro-Montenegro, 2007).

As previously mentioned, MDMA causes changes in levels of oxytocin, prolactin, and cortisol; physiological mechanisms by which the drug produces some of its most prominent effects. This is not the extent of its interaction with the endocrine system, however. It has also been discovered that large doses of MDMA cause elevated levels of thryoxine, a thyroid hormone associated with metabolic rate, physical development, and the production of nerve-growth factors (Sprague et al., 2003). This finding may very well directly relate to the changes in glucose metabolizing and energy production. Given the thyroid's vital role in the endocrine system and endocrine system's effects on the human body, in general, this observation may have significant and substantial implications on future MDMA research.

Psychological Effects

Introduction

MDMA has been found to induce a myriad of psychological effects on users. The phenomenological experience of ecstasy is a very aggressive one, particularly at moderate to large doses; this is the case throughout all age groups and demographics (Dumont, 2006). As previously mentioned, users of the drug typically experience acute psychological, emotional, and behavioral effects such as elation, hyperactivity, and over-exaggerated extraverted tendencies (Sharma, 2008). Users also stand a great risk of becoming addicted to the drug, a condition which initiates its own array of psychological changes as it basically results in the maladaption of a very important region of the brain. Exposure to the substance in adolescence has been found to modulate the addictive potential of the drug later in life, which is an important fact considering the young age at which many users are becoming initially exposed. Users with adolescent exposure are more easily addicted and experience longer durations of reward-response-related behavior after becoming addicted. Users who fit this profile also have their addiction to the drug reinstated more easily and more completely after much smaller doses than those without exposure at a younger age (Ribiero et al., 2011).

In light of the detrimental psychological effects and the risk of addiction, there is a growing population of clinicians and physicians who believe that ecstasy may have therapeutic applications. The US government has recently approved one organization, the Multidisciplinary Association for Psychedelic Studies (MAPS), which is currently investigating the drug's effect on PTSD treatment. The organization has currently completed one study which resulted in favorable outcomes in 83% of subjects (MAPS.org, 2012). The MAPS organization (2012)

believes that the increased emotional expression and prosocial behavior induced by small-to-moderate doses is primarily responsible for the promising outcome.

Memory and Learning

The primary psychological deficits that MDMA users experience are related to memory and learning, due in part to the aforementioned disruption of hippocampal neurogenesis (Nifosi, 2009). Large and repeat doses of the drug have been directly linked to deficits in learning and memory through conditioning studies with animals; it is believed that many aspects of these changes are long-term, but moderate doses have only been proven to cause transient, temporal changes at this point in time (Moyano et al., 2005). Several studies have also shown that MDMA produces loss of prospective memory and on recent double-blind placebo-controlled study, conducted by Ramaekers et al. (2009), showed that a single dose causes an increase in prospective memory performance errors. In another recent research project, Murphy et al. (2009) concluded that MDMA greatly reduces performance on any memory task requiring more than simple storage and retrieval. Specifically, visuospatial memory and verbal processing and memory were effected the most significantly; the findings of this study indicate changes in the dorsolateral prefrontal cortex, particularly that of the left hemisphere as it is involved in both verbal memory, which is a lateralized process, and visuospatial memory, which is a bilateral process (Murphy et al., 2009). In the same study it was found, however, that executive processes and the ability to shift between mental processes was relatively unaffected, though lasting neurochemical changes in the hippocampus were once again established—in this case, there were abnormally low neurotransmitter levels in the hippocampus several days after

administration of the drug (Murphy et al., 2009). This is concurrent with the aforementioned studies which found irregularities in hippocampal neurogenesis and cell proliferation in other areas of the brain—all issue which pose a tremendous threat to long-term memory, memory formation, and learning development (Catlow, 2009; Nifosi, 2009).

Repeated exposure to the drug, even for a period as short as five days, produces degradation in attention, working memory, and anxiety levels—an emotional condition which is known to interfere with several mental processes. Subsequent doses, even after periods of abstinence, produce even more significant drops in relevant cognitive performance. Though more research is needed, it is believed that many of these effects are contributed to by MDMA's ability to interfere with calcium (CA2+) dependent voltage-gated receptors (which are located all throughout the brain) as well as NDMA receptors, which play an important role in neural plasticity and memory formation (Piper, 2006). This fact, along with the extensive amount of research related to hippocampal irregularities places younger users at the greatest risk due to their still-developing brains, though much more research is needed to understanding the full extent of the risk they are taking.

Anxiety Disorders and Emotional Pathologies

As previously mentioned, MDMA is known to cause increased levels of anxiety in users, even after substantial periods of abstinence. In one study which was focused on MDMA-mediated anxiety, it was found that this effect was larger in subjects who had a lower premorbid anxiety level, though all subjects experienced an elevation in average anxiety levels (Ying-jui et al, 2004). This effect is suspected to be related to changes in neurotransmitter function,

particularly the aforementioned significant serotonergic changes. The same study noted that moderate doses led to elevated anxiety during and after intoxication while very large doses of the drug often have an anxiolytic, sedating effect, but this is a reaction that occurs when dosage levels approach that of an overdose (Ying-jui et al, 2004).

