Understanding MDMA

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-12-079-H01-P

Objectives
At the conclusion of this article, the participant should be able to:

- Describe the history of MDMA
- Discuss trends in MDMA use
- Explain the mechanism of action of MDMA
- Describe trials on the treatment of hyperthermia associated with MDMA

Introduction

The substance 3,4-methylenedioxymethamphetamine is commonly known as MDMA. MDMA has many names and can be referred to as: ecstasy, E, X, XTC, Rolls, Beans, Adam, or Molly. MDMA is popular with young people involved in the dance culture. MDMA tablets are commonly known to be impure and often mixed with other drugs of abuse. Although MDMA is not a prescription drug, it is important for pharmacists to be aware of this substance because it has many adverse effects that may require medical management.

A History of MDMA

MDMA was first known to be synthesized in 1912 by the German pharmaceutical company Merck. MDMA was a chemical by-product that was found while Merck was trying to develop a vasoconstrictor to stop bleeding. It was then patented in 1914 by Merck as a compound that might be of pharmaceutical value. However, as the substance had no known uses at the time, it was not developed further.
The next significant MDMA use was in the 1950s when the United States government was studying the effects of psychoactive drugs. It is believed that the government was studying mescaline and other related compounds to be used for psychological warfare. These experiments carried out by the United States government were the first studies of the toxicology of MDMA. MK Ultra was the study of psychoactive agents and their use in military situations. MK Ultra has since been declassified. In MK Ultra, the drug code name EA-1475 was MDMA. The experiments at the time never progressed past non-human test subjects. The psychoactive effects of MDMA were not elucidated.

The precursor of MDMA known as MDA (3,4-methylenedioxyamphetamine) was being used by SmithKline in 1960 as a tranquilizer. It was also being studied as an appetite suppressant, but clinical trials proved it to be too psychoactive, producing too many hallucinations and changes in mood, for medical use.

MDA differs only from MDMA in the addition of a methyl group to the nitrogen as seen above. MDA produces an empathy-enhancing effect which was explored by a Chilean anthropologist-psychiatrist Dr. Claudio Naranjo. Dr. Naranjo used MDA's effects in his private practice as a psychiatrist. Dr. Naranjo wrote a book called The Healing Journey, which was published in 1973. In the book, Dr. Naranjo discussed how he used MDA to enhance his patients' therapy. MDA was widely abused in the 1960s when it was known as the "Love Drug".
The first known studies of MDMA’s psychoactive effects were conducted by a chemist named Alexander Shulgin. Shulgin wrote about the effects and how to synthesize MDMA in his book *Pihkal*. In it, he described the ingestion of 120mg as such:

I feel absolutely clean inside, and there is nothing but pure euphoria. I have never felt so great, or believed this to be possible. The cleanliness, clarity, and marvelous feeling of solid inner strength continued throughout the rest of the day, and evening, and through the next day.²

Dr. Shulgin's work introduced the psychoactive component. Dr. Shuglin, along with Dr. David Nicholas, published a scientific study on the effects of MDMA, along with other drugs, in *The Pharmacology of Hallucinogens* (1978). The use of MDMA as an aide in psychotherapy began. By the early 1980s, it was estimated that over a thousand private practice psychotherapists were using MDMA in the course of treatment. The name "Adam" was first coined in reference to MDMA as the therapists felt MDMA returned patients to a more innocent state.²

The use of MDMA became public in June of 1984 when the *San Francisco Chronicle* ran an article titled "The Yuppie Psychedelic". Soon after the publishing of "The Yuppie Psychedelic" the use of MDMA in the general public began to gain popularity. A distributor of MDMA in Los Angeles was the first to describe MDMA as “Ecstasy” as a marketing ploy. The distributor, which was legal at the time, stated that the name empathy would have been more accurate, but he thought Ecstasy would sell better.²

MDMA usage began to increase significantly. Several manufacturers of MDMA began to pop up. In 1983, Texas had a group of chemists that made the distribution of MDMA widespread. MDMA was openly sold in bars and other nightspots. A toll free number was established that, with the use of a credit card for purchasing, MDMA would be shipped to the purchaser. Convenience stores began to
stock MDMA under the name "Sassyfras", which was thought to be an allusion to the drug's precursor MDA, which was of natural origin.²

The Drug Enforcement Agency (DEA) became aware of MDMA's widespread usage and began a campaign to illegalize the drug. In 1985, the petition to make MDA a schedule 1 drug, a drug of no medical value, was accepted and the substance was banned. The ban of MDMA was not successful in stopping the drug’s notoriety. The drug became popular in Europe and led to the development of a culture surrounding the drug. Use of MDMA a psychotherapeutic agent died, and MDMA was born as a drug related to partying and dancing. A ban of MDMA followed the substance around the world. Organized crime began to produce and distribute the drug which brings us to the current day.²

