An Exploration of the History and Controversies Surrounding MDMA and MDA

Alana R. Pentney, B.Sc.*

Abstract—In existence for nearly a century, 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") have gained quite a reputation. Perceived by some as dangerous neurotoxins, and by others as potential psychotherapeutics, these compounds have become a center of controversy among academics and law enforcement officials, and in the process have gained extensive media exposure. The classification of these drugs as illicit, controlled substances in the United States has not prevented their use, and MDMA, or Ecstasy, is currently one of the most popular substances used recreationally in North America. The scheduling of MDMA and MDA has, however, led to the distribution of contaminated, or falsely represented, Ecstasy tablets, and prevented responsible research into the detrimental and therapeutic effects of these drugs. A look at the history of these compounds suggests that they have the potential to be used safely as psychotherapeutic tools, and that the legal status of MDMA and MDA may be worth reconsidering.

Keywords—Ecstasy, entactogens, MDA, MDMA

Plotinus, an ancient roman philosopher, once stated that "You can only apprehend the infinite by a faculty superior to wisdom, by entering into a state in which you are your finite self no longer—in which the divine essence is communicated to you. This is ecstasy. It is the liberation of your mind from finite consciousness" (Plotinus 1991). 3,4-Methylenedioxymethamphetamine (MDMA) is a drug popularly known as "Ecstasy," both in name and in description of its effects. In accordance with Plotinus' interpretation of emotional ecstasy as an unlocking of the mind, MDMA is well known for its ability to remove mental barriers, abolish the fear response, and enhance sensuality (Riedlinger & Riedlinger 1994; Grinspoon & Bakalar 1986; Nichols 1986; Riedlinger 1985). Unfortunately for those who believe that MDMA and a similar compound, 3,4-methylenedioxyamphetamine (MDA), have the potential to be used as psychotherapeutic tools, both substances are strictly controlled in North America. It has been shown that MDMA and MDA are neither typical stimulants nor hallucinogens, and represent "entactogens," a new therapeutic class of pharmaceuticals (Nichols 1986). However, there is evidence that these compounds may cause degeneration of specific cells in the central nervous system (Sprague, Everman & Nichols 1998), and so they remain restricted in spite of the fact that their controlled status severely hinders medical research on one of the most popular recreational drugs today, Ecstasy. The dangers involved in consuming MDMA or MDA have been the subject of heated debate for over a decade. Some believe that one dose will cause irreversible damage, while others believe that these drugs

*Graduate student, Department of Pharmacology, University of Alberta, Edmonton, Alberta, Canada

Please address correspondence and reprint requests to Alana Pentney, Department of Pharmacology, 9-36 Medical Sciences Building, University of Alberta, Edmonton, Alberta T6G 2H7, Canada.

are relatively harmless. Both sides are exceedingly vocal, and the argument will most likely continue for quite some time. In the meantime, it is important that those new to the subject review the literature and come to a personal, informed opinion before making any assumptions about these compounds. While it has been suggested that MDMA and MDA cause neurodegeneration in animal models, effects on the human nervous system have not been adequately researched, due to the current legal status of these drugs. In addition, acute toxic responses to these substances may often be attributed to contaminants in, or falsely represented, street drugs. For the most part, the validity of studies that portray entactogens as beneficial therapeutic tools seems to outweigh the relevancy of detrimental findings. The current information available on MDMA and MDA suggests that these compounds, despite their classification as illicit substances, need to be researched as tools for understanding the human mind.

HISTORY OF MDA

In 1910, MDA was synthesized for the first time by two German chemists, Mannich and Jacobsohn (Hegadoren 1995; Shulgin 1978). The pharmacological properties of this drug were assessed in 1939, as part of a phenethylamine structure-activity study performed by Gunn, Gurd and Sachs on experimental animals. It was found that MDA caused substantial sympathomimetic effects, along with a marked stimulation of the central nervous system (CNS). It is worth noting that even the first researchers to examine MDA commented on the possibility that its central effects could be exploited therapeutically (Gunn, Gurd & Sachs 1939). The first human trials with MDA were performed in 1941, as part of an exploration of possible therapies for Parkinsonism. However, it was found to aggravate the disease (Loman, Myerson & Myerson 1941).

Immediately following World War II, government agencies in the United States were interested in developing new "truth serums" or incapacitating agents. In the search for these tools, it was not uncommon for unexplored chemicals to be given to unknowing subjects, at extremely high doses. One such project involved a military contract with several physicians at the New York State Psychiatric Institute to study new drugs from the Edgewood Arsenal. In 1953, one of these chemicals, EA-1298, was given to a patient named Howard Blauer on several occasions. Unbeknownst to everyone except for the authorities at Edgewood, EA-1298 was the chemical warfare code for MDA. MDA is psychoactive at 80 to 160 mg orally, but the final and lethal dose that Blauer received was 500 mg intravenously (Pellerin 1998; Shulgin & Shulgin 1990). Understandably, MDA was not adopted for use by the army. Instead, MDA was patented as a cough suppressant by H.D. Brown in 1958, as an ataractic by Smith, Kline, and French, Co. in 1960, and as an appetite suppressant under the trade name of Amphedoxamine (Shulgin & Shulgin 1990) in 1961 (Climko et al. 1987; Shulgin 1978). G.A. Alles described the central effects of MDA in 1959, and his observations included an increased self-awareness accompanied by elevated sensory intensity (Hegadoren 1995; Shulgin 1978). The empathy-producing effects of MDA were further explored by Naranjo, Shulgin, and Sargent (1967), leading to a recommendation that the drug be used as an adjunct to the psychotherapeutic process. Unfortunately, the central effects of MDA that would make it useful in psychiatry are also the effects that led to a widespread abuse of the drug during the 1960s. In 1970, the Drug Enforcement Administration (DEA) successfully petitioned to have MDA classified as a Schedule 1 illicit drug in the Controlled Substances Act (see Section 202: Schedules of controlled substances; Schedule 1 of the Comprehensive Drug Abuse Prevention and Control Act of 1970; Public Law 91-513), thereby preventing any further inquiry into its therapeutic potential. The scheduling, however, has not prevented the abuse of MDA, and 16 clandestine laboratories manufacturing the drug were found in the United States between 1978 and 1981 (Frank 1983), indicating that it continued to be used recreationally.