Repeated doses and heavy use, in particular produce anxiety in abstinent users and it is suspected that extensive use of the drug can produce intractable anxiety which may require pharmacological treatment (Piper, 2006). Regardless of the severity of use, however, all MDMA users (past or present) consistently scored significantly higher on measures of anxiety, depression, and behavioral impulsivity (Fingeret et al, 2005). Depression levels were found to strongly correlate to the number of lifetime doses; even a single dose typically causes a refractory period of depression immediately following the intoxication period, which is related to the acute serotonin and tryptophan depletion (Maartje et al, 2004; Parrott, 2001).

In addition to causing emotional disturbances and disorders, MDMA also affects users emotional intelligence, which was established in a more recent study aimed at emotional effects of the drug. In this study, Craig et al. (2008), determined that ecstasy produced greatly compromised emotional function, but also noted that emotional intelligence is greatly affected by anxiety and depression, which are nearly always present in users. It was also found that precautionary/protective measures produced less significant decreases in emotional intelligence. More research will be required to determine if MDMA's effect on emotional intelligence is direct or indirect, though it was postulated that the loss of emotional intelligence was likely related to serotonergic abnormalities as well as the changes and damage to the limbic system and various areas of the cortex (Craig et al., 2008).

Sensory and Cognitive Issues

Whilst intoxicated on ecstasy, users experience powerful amplification of physical stimuli (Starr, 2007). Even minor tactile stimulation provides intensely pleasurable sensations—this effect is so pronounced that it is common to see ecstasy users carrying around soft-textured objects such as pillows and stuffed animals while intoxicated for the sole purpose of enhancing the tactile sensory experience (Klein, 2009). Many users also engage in others behaviors that are specifically designed to further enhance this effect, such as massaging one another or applying various other physical stimuli to one another to maximize the pleasurable sensory experience (Klein, 2009). Though the physiological mechanisms by which this occurs are not fully understood, it is known that aforementioned MDMA-mediated release of the hormone oxytocin plays a central role and motivates people towards affectionate behaviors (Liechti, 2001). Another study also revealed that the tactile-modulating characteristics of MDMA also effect users' perception of pain. While intoxicated, users' were found to have a reduced tolerance for physical pain, which the researchers suggested was yet another function of irregular serotonergic activity (O-Regan, 2004). Clearly, very intense changes can occur when one disrupts the very delicate chemical balance that exists within the human nervous system.

Auditory sensory stimulation is an interesting topic with regards to MDMA use; the majority of users typically use the drug in sensory rich environments, such as nightclubs, which are full of music and lights (Feduccia, 2008). The drug creates a type of a self-perpetuating cycle between the chemical intoxication and the auditory sensory stimulus, which is often music. Ecstasy enhances users' enjoyment of music and studies have revealed that auditory stimulation, such as music, can modulate MDMA's effect on reward-related behaviors. This is of particular

interest because a large portion of ecstasy users take the drug at electronic music concerts (Feduccia, 2008). These concerts are often referred to as "raves," and the attendees of them as "ravers." This sub-group of the general population is of particular interest when studying MDMA as it is estimated that around 90% of "ravers" use MDMA on a regular or semi-regular basis compared to the approximated 5% of the general population (Feduccia, 2008). Perhaps the culture and activities surrounding these electronic-music parties has a complex effect on the reward-system and perhaps the auditory stimulation (music) is a key component.

Researchers and physician conducted an informal case study that resulted from an abstinent user seeking emergency medical attention after experiencing the sudden, acute onset of a very strange, very serious perceptual disorder. The subject was a twenty-two year old male subject and after being hospitalized it was discovered that his visual perception had been damaged in such as way that he seeing an innumerable amount of transparent "dots" throughout his field of vision. As he described, when his eyes were open it was "like a snow-storm on a defective television." When his eyes were closed, he reported seeing the same distortion but in color (Passie, 1999). This condition also had an element of photosensitivity. Apparently the condition was more intense in well illuminated areas and less intense in areas of low illumination. The subject was a polydrug abuser and had been using MDMA for eighteen months prior to the incident, consuming approximately 350 doses (pills) within that time (Passie, 1999). Thorough medical examination revealed that his eyes and optic nerves were in perfect condition. Thus, the doctors concluded that this disorder was permanent and could have only resulted from cortical damage to the visual cortex initiated by MDMA-induced neurotoxicity (Passie, 1999).