Epidemiology

Several studies have been conducted on the usage of MDMA in adolescents. The most impressive studies were conducted by the U.S. National Institute on Drug Abuse. Annually they conduct the study known as "Monitoring the Future", which measures the use of illegal drugs in school children. The study conducted in 2001 of 44,346 school children across 424 schools contained information on 8th, 10th, and 12th grade students. In this study, the usage of MDMA once in a subject’s lifetime was reported at 5.2%, 8%, and 11.7% respectively. Abuse of many substances have been declining, the use of MDMA actually increased from the study conducted in 1999 in which the percentages were 2.7%, 6%, and 8%. A similar trend was seen with college students. In 1991, the use of MDMA in the lifetime of college students (Age 19-22) and young adults (19-28) were 2% and 3.2% respectively. The study in 2001 showed a drastic increase in both college students and young adults with 14.7% and 13% respectively. In the United Kingdom, it is estimated that 500,000 young people ingest the drug every weekend. The United Kingdom reports approximately twelve deaths a year from MDMA use.¹
In the Monitoring the Future study that was released in 2011 they released graphs that showed the trend of MDMA use over the last fifteen years.

As you can see there was a spike in 2001 of usage of MDMA in the last twelve months. This is followed by a steep decline largely credited to educational programming. Educational programming focused on the risks associated with using MDMA. An incline can be seen in the risk associated with taking MDMA which began in approximately 2001. Since 2004, there has been a drop in the perceived risk which began with the 8th graders and then progressed through the other grades. The decrease in risk associated with MDMA use is thought to be a "generational forgetting" of the risks associated with MDMA use. After the decline in risk associated with MDMA use, an increase in use in the last twelve months was seen. A concern that another epidemic of MDMA was going to occur began, but levels started to plateau for several years. However, in the last year from 2010 to 2011, another increase in use was seen. The perceived risks of taking MDMA and MDMA usage seem to be tightly correlated.
Educational programming to inform the youth of the dangers of MDMA use should be encouraged and funded to prevent future increases in usage.

**Method of Action and Resulting Effects**

MDMA produces a euphoric like state by increasing the amounts of serotonin (5-HT) and dopamine inside the brain. This effect has been measured in rats, mice, and primates. MDMA will increase locomotor activity and a serotonin behavior syndrome in rats.¹

MDMA mechanism of action is the increase in the amount of 5-HT that is secreted into nerve terminals by direct and indirect mechanisms. MDMA produces the direct effects by binding to the sodium dependent serotonin transporters on the plasma membrane vesicles. This increases the amount of serotonin that is released from the plasma membrane vesicles. In membrane vesicles, MDMA inhibits ATP dependent accumulation of 5-HT and stimulates the release of previously accumulated 5-HT. This leads to a depletion of 5-HT stores.⁷ Acutely, recovery of 5-HT stores begins within a day; however, neurotoxic damage of the 5-HT nerve endings in the forebrain can last years in primates. Long-term loss of dopamine nerve endings has been observed in mice; however, this has not been duplicated in other research subjects. Tissue damage has been found in both rats and mice. The tissue damage is suspected to result from formation of free radicals.¹

The proposed mechanism of chronic 5-HT depletion is through oxidative stress. MDMA produces hydroxyl radicals which are thought to decrease the human body's ability to produce 5-HT. This is proposed to occur by the deactivation of tryptophan hydroxylase which is the rate limiting step in the conversion of L-tryptophan to serotonin. Treatment with anti-oxidants as well as free radical scavengers are known to be neuroprotective against MDMA depletion of 5-HT. Anti-oxidants that have shown to decrease the 5-HT depletion include ascorbic acid, lipoic acid, and cysteine. A known free radical scavenger that has proven to decrease 5-HT depletion is phenyl butyl nitrone. Not only does MDMA
produce free radicals but it has been observed as decreasing the anti-oxidant capacity of brain in the striatum and hippocampus. Although the administration of anti-oxidants and free radical scavengers has demonstrated to decrease the 5-HT depletion caused by MDMA, it is not the only theory on 5-HT depletion. Chronic serotonin depletion by MDMA has also been proposed to act by down regulation of production of 5-HT. It is not definitive as of now which is the actual cause of the depletion of 5-HT, but it may be a combination of factors. ⁸