HISTORY OF MDMA

The first recorded preparation and description of MDMA is found in a patent filed on December 24, 1912, and issued on May 16, 1914, by E. Merck Pharmaceuticals in Darmstadt, Germany (Shulgin 1986). A popular misconception about MDMA is that it was first produced as an appetite suppressant. However, "they were not concerned with obesity in Germany in [1914]" (Nichols 2000), and the only claims in the patent are that MDMA can serve as an intermediate in the production of therapeutic compounds (Shulgin 1990). The drug remained unnoticed until 1953, when a large toxicological study was done at the University of Michigan under a classified contract with the U.S. Army. MDMA, with a chemical warfare code of EA-1475, was among the eight Edgewood Arsenal compounds to be tested on five different animal species: the mouse, rat, guinea pig, dog, and rhesus monkey. The research, concerning toxicity and behavioral effects, was declassified in 1969, and published in 1973 by Hardman, Haavik, and Seevers (Shulgin 1990). In this initial study of the pharmacology of MDMA, no brain damage or neurotoxicity was observed, and MDMA was found to be less toxic than MDA (Hardman, Haavik & Seevers 1973).

In 1976, Leo Zeff, Ph.D. became the first psychotherapist to use MDMA as an adjunct to psychiatric treatment (Greer & Tolbert 1990). Zeff performed hundreds of sessions quietly, without publication, and referred to the drug as "Adam" (Shulgin 1990). The use of MDMA became widely popular among psychotherapists, although preliminary findings were not made public for fear of alerting the

DEA and media to this newfound "psychedelic" tool. The effects of MDMA in humans were not published until 1978 (Shulgin & Nichols 1978), and the first comprehensive report on MDMA as an adjunct to psychotherapy was distributed privately in 1983 (Shulgin 1990). In this paper, George Greer, M.D., detailed 29 therapeutic sessions that had required written informed consent from the patients, and were conducted using Zeff's original methods (Greer & Tolbert 1990). MDMA was adopted by Greer and other psychotherapists because it produces an easily controlled altered state of consciousness (Shulgin 1986) that facilitates communication by eliminating the neurophysiological fear response that is normally elicited by a perceived threat to one's emotional integrity (Greer & Tolbert 1990). Communication is thereby enhanced, and a strong therapeutic alliance may be formed (Grinspoon & Bakalar 1986). MDMA sessions were held in places where patients would feel comfortable, usually in the home of either the patient or the doctor, and where they would have access to music, food, and anything else they might need. In contrast to more common methods of psychotherapy, the therapist played a very small role in MDMA sessions. Patients were asked to refrain from discussing their feelings until after the effects of the drug had worn off, and were told to move about independently (Greer & Tolbert 1998). The aim of these episodes was to allow the patient to experience intense self-discovery accompanied by feelings of love and empathy. There are a vast number of case reports illustrating a long-lasting benefit of MDMA therapy, dozens of which occurred after only one session (Greer & Tolbert 1998, 1990; Grinspoon & Bakalar 1986). MDMA has been implicated in the treatment of depression (Riedlinger & Riedlinger 1994), substance abuse, relationship problems (Shulgin 1990), premenstrual syndrome (Greer & Tolbert 1990), autism (Riedlinger 1985), and several other psychiatric disorders. In the words of Thomas De Quincy (1995), "most men are disguised by sobriety," and so intoxication by MDMA may consequently reveal a person's true being.

While psychotherapists were busy discovering new curative uses for MDMA, the drug was enjoying a slow expansion in recreational use. During this period, most people were trying "Adam" for the first time, and their suppliers were usually close friends who wanted to share the therapeutic experience. A small organization of chemists in Boston, called the "Boston Group," dominated the production of publicly accessible MDMA into the early 1980s. The drug became commercialized as "Ecstasy" in 1981, and the Southwest distributor for the Boston Group began his own operation in Texas (the "Texas Group") to keep up with a growing demand for MDMA. The Texas Group commenced a mass production of the drug in 1983 and quickly became the largest and most audacious Ecstasy distribution network in the United States (Beck & Rosenbaum 1994). MDMA was promoted shamelessly in the public eye as a "fun drug" that was "good to dance to," and purchases could be charged to credit cards. The drug was sold openly at bars in Austin and Dallas, causing a wave of alarm, shock, and disgust to move through both the therapeutic and law enforcement communities (Beck & Rosenbaum 1994). On July 27, 1984, the DEA administrator recommended that MDMA be placed on Schedule 1 of the Controlled Substances Act (Shulgin 1986). The proposed scheduling was quickly protested by a well-organized group of psychiatrists and health care professionals who believed that a Schedule 1 status would prevent any research into MDMA's therapeutic potential (Beck 1990; Riedlinger 1985). The government was surprised by the psychotherapists' opposition, and a DEA pharmacologist stated that they "had no idea psychiatrists were using it," due to the fact that the drug was known as "Adam" in therapeutic circles, a name unfamiliar to the DEA (Beck & Rosenbaum 1994). In response to the challenges made by MDMA supporters, hearings were scheduled to be held in Los Angeles on June 10, 1985, in Kansas City on July 10-11, 1985, and in Washington D.C. from October 8-11, 1985 (Shulgin 1990).