An essential part of perception is integration: our ability to take raw sensory information, processes it within the framework of our memories, and then interprets the sensory information in a meaningful way. Findings from numerous studies indicate that MDMA has great potential to threaten this very critical neural process. As mentioned before, ecstasy disrupts the process of neurogenesis, which is a critical mechanism of long-term memory function (Catlow, 2009). We utilize our memories to add meaning to sensory stimulation, therefore anything that damages memory function can also damage our capacity for sensor interpretation. It is also know that ecstasy causes tremendous serotonin (tryptophan) and dopamine (tyrosine) dysfunction in the brain, which has the potential to exacerbate virtually any neurological symptom as there are so many critical pathways in the brain that depend on these neurotransmitters (van Donkelaar et al., 2010; Reneman, 2001). Furthermore, de Sola (2008) discovered that MDMA use produces significant deficits in cognitive speed and processing time, even after a one-year period of complete abstinence from all chemical intoxication. It is reasonable to assume that deficits in sensory integration and sensory-response time are corollary to these findings, though specific studies have yet to be done to confirm these beliefs. In the aforementioned study, P300 Event-Related Potentials were used to measure subjects' responses to various cognitive tasks. The results clearly demonstrated that the experiment group (abstinent MDMA users) significantly underperformed the control group (no previous drug-use) within the following parameters: word fluency, memory recognition, and processing speed (de Sola, 2008). In conclusion, the discovery of these cognitive deficiencies signifies the high likelihood of corresponding deficiencies in sensory integration and sensory-response time

MDMA and PTSD: The Therapeutic Potential of Ecstasy

As discussed in the introduction of this paper, there has nearly always been much controversy surrounding MDMA, particularly as it pertains to the nature of the damage it causes and the potential for clinical use of the drug. The Drug Enforcement Agency's ultimate scheduling of the drug in 1986 galvanized the efforts of many MDMA–advocate groups. One of these groups, in particular, is of great importance; the Multidisciplinary Association for Psychedelics Research, referred to herein as "MAPS" or the "MAPS" organization. This group, formed shortly after the DEA's aforementioned ruling on MDMA, has recently succeeded in conducting ground-breaking studies regarding MDMA in a clinical capacity and the publications born of these studies are very compelling (Mithoefer et al, 2010; MAPS.org, 2012). Though much more investigation is required, MAPS has made great strides in demonstrating the intriguing therapeutic characteristics of MDMA, specifically in the treatment of patients suffering from post-traumatic stress disorder (PTSD).

Recent efforts by the MAPS organization, which have been very successful and have attracted international participation and collaboration, are in many ways the continuation of the very heated debate which circled MDMA in the 1980s. The MAPS organization formed shortly after the conclusion of the DEA hearings and many of the key members of MAPs have been diligently working to make progress in this area since (Mithoefer et al, 2010; MAPS.org, 2012). As stated before, the success of MAPS with the US government in the early 2000s garnered the support of health authorities in other countries such as Spain and Israel, with still more countries planning similar studies in the years to come (MAPS.org, 2012). This section will examine the

most salient pieces of information that have been produced by the MAPS organization's pilot studies and associated works.

Spain was one of the first countries to begin participating with the MAPS organization and it was in this country that the first would-be pilot study aimed at the clinical benefits of MDMA was commenced (Bouso et al., 2008). Unfortunately, this study was cut short due to political pressures, but not before a small bit of interesting, however limited, data was collected. This study, announced in 2002 and completed in 2008, targeted adult women suffering from severe cases of PTSD. The primary goal of this study was to assess the safety of a single therapeutic dose of MDMA administered in order to enhance the benefits of psychotherapy (Bouso et al., 2008). The lead researchers of this study postulate that it is MDMA's unique, entactogenic emotional profile which makes it so compelling for clinical use and they note that the substance produces only minimal perceptual and cognitive effects at conservative doses. This combination of emotionally beneficial effects and minimalized side effects gives MDMA a very high efficacy in the treatment of PTSD (Bouso et al., 2008).

Originally, the Spanish study was intended to include up to 29 subjects, but due to complications related to political pressure, only included 6 subjects in its final form. All subjects were between 29 and 49 years of age, in good health, and were all experiencing PTSD symptoms of varying intensity resulting from sexual or violent traumatic events (Bouso et al., 2008). Though this sample size was small, there is a respectable range of symptomology and time elapsed between study and the subjects' disorder-initiating traumatic events. This study was double-blind, placebo-controlled, and including dosing ranging from 50-150mgs, as was determined by considering the experimental design and methods of other, similar clinical studies.

The only doses which were administered, however, were 50mg doses (to three subjects) and 75mg dose (to one subject). Extensive psychological assessment in a clinical setting was conducted prior to administration of the drug and substantial assessment was conducted following administration (Bouso et al., 2008).