Another major adverse effect produced by MDMA is the dose dependent hyperthermia reaction. In some patients with hyperthermia, MDMA has produced temperatures reaching 43° Celsius. This hyperthermic state has been replicated in in rodents, primates, and humans. Hyperthermia with temperatures this high can potentially lead to fatalities.¹ The administration of MDMA with monoamine oxidase inhibitors is more likely to lead to a hyperthermic reaction.⁹ A hyperthermic reaction can lead to rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation. Hyperthermic reactions are also observed in rats and are therefore mainly studied in rats. Ambient room temperature effects the hyperthermic reaction in rats. Rats in relatively cold rooms (11°C) can undergo a hypothermic reaction while rats in a relatively hot room (24°C) underwent hyperthermic reactions. The hot crowded rooms of clubs and raves are not safe environments for MDMA users, but that is where it is commonly abused. A study done on rats indicated that their primary way of regulating heat, the vasodilation of blood vessels in the tail, was impaired and that similar reaction was expected to be seen in humans. Other factors may play a role in the hyperthermic reaction. Rats that were given MDMA also demonstrated a higher metabolic rate, and a greater water loss from evaporation was documented. The release of neurotransmitters such as serotonin and dopamine are also expected to play a role.¹⁰

Treatment of the hyperthermic reaction associated with MDMA is still in development. Mirtazapine has been shown to decrease the hyperthermic response seen in rats on MDMA.
Mirtazapine can be used prophylactically or in treatment to decrease the temperature of rats. It is thought that mirtazapine’s 5-HT2A antagonism is suspected to be responsible for the attenuation of the hyperthermic reaction. The use of fluoxetine prophylactically in rats has also been studied. Fluoxetine proved effective only prophylactically and did not attenuate the hyperthermic reaction when given in treatment. Risperidone has also been shown to attenuate the hyperthermic reaction associated with MDMA in rats. Risperidone could be given before the administration of MDMA or after and attenuated the response in both circumstances. Risperidone like mirtazapine blocks the 5-HT2A receptor and is thought to be responsible for the attenuation of the hyperthermic reaction. Haloperidol blocks dopamine receptors D1 and D2 and attenuated the hyperthermic reaction when given prophylactically or in treatment of rats.

Recently evidence of hippocampal damage has been linked to MDMA. A study was conducted on ten chronic users of MDMA and they were compared with seven individuals who were known poly drug abusers. The chronic users of MDMA on average ingested 281 tablets over six and a half years. A control group of poly drug abusers was chosen to closely approximate the other substances abused by the chronic MDMA group. A volumetric MRI was taken of all subjects and then the hippocampus was manually outlined. The MDMA experimental group demonstrated on average a 10.5% reduction in the hippocampus volume compared to the control group. The reduction in hippocampus volume is important, because the hippocampus is linked to long term memory. When given cognitive tests, the MDMA users will keep up with their counterparts; however, many studies have indicated that MDMA users have memory impairments. This was an extremely small scale study but the evidence provided may be used to field larger studies.

Acutely, MDMA produces a variety of physiological adverse effects including: increased blood pressure, increase heart rate, nausea, chills, sweating, tremors, jaw clenching, bruxism, hyperreflexia,
urinary urgency, muscle aches or tension, hot and cold flashes, nystagmus, and insomnia. In addition to the physiological adverse effects, other damage can include subarachnoid hemorrhage, intracranial hemorrhage or cerebral infarction, and cerebral venous sinus thrombosis. Chronic physiological adverse effects of MDMA include development of temporomandibular joint (TMJ) syndrome, dental erosion (from bruxism), and myofacial pain. Hepatotoxicity is reported in chronic MDMA users, but it is expected to be a result of other drugs mixed with the MDMA.

Psychological effects of MDMA can include a wide range of positive and negative reactions. The positive reactions observed tend to be while under the peak of MDMA’s effects, while the negative psychological reactions tend to come while the drug is wearing off. The wearing off of the drug is commonly known as “coming down”. Positive reactions of MDMA include; elation, increased energy, happiness, exhilaration, warmth, friendliness, calmness, relaxation, confusion, heightened perception of sound, color, and touch. The negative effects while “coming down” include: lethargy, moodiness, irritability, insomnia, depression, and paranoia. Visual hallucinations and paranoia delusions have been reported in some studies to last days or weeks.¹

Conclusions

MDMA is a diversely studied but poorly understood drug. Research on MDMA faces many challenges in the current political climate. Current research methods are limited to animal test subjects which have not been fully replicated in humans. Other studies conducted on MDMA must be retroactive studies and controlling the exposure of the drug in these situations is often impossible. The current use of MDMA as a main ingredient in a cocktail of substances limits the credibility of retroactive research by adding confounding factors. Through the data collected it is extremely likely that the dosage and frequency of MDMA exposure directly relates to both the mood effects as well as the adverse effects. In the year 2000, over 100 scientific articles were published on the effects of MDMA. As the number of
abusers of MDMA rises, so too will the interest in the effects by the scientific community. The implications of this are yet to be seen; therefore, Pharmacists should try to keep up with the increasing amount of literature being generated, as it could save a patient's life.

Citations
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