The interaction between MDMA proponents and the DEA sparked a media frenzy. Newspapers and magazines were soon filled with sensationalized stories of Ecstasy use and abuse, which would act as free advertising for the effects of the drug. In addition, the Texas Group responded to the proposed scheduling by manufacturing and distributing as much MDMA as possible (Beck & Rosenbaum 1994). This combination of increased demand and unlimited supply led to a blatantly out of control market, so the DEA decided to take advantage of the Comprehensive Crime Control Act of 1984 (Beck 1990; Shulgin 1986). This act allows the attorney general to place any substance posing "an imminent hazard to public safety" onto Schedule 1 for a period of one year while the final scheduling process is under way (Beck & Rosenbaum 1994). On May 31st, 1985, only ten days before the hearings to decide the legal fate of MDMA were going to begin, the DEA invoked the Emergency Scheduling Act and elected July 1st, 1985, as the effective date for a temporary Schedule 1 placement of MDMA (Shulgin 1990). It is interesting to note that the Comprehensive Crime Control Act was enacted as an attempt to arrest the production of "designer drugs" (Hegadoren 1995), or barely legal synthetic derivatives of existing controlled substances. The emergency scheduling of MDMA due to its resemblance to MDA, a Schedule 1 drug, is disputable because MDMA had been synthesized 71 years earlier in Germany. Additionally, the fact that MDA was synthesized originally in 1910 does not prevent it from being commonly classified as a designer drug due to its structural resemblance to amphetamine and mescaline. The renowned chemist and "stepfather" of MDMA, Alexander Shulgin, Ph.D., points out the vagueness of the term "designer drug" in his statement that, "one would be hard put to find a structure of any drug, anywhere, which could not be argued by some person, somewhere, as being in some

way structurally related to a Schedule 1 or a Schedule II drug" (Shulgin & Shulgin 1997).

Designer drug or not, MDMA remained under emergency scheduling and the hearings took place as planned. Dozens of psychiatrists and MDMA supporters were present to dispute the three criteria that would make MDMA a Schedule 1 drug: a high potential for abuse, no currently acceptable medical use, and a lack of safety for use under medical supervision (Beck & Rosenbaum 1994). The judicial recommendation that followed was that MDMA should be placed in Schedule III (Shulgin 1990), where it would be classified as having an accepted medical use and a low potential for abuse, enabling research and therapeutic sessions to continue. Not surprisingly, the DEA Administrator rejected this ruling and maintained that the Schedule 1 placement of MDMA was to become permanent on November 13, 1986 (Beck 1990; Shulgin 1990). An appeal made by Lester Grinspoon, M.D., removed MDMA from Schedule 1 on December 22, 1987, but it was quickly rescheduled by the DEA on March 23, 1988 (Shulgin 1990). MDMA now has a permanent place within Schedule 1, to the dismay of many psychotherapists and researchers.

THE ENTACTOGENS

Following the scheduling, several chemists and pharmacologists discovered that MDMA is a truly distinct compound with novel therapeutic effects. Using a technique known as "drug-discrimination," where animals are trained to recognize certain drugs by their effects (Pellerin 1998), these researchers made important observations regarding the relation of MDMA to other compounds. The substance that MDMA is most often compared to, MDA, had been studied in a similar manner previously, and it was recorded that the more potent levo-, or R-(-), isomer of MDA had effects resembling those of lysergic acid diethylamide (LSD), while the effects of the dextro-, or S-(+), isomer were more like those of amphetamine. At the time, no other substituted hallucinogenic amphetamine had been found to have two biologically active stereoisomers, each with different effects (Nichols 1986). The hallucinogenic activity of MDA, while not profound, causes it to be classified as a hallucinogen under Schedule 1, even though the drug also possesses atypical "empathogenic" (empathy-producing) effects (Nichols et al. 1986). In 1986, David E. Nichols, Ph.D. and his associates embraced the task of comparing MDMA with MDA, as well as the amphetamines and the hallucinogens, in order to determine how the effects of these substances are related.

Surprisingly, the simple N-methylation of MDA to produce MDMA causes several changes in activity. First of all, the duration of action is decreased from between eight to 12 hours to four to six hours, and the overall effects are less powerful (Nichols et al. 1986). Second, and most importantly, all hallucinogenic activity is abolished in MDMA (Nichols 1986). This may be due to the fact that, unlike MDA, it is the S-(+) isomer of MDMA that is more biologically active (Shulgin & Shulgin 1990; Nichols et al. 1986). It is also important to note, in contradiction to the DEA's assumption that MDMA's structural similarity to MDA indicates comparable abuse potential, that there is absolutely no cross-tolerance between MDA and MDMA (Shulgin & Shulgin 1990). These findings would indicate a distinct mechanism of action for MDMA that is unrelated to MDA, the hallucinogens, or the amphetamines. Upon recognition of this fact, Dr. Nichols (1986), felt justified in naming a new category of psychoactive drugs. The name "empathogens" was contemplated because these drugs enhance empathy, but this title was rejected because people dislike hearing the word "pathogen." With the therapeutic use of these drugs in mind, the name "entactogen" was decided on, with roots in the Latin word *tactus*, for touch, and the Greek words *en* (within or inside) and *gen* (to produce). In short, entactogens such as MDMA produce a "touching within" which is pharmacologically distinct from the activity of any other class of drugs (Nichols 1986). It has been suggested that MDA should also be included under this new designation, and that the uniqueness of the entactogens may warrant the creation of a new scheduling category in the Controlled Substances Act (Riedlinger 1985). However, the DEA failed to recognize this new pharmacological class of drugs, and MDMA remained on Schedule 1.