Due to the study's abrupt termination, meaningful statistical analysis is not possible. This limited the quantitative extrapolations that researchers could make, though they did offer some qualitative observation from their results. Differences in outcome measures between subjects who received the 50 mg doses and the 75mg doses indicate that there may exist a relationship between magnitude of dose and efficacy of treatment, which would stand to reason as so many of the drug's other effects are dose-dependent even at conservative dosing levels (Bouso et al., 2008). It is important, however, to keep in mind the the need to develop an accurate risk-reward profile for the drug, as there is almost certainly an upper limit to this beneficial relationship. This observation demonstrates the importance of a well-established dose-response curve for MDMA prior to the development of a clinical protocol. Other observations stated by the researchers include the concern that concomitant applications of MDMA and exposure therapy may induce retraumitization at a time when subjects or patients are in an overly-sensitive state with regards to emotional control and cognition. Conversely to this concern, none of the subjects from the Spain study experienced increased scores on the re-experiencing subscales of the study's follow-up psychological assessment, indicating that no subjects experienced detrimental retraumitization as a result of the study's MDMA administration and concurrent clinical proceedings (Bouso et al., 2008). This favorable outcome may very well be linked to the aforementioned suppression of the amygdale and stimulation of

the midbrain which results in increased emotional engagement. Furthermore, the subjects of this study who demonstrated the most severe premorbid PTSD symptoms also experienced the most substantial symptomatic improvements per the study's follow-up assessments (Bouso et al., 2008). Finally the researchers observed that none of the subjects experienced any clinically significant physiological changes as a result of participation in the study. The conclusion of this study is that MDMA very likely has an appealing risk-reward profile and, in keeping with the studies aforementioned primary goal, there is no evidence here that single, clinical doses of MDMA are unsafe, particularly as relates to patients with similar symptomologies. Though the results of this study are very compelling, it should be noted, again, that this study was cut short and is statistically insignificant. The principal researchers in this study commented that future studies should pay special attention to any experimental parameters which would aid in the formation of a dose-response curve and/or an accurate risk-reward profile. Additionally, future studies of this nature regarding MDMA would be well-served by having results examined by other associations so as to minimize the potential for biases and confounds as the popular media and preexisting public perceptions of the substance are a constant obstacle for academics and professionals in this field of research.

Just a few years after the publications resulting from the Spain pilot study, the MAPS organization released another publication, summarizing the results of their United States pilot study which is regarded as the first randomized controlled study effort regarding clinical uses of MDMA (MAPS.org, 2012). This study, unlike the Spanish one, was carried out as intended in its completion, save some constructive modifications along with way. This study was also targeted at PTSD patients with more severe, often protracted symptoms. Many potential

participants were thoroughly interviewed and examined, resulting in a sample of twenty adults who met the researchers' very specific criteria. Subjects were required to have a definitive PTSD diagnosis as defined by the DSM-IV-R and were required to have treatment-resistant, severe cases of the disorder (Mithoefer et al., 2010). Severity of the PTSD symptoms was assessed using the Clinically-Administered PTSD Scale (CAPS). Additionally assessment and evaluation of potential subjects included the Structured Interview for Axis I Diagnosis (SCID), general medical history, physical examination, complete blood analysis including blood count, thyroid-simulation hormone testing, free Thyroxine testing, HIV serology, urinalysis, and electrocardiogram (ECG/EKG). Though the MAPS organization, led by principal researcher Dr. Michael Mithoefer, wished to have a larger sample size, the unprecedented nature of this experiment combined with its rigorous requirements for participants resulted in the smaller sample size (Mithoefer et al., 2010). The final set of subjects, which included war veterans, rape victims, a victim of a suicide bomber, and a subjects whose parents had committed suicide, were randomly assigned to groups and testing was conducted in two stages, the primary stage being double-blind and placebo controlled. Stage one consisted of an eight-hour therapy session aided by the administration of MDMA; follow-up therapeutic sessions and assessment were conducted at four-days post-testing and two-months post-testing. Stage two deviated from the blind structure of stage one, but allowed participants who received the placebo to undergo MDMA therapy sessions. Like stage one, the experimental therapy sessions with MDMA administration were eight hours long and subjects were given follow-up sessions and assessment at two-months post-testing. Though stage two treatments deviated from the precise structure of stage one administrations, this additional stage of administration and therapy allowed the researchers to

generate more data from the same sample. Of the eight subjects who were originally in the placebo control group, seven consented to participate in the stage two testing (Mithoefer et al., 2010).

Outcome measures for assessing the effects of the MDMA-assisted therapy included the CAPS measure, the Impact of Events Scale-Revised (IES-R), and the Symptom Checklist 90-Revised (SCL-90-R) as well as a battery of neurocognitive measures including assessments of attention, information processing speed and capacity, language skills, visual and spatial comprehension and processing, and assessments for various neuropathological factors. In general, both experimental and control groups showed measureable signs of improvement at the time of follow-up assessment (Mithoefer et al., 2010). The group that underwent MDMA-assisted therapy sessions, however, showed much more significant improvements per the outcome measures. The CAPS measure was conducted as part of the follow-up and per this scoring, two subjects from the experimental group, in particular, showed very significant symptomatic improvements. One of these two subjects' CAPS score dropped from a 67 to a 15 at the two-month follow-up (77.6% reduction of clinically significant symptoms) and the other subjects' CAPS score dropped from a 54 to a 15 (72.2% reduction of clinically significant symptoms). Paired t-tests were used to statistically analyze CAPS and IES-R scores; mean change in CAPS scores was a -31.7 (SD=15) and mean change in IES-R scores was -15.9 with a standard deviation of 12.1. Specifically, in evaluating the subjects' before and after CAPS scores, the researchers defined a clinically significant response as minimum CAPS score change of -30%. Per this standard, 83.3% of stage one subjects (10/12 subjects) and 100% of stage two subjects (7/7 subjects) experienced a clinically significant reduction in PTSD symptoms at the

time of two-month follow-up (Mithoefer et al., 2010). These very compelling beneficial results can be confidently attributed to the administration of MDMA in combination with exposure-centered psychotherapy. Unwanted side effects of the MDMA administration included non-significant elevation of blood pressure and pulse, jaw tightness, dizziness, and loss of appetite. However, all of these side effects were mild and easily managed via basic medical care (Mithoefer et al., 2010).

Mithoefer and colleagues (2007; 2010) postulate that the psychological mechanisms contributing to the effects of MDMA-assisted therapy may include tenets of learning theory, emotional processing theory, or possibly social-cognitive theories (Foe et al., 2009). Physiological mechanisms of these beneficial effects may include elevated serotonergic function, increased oxytocin release and response, or may possible be related to increased levels of prolactin and cortisol. Given current paradigms of human neurophysiology and the findings of many other studies, it is likely that serotonin (and to a lesser extent dopamine) are primarily responsible for the subjective effects of MDMA—these effects, however, are very complex and are modulated by many other physiological mechanisms (Mithoefer et al., 2007; Mithoefer et al., 2010). Though more research is needed, it has been suggested and it stands to reason that MDMA's ability to increase therapeutic alliance between patient and therapist is mediated by oxytocin. Additionally, oxyotcin is believed to be a key mitigated factor in the suppression of fear response (via inhibition of amygdala activation) while patients are re-experiencing traumatic events while undergoing MDMA-assisted psychotherapy (Kirsh et al, 2005). These effects are regarding by Mithoefer and colleagues as speculative in nature and require more empirical support, though the significance .

These recent studies which have been conducted make a strong case for the medicinal properties of MDMA to be heavily considered and further explored, but are certainly not considerable enough to merit the modification of the law as it pertains to MDMA. Conversely to this notion, though, there is the long-standing argument that the DEA's actions of the mid 1980s may have been hastily made and subsequently hindered MDMA research for years. Regardless of the government's action in the years to come, though, it is clear that more research should be welcomed so that the relevant authorities can make an informed decision. One of the most promising elements of the U.S. pilot study is the promising CAPS scores, given that the CAPS measure is widely accepted as a standard for assessing PTSD symptomologies and is very psychometrically sound and robust. This study, however, does have some obvious limitations which must be addressed in subsequent endeavors. First of all, the sample size is so small that it cannot be considered representative of the greater population of PTSD patients. This was a limitation that the MAPS organization accepted as they knew they could not tackle all the obstacles which lay ahead in one effort. Furthermore, it was of great benefit for a pilot study to have a small, manageable group of participants. In addition to being small, the sample was lacking in diversity along certain spectrums such as ethnicity, socioeconomic status, and gender; that is to say that the sample consisted of nearly entirely middle-class Caucasian females. Given the necessity to consider such factors in mental health modalities, future studies must strive to eliminate these potential confounding elements. Finally, the U.S. pilot study had a large issue pertaining to the transparency of the blinding measures, so much so that 95% of the subjects and therapists correctly guessed which patients were in the control group, although some patients (who turned out to be correct), were not confident in their answers. Considering the fact that

MDMA produces reasonably mild perceptual and cognitive changes at conservative clinical doses, it is plausible that there is a dosing level which would provide an adequate combination of clinical benefit and impact with regards to perception and cognition. Contrarily, although, MDMA is powerful entactogenic substance and it is also plausible that the optimal dose in terms of the as yet to be determined risk-reward profile may be such that cognitive and perceptual effects are observably pronounced.

The statistical data produced by these pilot studies are interesting and produce a firm groundwork for subsequent works, but even more compelling than the quantitative information resulting from these works is the qualitative information that they provided. For instance, some of the patients who participated in these studies were motivated to share their experiences in the hopes that their stories would be of comfort to others suffering from PTSD and of academic benefit to those wishing to further research pertaining to MDMA-assisted therapy. One such patient, a woman by the name of Donna Kilgore, was actually the very first to be selected for the MAPS organization's U.S. pilot study. Though not much scientific value can be extrapolated from a singular experience, her story is moving, inspiring, and if nothing else, incredibly interesting. Kilgore's traumatic event which initiated her PTSD symptoms was a sexual assault which occurred in her home in 1994. Shortly following this event, she began experiencing nightmares, emotional impairment and numbness, and a discomforting feeling of distance from her loved ones (maps.org, 2012). These symptoms persisted for years and ultimately escalated to more severe problems such as flashbacks, anxiety attacks, instances of syncope, and frequent migraine headaches. When her symptoms elevated to the point where she was finding it difficult to lead a normal life, Donna sought professional help. She was quickly diagnosed with a severe