RECREATIONAL MDMA USE

Despite the controlled status of MDMA, recreational Ecstasy use has significantly increased over the years. In a 1987 survey of an undergraduate campus, 39% of subjects reported that they had used MDMA at least once (Peroutka 1990b). More recently, a survey displayed on the National Institute on Drug Abuse (NIDA) website for MDMA (http://www.nida.nih.gov/Infofax/ecstasy.html) has shown that the number of 12th-graders who had used MDMA in their lifetime increased from 5.8% in 1998 to 8.0% in 1999, and the heaviest use of Ecstasy occurs between the ages of 18 and 25. This evidence is commonly interpreted to suggest that MDMA is a dangerous addictive chemical. On the contrary, as one college student has been quoted as stating, "freshmen love [MDMA]; sophomores like it; juniors are ambivalent; and seniors are afraid of it," indicating a rapid decrease of use within individuals (Peroutka 1990a). It has been shown that the most frequent use of MDMA occurs immediately after initial exposure, and the "magical" effects of the drug diminish after repeated use, even with extended periods between doses (Shulgin 2000; Beck & Rosenbaum 1994; Peroutka 1990a). Occasional users often have the mindset that "the first time was the best," and that they have learned everything that MDMA can teach them, spiritually. Additionally, the burn-out after each use

becomes increasingly disagreeable (Beck & Rosenbaum 1994). With no reports of subjects who take large amounts of MDMA for long periods of time (Peroutka 1990a), indicating that the drug is not addictive, the recent rise in recreational MDMA use is quite surprising. However, this phenomenon may be explained by the fact that Ecstasy is currently a very popular substance among certain groups.

On the Spanish island of Ibiza in 1985, MDMA was fused with an intense public environment that included a distinctive type of music and dancing, called "acid house." The island was frequented by European tourists, and was informally renamed "XTC Island" by the summer of 1986 (Beck & Rosenbaum 1994). People returning to other parts of Europe brought back the drug-enhanced musical concept, and so the rave scene was born in the United Kingdom (Milroy 1999). Raves, which have since spread to North America, are large parties where people gather and dance to loud rhythmic music until dawn and beyond, reminiscent of the 1960s "acid tests" (Beck & Rosenbaum 1994). MDMA is commonly associated with this phenomenon, although several other drugs are frequently used (Milroy 1999), and quite often dancers are not intoxicated at all. Fashion is a large part of the rave culture (Beck & Rosenbaum 1994), and it is easy to see that the clothing worn to these parties often serves a "psychedelic" purpose. Phosphorescent glow sticks are common components, as well as oversized pants and seemingly ridiculous accessories, which may make the experience more surreal for people using sense-enhancing drugs such as Ecstasy. It is important to note that a common rave motto is "P.L.U.R.," or Peace, Love, Understanding, and Respect, indicative of the accepting attitude possessed by people who frequent these gatherings. It may not be a coincidence that MDMA generates feelings of love, empathy, and peace in those who use it (Greer & Tolbert 1990; Grinspoon & Bakalar 1986; Nichols 1986). Unfortunately, the media has glorified and condemned the rave scene repeatedly, leading to an increase in the popularity of these parties and a pronounced disapproval from law enforcement officials (Milroy 1999). The motto of "P.L.U.R" has been somewhat abandoned as raves grow larger and the people attending them come not for the dancing, but for the drugs. The rave scene has gone from a healthy dancing environment to a dangerous, overcrowded phenomenon (Milroy 1999; Rochester & Kirchner 1998) where one can never be sure of the composition of the drugs that are purchased (Ramsey 2000; De Boer et al. 1999; Shewan, Dalgarno & King 1996; Winstock & King 1996). Ecstasy, a formerly integral part of these gatherings, has become contraindicated in the rave scene.

ACUTE TOXICITY OF MDMA

When MDMA is taken as part of a therapeutic session, in the dose range of 75-150 mg, the common peripheral side effects consist of increased heart rate, tremor, tightening of the jaw muscles, grinding of teeth (bruxism), sweating, and occasional nausea (Dowling 1990). At a rave, these normally minor annoyances can become dangerously aggravated. It has been shown that laboratory animals that are housed together, rather than on their own, are more likely to experience amphetamine toxicity (Milroy 1999). This phenomenon, known as "aggregation toxicity," is consistent with the fact that the hot, crowded rave environment combined with excessive physical exertion can elevate the side effects of MDMA into tachycardia (a high heart rate) and hyperthermia (an elevated body temperature) (Rochester & Kirchner 1998). Ecstasy-induced tachycardia only causes a major problem in people with underlying cardiovascular diseases (Dowling 1990), and so the most common acute toxic effects associated with MDMA use are rhabdomyolysis (the breakdown of skeletal muscle), coagulopathy (a disorder involving blood clotting mechanisms), and organ failure due to hyperthermic reactions (Hegadoren, Baker & Bourin 1999; Milroy 1999; Rochester & Kirchner 1998; Dar & McBrien 1996). However, these three complications occur rarely, and when these problems first became associated with MDMA ingestion, several harm limitation pamphlets were distributed at raves, telling Ecstasy users to drink fluids (Milroy 1999). Inadvertently, ravers created an entirely new set of toxic symptoms when they began drinking excessive amounts of water to counteract overheating. In a small proportion of people, MDMA increases the secretion of antidiuretic hormone (ADH) and therefore reduces the kidney's ability to rid the body of excess water (Henry 2000; Milroy 1999; Hall 1997; Holden & Jackson 1996). Ergo, the increased ingestion of fluids by people under the influence of MDMA may lead to "water intoxication," or severe hyponatraemia, which can cause cerebral oedema ("swelling" of the brain) and even death (Hall 1997; Parr, Low & Botterill 1997; Matthai et al. 1996). Since the discovery that MDMA may be involved in hyponatraemia, dancers have been advised that water is not an antidote to the side effects of Ecstasy, and are now told to drink only one pint of water per hour of physical activity (Henry 2000; Matthai et al. 1996). Besides water intoxication, hyperthermic reactions, and possible cardiac symptoms, the side effects of MDMA at raves are relatively minor. However, it has been shown that frequent Ecstasy users have significant toothwear, which may be associated with the bruxism that accompanies the high (Milosevic et al. 1999). After the effects of MDMA wear off, users may feel fatigued and sometimes depressed. These symptoms increase with each ingestion of MDMA and, in contradiction to the drug's Schedule 1 placement, discourage repeated use (Peroutka 1990b). Anecdotally, the number of deaths connected to MDMA ingestion is relatively small in comparison to its widespread use, especially when one considers that it is often taken in non-ideal surroundings (Hegadoren, Baker & Bourin 1999; Milroy 1999; Dowling 1990).