case of PTSD and began undergoing traditional psychotherapy combined with anti-depressants (maps.org, 2012). Finding little relief from this, she went from therapist to therapists to no avail. At this point, she remembers being suicidal and absolutely frustrated with her life. "I was getting to the point where it was either go sit on a mountaintop or dive off of a cliff," she said, recollecting this difficult period. However, after her MDMA-assisted treatment, Donna experienced a significant reduction in her symptoms which provided an immeasurable degree of comfort to her (MAPS.org, 2012). She went on to say that "I knew the path through was the battlefield, but I just could not get through it. [but during MDMA therapy] I knew I could walk through it, and I wasn't afraid." This lay interpretation of the emotional profile of MDMA characterizes the substances ability to suppress activity in the amygdala and thus reduce the acute fear often association with experiencing of traumatic events during exposure therapy. As previously mentioned, the physiological mechanisms which mediates this effect is believed to be related to the endocrine system, although much more empirical support is needed (Mithoefer et al., 2007; Mithoefer et al., 2010). Though the MDMA-assisted therapy was not a cure for her, it was a means of offering her a great degree of relief in a very difficult life; it was, in short a very effective treatment which helped restore some normalcy to her life. Another participant in the MAPS organization's pilot study, a member of the U.S. army, remarked that MDMA-assisted therapy is "basically like years of therapy in two or three hours. You can't understand it until you've experienced it." Though this is hardly a scientific evaluation, it provides insight into the phenomenological experience of this experimental new treatment. This qualitative feedback provided by the aforementioned subjects is concurrent with the opinion of psychiatrist Dr. Peter Oehen, who says that "substances such as MDMA can produce results were conventional

methods fail. In light of these recent findings, the positive feedback provided by various patients, and the growing enthusiasm from mental health professionals, there is a strong case to be made for the continuation of research regarding MDMA-assisted psychotherapy. It is quite possible that the general opinion regarding this substance has been fundamentally flawed, in large for several decades. However, it is important to consider the damage that MDMA has done to some users. Though we may not fully understand the mechanisms or full nature of this damage, the scientific, medical, and mental health communities must maintain a diligent regard for the detrimental potential.

Recommendations for Future Research

It is obvious that MDMA's recreational popularity will not be waning anytime soon and similarly, neither will its popularity in the world of research. The public health concerns related to the drug as well as the enigmatic nature of its affects on the human brain and body are powerful motivators for researchers. However, there are seemingly infinite topics and subtopics for the world of academic to investigate and very limited resources with which to investigate them. As such, it is important that future research efforts are pointed and organized in order to provide maximum benefit to the greater population, which is, of course, one of the primary goals of academic research. Given the history and recent progress in the world of MDMA research, there are generally two directions which the work is likely to develop: investigation of recreational use and the continuation of therapeutic research. Investigation of recreational use is, as previously discussed, marked by various confounding factors which are not easy to control for. Reliance on self-report data, varying occurrence of premorbid conditions, impurities in the street drug, and the frequent occurrence of polydrug abuse among users all contribute to the compromised clarity of results in this type of work. Additionally, researchers have a hard time accounting for recreational dosing patterns; it is not practical to administer recreational doses to healthy volunteers and regulations on clinical use of MDMA are still very stringent. Though there are ways and means of limiting the effect of these factors, it is unlikely they can be completely eliminated and shall therefore continue to work against progress in this area. In consideration of this, efforts into further researching the impact of recreational use should be limited and aimed at a couple of key subtopics such as treatment of MDMA-mediated pathologies and interventional methods which may be effective in dissuading recreational use.

Regarding future studies aimed at recreational use, it would be most advantageous, given the aforementioned factors, to develop correlations between patterns of use and associated pathologies. Treatment of abstinent users could be aided by understanding the relationships that exist between MDMA use, polydrug use, premorbid conditions, and various pathological conditions and symptoms. Additionally, the application of traditional treatment measures for conditions such as depression and anxiety have been found in to have limited efficacy on MDMA-mediated conditions; it would be helpful to understand what modified measures can be taken to maximize the efficacy for MDMA and polydrug abusers. Simply investigating the relationship between recreational MDMA use and its effects will always be rife with the aforementioned confounds and, as such, future efforts must be concentrated on those issues which will provide the greatest benefit from a public health standpoint. In short, we understand from the research that has already been conducted that recreational MDMA use can be very detrimental to neural health and unless subsequent studies can administer the drug in a controlled environment in order to pinpoint specific mechanisms responsible, their benefit will be limited. Investigation of MDMA-mediated neurological damage should also attempt to establish correlations between level of dosing and level and type of damage. In summary, the goals of future research of this type should target specific mechanisms of damage, treatment of that damage, relationships between MDMA use, polydrug abuse, associated pathologies, and treatment methods designed specifically for these pathologies.

Given the studies reviewed herein and their evidence, it would be most advantageous to focus future studies on the investigation of MDMA's therapeutic use. These studies could not only be beneficial for patients with relevant disorders, but would also provide data regarding

MDMA use which is less polluted by confounds. Since these studies are administering pure MDMA in a controlled environment there is no need to rely on self-report data and it would be much easier to establish a connection between magnitude of dosing and the nature and severity of the associated effects. We have seen that extensive MDMA use can cause great harm and so belaboring that point with more, similar studies regarding recreational use seem of little benefit. However, exploring the impact of moderate, conservative doses (such as those used in a clinical setting) is of great benefit to all future MDMA studies, especially those attempting to further refine the clinical protocol for MDMA-assisted therapy.

Based upon the current body of MDMA research, the most logical and beneficial goals for future research into MDMA's therapeutic application should be the establishment of an accurate, thorough risk-reward profile, the calculation of an accurate dose-response curve, and eventually the development of a clinical protocol. In order for the protocol to garner wider support, researchers need to understand the full extent of the effects of conservative, clinical dosing patterns and they must also be able to establish a reliable level of efficacy. Successful completion of these goals may demonstrate that there is a reasonable argument behind rescheduling MDMA with the goal of implementing the clinical protocol on a larger scale. However, before these actions can be taken, there needs to be a detailed examination of the logistics involved with rescheduling MDMA or even, on a smaller scale, allowing more widespread clinical trials. For instance, the substance would have to be produced, distributed, stored, and secured. Physicians would have to be trained on the proper application of the drug and marketing would need to be implemented to increase public awareness. Given the potentially small population for which MDMA-assisted psychotherapy is a logical choice, it may

very well be the case that is not reasonable to reschedule MDMA. Further research and cost-benefit analysis may indicated that it is more reasonable to have a small number of specialized clinics which can administer MDMA-assisted psychotherapy to patients who are suffering from protracted cases of PTSD. This would not only limit the potential for misuse, but would limit the costs associated with making such a modality accessible to applicable patients. This could also relieve a financial and practical burden from the healthcare system. It is possible patients would have to undergo fewer treatments to manage their symptoms so that more patients would have access to the services and healthcare providers could responsibly care for a larger number of patients, thereby lowering the cost and labor-burden of treating patients with such disorders.

There are many potential arguments which may be posed against future research into MDMA's therapeutic potential. For instance, it is widely known that MDMA can be very harmful and many people may question the use of such a substance as a pharmacological agent. In response to this, it must be stressed that, empirically speaking, only abusive dosing patterns lead to serious consequences and, furthermore, this abuse is usually combined with the abuse of many other (polydrug abuse). It is also important to note that many pharmacological agents which are used in a therapeutic capacity can cause harm if abused. MDMA is not different than most pharmaceutical agents, in this regard, as according to current evidence it can help alleviate suffering from certain pathologies in conservative doses but can also cause pathologies in healthy individuals when abused. Many individuals and organizations may also argue that if clinicians are allowed to prescribe MDMA that it will lead to misuse of the substance; it will then be possible for unintended persons to access the drug and for mental health professionals to misapply it. In response to this, it must be stressed that according to current evidence, there is no

need for MDMA to be taken outside of a carefully controlled, monitored environment in order to reap the full therapeutic benefits. MDMA abuse can lead to health detriments and, as such, should likely never be used outside the presence of a health professional. In this way, it will be easy to regulate the administration of the substance and, by extension, to prevent abuse of it by either patients or health professionals. Finally, even if all of the aforementioned issues are addressed, there will be a very widespread public opinion and perception that MDMA-assisted therapy advocates will have to combat. These opinions and perceptions, however, can be reformed via the distribution of newer data regarding the research and its results. Clinical trial participants who have experienced favorable results can help in this capacity by sharing their stories and experiences in a public forum so that people will be more apt to humor the idea of MDMA-assisted psychotherapy. More to the point, if the subsequent clinical trials of the drug are as promising as the preliminary ones explored herein, then it will be most advantageous to public health as well as mental health providers to entertain the possibility that a substance commonly associated with pathology can actually be used to improve health.

The world of scientific research is guided by a few key ideals which must be upheld. First of all, scientific research must be objective and unbiased. Secondly, these objectives must be aimed at providing information which will produce some benefit, whether it be public health, the sum of human knowledge, or some other goal. In concordance with these guidelines, it is only logical to continue investigating the therapeutic potential of MDMA. Specifically, future research efforts should be centered around this topic until the following question can be answered: can MDMA be safely and effectively used to treat psychopathologies? Once this

question can be thoroughly answered it will be time to consider a second question: what can be done to maximize its efficacy while minimizing the risk of side effects?