ILLICIT ECSTASY

The source of black-market Ecstasy is one major factor to consider in the discussion of acute reactions to MDMA. The "chemists" who manufacture MDMA in clandestine laboratories are usually not trained professionals, and impure or incorrect synthesis can result in dangerously toxic contaminants (Rochester & Kirchner 1998; Beck 1990; Shulgin 1986). Acute reactions to Ecstasy may also be due to overdose, as the amount of MDMA in these illicit pills varies widely and it has been shown that higher doses of the drug are more likely to produce toxic effects (Dowling 1990). In addition, substances which have effects, psychoactive doses, and toxicities that are quite different from MDMA are often falsely represented as Ecstasy, such as MDA, 3,4-methylenedioxyethylamphetamine (MDEA, "Eve"), N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butamine (MBDB), ketamine ("Special K"), ephedrine, amphetamine ("speed"), LSD ("acid") (Winstock & King 1996; Shewan, Dalgarno & King 1996), and 4-Bromo-2,5-dimethoxyphenethylamine (2CB) (De Boer et al. 1999). According to the Laboratory Pill Analysis Project, which is sponsored by DanceSafe (an international harm reduction group) and the Mulitidisciplinary Association for Psychedelic Studies (MAPS), several Ecstasy pills have recently been found to contain a common cough suppressant, dextromethorphan (DXM) (Sferios 1999). At high doses, DXM acts as a dissociative, or dissociates the mind from the body, much like phencyclidine (PCP, "Angel Dust") and ketamine. DXM alone, incidentally, can cause hyperthermia to a greater degree than MDMA, and its anticholinergic effects precipitate the elevation of body temperature by preventing perspiration. As a result, these fake Ecstasy pills caused several hyperthermic reactions to occur at raves in Oakland, California during the summer of 1999 (Sferios 1999). Paramethoxyamphetamine (PMA), another substance that has been marketed as, or in combination with, MDMA, recently caused several deaths in Australia (Byard et al. 1998; White, Bochner & Irvine 1997). This compound has also been marketed as MDA in Canada, causing several deaths by overdose (Shulgin & Shulgin 1990). In January of 2000, an Ecstasy pill was seized in Holland that contained strychnine, a substance that causes convulsions in humans and is commonly used as a rat poison (Ramsey 2000). Certainly, the compounds that are falsely represented as Ecstasy are often much more dangerous than MDMA itself, and unusual reactions such as seizures and death are frequently due to adulterants in the tablets.

Another problem that may cause the toxic reactions seen in some people who take MDMA is drug-drug interactions. There are two different ways in which drugs may interact with MDMA. First, when taken at the same time as MDMA, drugs that have a similar mechanism of action may elevate the effects of each to a dangerous level. For example, monoamine oxidase inhibitors (MAOIs), commonly used as antidepressants and anxiolytics, can elevate the sympathomimetic effects of MDMA and thereby cause symptoms such as hypertension, tachycardia, and hyperthermia (Rochester & Kirchner 1998; Dowling 1990). Another, more important, interaction that drugs may have with MDMA is the sharing of metabolizing enzymes. MDMA is metabolized in the human body by a liver cytochrome P450 enzyme known as CYP2D6 (Harrington et al. 1999; Wu et al. 1997). It has been shown that MDMA potently inhibits CYP2D6 (Wu et al. 1997), and so a person who ingests another drug that is metabolized by the same enzyme may experience adverse effects. The aforementioned DXM is metabolized by CYP2D6 (Klassen & Watkins 1999), and can cause "serotonin syndrome" (excessive serotonin release in the brain) and extreme hyperthermia if ingested with MDMA (Sfecios 1999). Ritonavir, an inhibitor of the human immunodeficiency virus 1 (HIV-1), has been shown to compete with MDMA for CYP2D6, thereby causing the effects of Ecstasy to last up to 24 hours (Harrington et al. 1999). CYP2D6 is involved in the metabolism of dozens of different types of drugs, such as codeine and the tricyclic antidepressants (TCAs: Amitriptylene, for example) (Klassen & Watkins 1999), and dangerous interactions may result if these substances are used in combination with MDMA.

EXAMINING THE NEUROTOXICITY OF MDMA

By far the most well known controversy surrounding MDMA has to do with its neurotoxic potential. It has been shown in several laboratories that MDA and MDMA induce selective degeneration of serotonergic axons and axon terminals in the brain, and this damage may be due to a cascade of events that leads to the production of toxic free-radicals (Sprague, Everman & Nichols 1998). However, no such studies have been performed on humans, and it has been shown that MDMA may have species-specific mechanisms of action (Vollenweider et al. 1999; Sprague, Everman & Nichols 1998). The research that has been performed on human users of MDMA is not entirely reliable as there are several methodological flaws, subjects are often polydrug users (Sprague, Everman & Nichols 1998; Grob et al. 1992), and the MDMA they received in the past may have been contaminated (Sprague, Everman & Nichols 1998). One of the most frequently cited papers that claims to have found "central serotonergic dysfunction" in MDMA users (Price et al. 1989) failed to mention that the nine subjects that had been selected out of 34 heavy MDMA users were among those with the lowest levels of 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, in their cerebrospinal fluid (Grob et al. 1992). In the animal studies that have been performed, no significant changes in behavior have been noted, indicating that the serotonergic damage may be asymptomatic (Pellerin 1998; Sprague, Everman & Nichols 1998). Additionally, it has

been repeatedly shown that MDMA-induced nerve degeneration is reversible in rats, with complete reinnervation over time (Hegadoren, Baker & Bourin 1999; Pellerin 1998; Grob et al. 1992). However, MDMA's possible neurotoxic potential may best be disputed when it is compared to that of a similar substance. Fenfluramine, a popular appetite suppressant, has been shown to be five times more potent at producing the same serotonergic damage as is seen with MDMA, yet it has been given over 30 years to 25 million people worldwide with no reports of neurotoxicity (Hegadoren, Baker & Bourin 1999; Pellerin 1998; Shulgin & Shulgin 1997; Molliver & Molliver 1990). Furthermore, legal MDMA psychotherapy research was recently performed in Switzerland without any reports of adverse neuropsychiatric sequelae. (Grob et al. 1992).

Part of the reason that there seems to be so much evidence in the literature for MDMA neurotoxicity may be the fact that the National Institute on Drug Abuse (NIDA) is one of the major sources of support for graduate and postdoctoral research grants. The scientific community is very competitive, and proposed research topics involving illegal drugs often need to suggest that the findings will be useful in advancing an antidrug stance if they are to be funded (Shulgin & Shulgin 1997). In the words of Alexander Shulgin (2000):

> The art of applying and getting grant money in the area of drugs is intimately associated with the ability to craft the request in a way that implies that the findings will be of use to the provider of the money. There are a few professional prostitutes that will provide what is needed, but will not publish any findings that are positive. And neutral findings are almost always framed in a negative manner. A recent example: "These results are not statistically significant, but are highly suggestive." I find it hard to believe that with the many . . . MDMA users, that no one has been killed in some tragic drug-unrelated accident which would allow a postmortem autopsy to address the brain-damage question. Maybe researchers have looked there and choose not to publish their findings!

It is clear that there may be a bias involved in MDMA research, and this bias will exist as long as the studies are financed by government agencies. Pharmaceutical companies are not willing to invest in research for possible therapeutic uses of MDMA because it was patented in 1914, and is now in the public domain. It would not be profitable for a company to spend time getting Food and Drug Administration (FDA) approval, and then pay for research, if the drug can be marketed by other firms (Beck 1990). Unfortunately, all studies involving MDMA are hindered by legal and financial obstacles.

CONCLUSION

Both MDA and MDMA can be synthesized from the essential oil safrole, a component of nutmeg (Shulgin & Shulgin 1990). It is surprising that such controversy can surround compounds that arise from something so simple. It has been shown that MDMA is not addictive in humans (Beck & Rosenbaum 1994; Peroutka 1990a; Riedlinger 1985), has possible medical use as a psychotherapeutic tool (Riedlinger & Riedlinger 1994; Greer & Tolbert 1990; Grinspoon & Bakalar 1986; Riedlinger 1985), and is relatively safe to use in a therapeutic setting (Greer & Tolbert 1998). MDMA does not fill the criteria for an illicit drug, yet it remains under Schedule 1 of the Controlled Substances Act. MDMA's structural similarity to MDA was used as an indicator of abuse potential initially, but it has been shown that MDA and MDMA have different mechanisms of action and are therefore very different drugs (Shulgin & Shulgin 1990; Climko et al. 1987; Riedlinger 1985). The neurotoxic potential of MDMA is another factor that is used to justify its Schedule 1 placement, but it has not been proven that the drug causes irreversible serotonergic damage in human brains (Shulgin 2000; Grob et al. 1992). Arguably, the classification of MDMA has not accomplished much more than preventing any responsible research into the detrimental and therapeutic effects of a drug that continues to be used as a popular recreational euphoriant (Shulgin 2000; Shulgin & Shulgin 1997; Beck 1990). The current status of MDMA is best summed up in a statement made by Smith, Wesson, and Buffum: "Moving a drug to Schedule 1 does not stop illicit availability. The whole notion of controlled drugs is a misnomer. Nothing is so out of control as those drugs the DEA and FDA have approved to Schedule 1. Moving a drug to Schedule 1 does, however, have consequences. Price generally increases, the quality control of . . . manufacture is destroyed, and responsible research becomes almost impossible." (Beck 1990)

MDMA must be placed in a less restricting schedule if its effects—toxic, beneficial, and otherwise—are ever going to be fully understood. The possible therapeutic applications of MDMA need to be explored, as well as the possible consequences of recreational use. Until the compound is removed from Schedule 1, however, the funding for such research is hard to come by and may be granted by biased sources (Shulgin & Shulgin 1997). Proponents for the medical use of MDMA have gathered substantial evidence that the drug is not a hallucinogen, as the DEA has classified it, and belongs to an entirely new class of drugs, called entactogens (Nichols 1986). These compounds have psychoactive effects that no existing psychiatric drug shares, and are relatively safe when given in a therapeutic setting. However, the legal status of MDMA and MDA prevents their psychotherapeutic use. In the words of Voltaire, "It is dangerous to be right in matters on which the established authorities are wrong" (Shulgin & Shulgin 1997), and so the controversy surrounding MDMA will inevitably reduce the number of scientists who are willing to risk their reputation on supporting an illegal substance. Until all

proponents of MDMA give up, however, there is still hope for the medical use of this compound. Currently, there are clinical trials being done in Spain and Israel for the use of MDMA in treating posttraumatic stress disorder (Nichols 2000). Perhaps the results of these studies, and others, will help remove MDMA from its restricting Schedule 1 status.