Conclusion

Though MDMA is not a new drug, clinical research with the capacity to form causal relationships regarding the drug are only just beginning. In nearly all respects, there is much more work needed before the therapeutic merits of MDMA can be fully understood. Though the MAPS organization has made tremendous progress in the area, it will likely be years before any major changes can be made to MDMA's legal status or DEA scheduling if there will ultimately be any such change at all—there just isn't enough data at this point. However, that is not to say that there isn't potential in the data that does exist. In fact, the studies which have currently been completed (particularly the MAPS flagship study) are very promising. MDMA's potential for harm must be carefully weighed and it is indispensible that we thoroughly understand the relationship between dosing patterns and physiological risk (as well as therapeutic benefit). More work must be done to establish an accurate risk-reward profile and dose-response curve. Furthermore, once these relationships are established, an incredibly detailed clinical protocol must be developed which will ensure that patients undergoing such treatments are provided the greatest potential for treatment with minimal risk of harm. There will also need to be careful considerations regarding the type of clinical modality (or combination thereof) to administer with MDMA. The current studies have been fairly conservative psychotherapeutic methods, but perhaps cognitive-behavioral methods could pair well with MDMA given their dependence on condition and the drugs excitation of the mesolimbic reward system.

Assuming all of these questions can be answered and subsequent studies go as well as the initial ones did, there are additional questions to be answered regarding logistics and pragmatics of the treatment. That is to say, assuming MDMA-assisted therapy is ultimately approved by all

of the appropriate organizations, how would it best be made available? As previously stated, it may not be practical to reschedule the drug and treat it as any other prescription pharmaceutical due to the many complications and costs that could arise. It may, instead, be more practical to set up specialized clinics where certain patients would be able to participate in MDMA-assisted psychotherapy. This way, nearly every aspect of the treatment could be carefully controlled such as the patient selection, clinical environment, parameters and characteristics of the therapy, and, of course, the administration of the drug. Currently, though, the best that can be said for research targeting MDMA-assisted therapy is that it is off to a promising start. The scientific and academic communities will certainly continue to monitor the works of the MAPS organization and their investigation into the therapeutic merits of MDMA.

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Appendix A: DEA Scheduling of Controlled Substances

The United States Drug Enforcement Agency divides controlled substances into distinct categories. These categories are numbered one through five, with one being the most restricted and five being the least. These categories are described in more detail below. This information is intended to provide a basic understanding of the implication behind rescheduling a substance such as MDMA. This material was taken from the US Drug Enforcement Agency's website "http://www.deadiversion.usdoj.gov/schedules/index.html" on April 10th, 2012.

Schedule I Controlled Substances

Substances in this schedule have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and there is a lack of accepted safety for use of the drug or other substance under medical supervision.

Some examples of substances listed in schedule I are: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine ("ecstasy").

Schedule II Controlled Substances

Substances in this schedule have a high potential for abuse which may lead to severe psychological or physical dependence.

Examples of single entity schedule II narcotics include morphine and opium. Other schedule II narcotic substances and their common name brand products include: hydromorphone (Dilaudid®), methadone (Dolophine®), meperidine

(Demerol®), oxycodone (OxyContin®), and fentanyl (Sublimaze® or Duragesic®).

Examples of schedule II stimulants include: amphetamine (Dexedrine®, Adderall®), methamphetamine (Desoxyn®), and methylphenidate (Ritalin®). Other schedule II substances include: cocaine, amobarbital, glutethimide, and pentobarbital.

Schedule III Controlled Substances

Substances in this schedule have a potential for abuse less than substances in schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence.

Examples of schedule III narcotics include combination products containing less than 15 milligrams of hydrocodone per dosage unit (Vicodin®) and products containing not more than 90 milligrams of codeine per dosage unit (Tylenol with codeine®). Also included are buprenorphine products (Suboxone® and Subutex®) used to treat opioid addiction.

Examples of schedule III non-narcotics include benzphetamine (Didrex®), phendimetrazine, ketamine, and anabolic steroids such as oxandrolone (Oxandrin®).

Schedule IV Controlled Substances

Substances in this schedule have a low potential for abuse relative to substances in schedule III. An example of a schedule IV narcotic is propoxyphene (Darvon® and Darvocet-N 100®).

Other schedule IV substances include: alprazolam (Xanax®), clonazepam (Klonopin®), clorazepate (Tranxene®), diazepam (Valium®), lorazepam (Ativan®), midazolam (Versed®), temazepam (Restoril®), and triazolam (Halcion®).

Schedule V Controlled Substances

Substances in this schedule have a low potential for abuse relative to substances listed in schedule IV and consist primarily of preparations containing limited quantities of certain narcotics. These are generally used for antitussive, antidiarrheal, and analgesic purposes.

Examples include cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams (Robitussin AC® and Phenergan with Codeine®).