Editors' Note:

The above article by Alana R. Pentney serves as an introduction to the complex and controversial world of MDMA use and research. Due to the widespread interest in the drug methylenedioxymethamphetamine, also known as Ecstasy, and its cogeners, *Journal of Psychoactive Drugs* is currently developing a theme issue on the topic that will appear as our April-June 2002 issue (Volume 34, Number 2). Co-theme editors will be David E. Smith, M.D., and Steve Heilig, M.P.H.

REFERENCES

Beck, J. 1990. The public health implications of MDMA use. In: S.J. Peroutka (Ed.) *Ecstasy: The Clinical, Pharmacological, and Neurotoxicological Effects of the Drug MDMA*. Boston, Massachusetts: Kluwer Academic.

Beck, J. & Rosenbaum, M. 1994. *The Pursuit of Ecstasy: The MDMA Experience*. New York: SUNY.

Byard, R.W.; Gilbert, J.; James, R. & Lokan, R.J. 1998. Amphetamine derivative deaths in South Australia—Is "ecstasy" the culprit? *American Journal of Forensics and Medical Pathology* 19: 261-65.

Climko, R.P.; Roehrich, H.; Sweeny, D.R. & Al-razi, J. 1987. Ecstasy: A review of MDMA and MDA. *International Journal of Psychiatry in Medicine* 16: 359-71.

Dar, K.J. & McBrien, M.E. 1996. MDMA induced hyperthermia: Report of a fatality and review of current therapy. *Intensive Care Medicine* 22: 995-6.

De Boer, D.; Gijzels, M.J.; Bosman, I.J. & Maes, R.A.A. 1999. More data about the new psychoactive drug 2C-B. *Journal of Analytical Toxicology* 23: 227-8.

De Quincy, T. 1995. [1821] *Confessions of an English Opium-Eater*. New York: Dover Publications.

Dowling, G.P. 1990. Human deaths and toxic reactions attributed to MDMA and MDEA. In: S.J. Peroutka (Ed.) *Ecstasy: the Clinical, Pharmacological, and Neurotoxicological Effects of the Drug MDMA*. Boston, Massachusetts: Kluwer Academic.

Frank, R.S. 1983. The clandestine drug laboratory situation in the United States. *Journal of Forensic Science* 28: 18-31.

Greer, G.R. & Tolbert, R. 1998. A method of conducting therapeutic sessions with MDMA. *Journal of Psychoactive Drugs* 30: 371-79.

Greer, G.R. & Tolbert, R. 1990. The therapeutic use of MDMA. In: S.J. Peroutka (Ed.) *Ecstasy: The Clinical, Pharmacological, and Neurotoxicological Effects of the Drug MDMA*. Boston, Massachusetts: Kluwer Academic.

Grinspoon, L. & Bakalar, J.B. 1986. Can drugs be used to enhance the psychotherapeutic process? *American Journal of Psychotherapy* 40: 393-404.

Grob, C.S.; Bravo, G.L; Walsh, R.N. & Leister, M.B. 1992. The MDMA-neurotoxicity controversy: Implications for clinical research with novel psychoactive drugs. *Journal of Nervous and Mental Disease* 180: 355-6.

Gunn, J.A., Gurd, M.R. & Sachs, I. 1939. The action of some amines related to adrenaline: Methoxyphenylisopropylamines. *Journal of Physiology* 95: 485-500.

Hall, A.P. 1997. Hyponatraemia, water intoxication and "ecstasy". *Intensive Care Medicine* 23: 1289.

Hardman, H.F.; Haavik, C.O. & Seevers, M.H. 1973. Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals. *Toxicology and Applied Pharmacology* 25: 299-309.

Harrington, R.D.; Woodward, J.A.; Hooton, T.M. & Horn, J.R. 1999. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. *Archives of Internal Medicine* 159: 2221-4.

Henry, J.A. 2000. Personal communication.

Hegadoren, K.M. 1995. *Metabolic, Behavioral, and Neurochemical Studies of 3,4-Methylenedioxy Analogues of Amphetamine*. PhD. Thesis, University of Alberta, Edmonton, Alberta, Canada.

Hegadoren, K.M.; Baker, G.B. & Bourin, M. 1999. 3,4-Methylenedioxy analogues of amphetamine: Defining the risks to humans. *Neuroscience and Biobehavioral Review* 23: 539-55.

Holden, R. & Jackson, M.A. 1996. Near fatal hyponatraemic coma due to vasopressin over-secretion after "ecstasy" (3,4-MDMA). *Lancet* 347: 1052.

Klassen, C.D. & Watkins, J.B. 1999. *Cassarett and Doull's Toxicology: The Basic Science of Poisons, Fifth Ed. Companion Handbook*. New York: McGraw-Hill.

Loman, J.; Myerson, P.G. & Myerson, A. 1941. Experimental pharmacology of post-encephalitic Parkinson's disease. *Trans-American Neurology Association* 67: 201-03.

Matthai, S.M.; Davidson, D.C.; Sills, J.A. & Alexandrou, D. 1996. Cerebral oedema after ingestion of MDMA ("Ecstasy") and unrestricted intake of water. *British Medical Journal* 312: 1359.

Milosevic, A.; Agrawal, N.; Redfearn, P.J. & Mair, L.H. 1999. The occurrence of toothwear in users of ecstasy (3,4-methylenedioxymethamphetamine). *Community Dentistry and Oral Epidemiology* 27: 283-7.

Milroy, C.M. 1999. Ten years of "ecstasy." *Journal of the Royal Society of Medicine* 92: 68-72.

Molliver, D.C. & Molliver, M.E. 1990. Anatomic evidence for a neurotoxic effect of fenfluramine upon serotonergic projections in the rat. *Brain Research* 511: 165-68.

Naranjo, C.; Shulgin, A.T. & Sargent, T. 1967. Evaluation of 3,4-methylenedioxyamphetamine (MDA) as an adjunct to psychotherapy. *Medicina et Pharmacologia Experimentalis* 17: 359-64.

Nichols, D.E. 2000. Personal communication.

Nichols, D.E. 1986. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: Entactogens. *Journal of Psychoactive Drugs* 18: 305-13.

Nichols, D.E.; Hoffman, A.J.; Oberlender, R.A.; Jacob, P. & Shulgin, A.T. 1986. Derivatives of 1-(1,3-benzodioxol-5-yl)-2-butanamine: Representatives of a novel therapeutic class. *Journal of Medicinal Chemistry* 29: 2009-15.

Parr, M.J.A.; Low, H.M. & Botterill, P. 1997. Hyponatremia and death after "ecstasy" ingestion. *Medical Journal of Australia* 166: 136-7.

Pellerin, C. 1998. *Trips: How Hallucinogens Work in Your Brain*. New York: Seven Stories Press.

Peroutka S.J. 1990a. Preface. In: S.J. Peroutka (Ed.) *Ecstasy: The Clinical, Pharmacological, and Neurotoxicological Effects of the Drug MDMA*. Boston, Massachusetts: Kluwer Academic.

Peroutka, S.J. 1990b. Recreational use of MDMA. In: S.J. Peroutka (Ed.) *Ecstasy: the Clinical, Pharmacological, and Neurotoxicological Effects of the Drug MDMA*. Boston, Massachusetts: Kluwer Academic.

Plotinus. 1991. *The Enneads*. Translated by: Stephen MacKenna; introduction by: John Dillon. New York: Penguin Books.

Price, L.H.; Ricaurte, G.A.; Krystal, J.H. & Henninger, G.R. 1989. Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methylenedioxyamphetamine (MDMA) users. *Archives of General Psychiatry* 46: 20-22.

Ramsey, J. (London Toxicology Group). 2000. Personal communication.

Riedlinger, J.E. 1985. The scheduling of MDMA: A pharmacist's perspective. *Journal of Psychoactive Drugs* 17: 167-71.

Riedlinger, T.J. & Riedlinger, J.E. 1994. Psychedelic and entactogenic drugs in the treatment of depression. *Journal of Psychoactive Drugs* 26: 41-55.

Rochester, J.A. & Kirchner, J.T. 1998. Ecstasy (3,4-methylenedioxy-methamphetamine): History, neurochemistry, and toxicology. *Journal of the American Board of Family Practitioners* 12: 137-42.

Sferios, E. 1999. Laboratory analysis program reveals DXM tablets sold as "ecstasy." *Bulletin of the Multidisciplinary Association for Psychedelic Studies* 9 (4): 47-8.

Shewan, D.; Dalgarno, P. & King, L.A. 1996. . . . Such as ketamine. *British Medical Journal* 313: 424.

Shulgin, A.T. 2000. Personal communication.

Shulgin, A.T. 1990. History of MDMA. In: S. J. Peroutka (Ed.) *Ecstasy: The Clinical, Pharmacological, and Neurotoxicological Effects of the Drug MDMA*. Boston, Massachusetts: Kluwer Academic.

Shulgin, A.T. 1986. The background and chemistry of MDMA. *Journal of Psychoactive Drugs* 18: 291-304.

Shulgin, A.T. 1978. Psychomimetic drugs: Structure-activity relationships. In: L.L. Iverson; S.D. Iverson & S.H. Snyder (Eds.) *Handbook of Psychopharmacology*. New York: Plenum Press.

Shulgin, A.T. & Nichols, D.E. 1978. Characterization of three new psychomimetics. In: Stillman and Willette (Eds.) *The Psychopharmacology of Hallucinogens*. New York: Pergamon Press.

Shulgin, A. & Shulgin, A. 1997. *TIHKAL: The Continuation*. Berkeley, California: Transform Press.

Shulgin, A. & Shulgin, A. 1990. *PIHKAL: A Chemical Love Story*. Berkeley, CA: Transform Press.

Sprague, J.E.; Everman, S.L. & Nichols, D.E. 1998. An integrated hypothesis for the serotonergic axonal loss induced by 3,4-methylenedioxymethamphetamine. *Neurotoxicology* 19: 427-42.

Vollenweider, F.X.; Remensberger, S.; Hell, D. & Geyer, M.A. 1999. Opposite effects of 3,4-methylenedioxyamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. *Psychopharmacology* 143: 365-372.

White, J.M.; Bochner, F. & Irvine R.J. 1997. The agony of "ecstasy." *Medical Journal of Australia* 166: 117-18.

Winstock, A.R. & King, L.A. 1996. Tablets often contain substances in addition to, or instead of, ecstasy . . . *British Medical Journal* 313: 423-4.

Wu, D.; Otton, S.V.; Inaba, T.; Kalow, W. & Sellers, E.M. 1997. Interactions of amphetamine analogs with human liver CYP2D6. *Biochemical Pharmacology* 53: 1605-12.