3,4-methylenedioxymethamphetamine (MDMA): A Review

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This article reviews the history, pharmacology, and adverse events associated with the use of 3,4-methylenendioxymethamphetamine (MDMA), commonly known as Ecstasy. Past research describing the neurotoxic effects of MDMA in animals, current research on the neurotoxic effects of MDMA in humans, and the attendant changes in psychologic functioning will be highlighted in this review. Finally, the limitations of human research on the effects of MDMA and suggestions for future MDMA research will be discussed.

Introduction

3,4-methylenedioxymethamphetamine (MDMA) is a psychoactive compound that is structurally similar to amphetamine (a stimulant) and mescaline (a phenethylamine-type hallucinogen). MDMA is commonly known as *Ecstasy*, but is also called *Adam*, *XTC*, *hug*, *beans*, and *the love drug*. The Monitoring the Future (MTF) survey, funded by the National Institute on Drug Abuse and the National Institutes on Health, examined trends in illicit drug use in high school students nationwide. The 2000 MTF study surveyed over 45,000 students and reported increased Ecstasy use in eighth, 10th, and 12th graders when compared with Ecstasy use in previous years [1•]. In 2000, 8.3% of 12th graders reported Ecstasy use at least once in the past year, an increase from 5.6% in 1999 and 3.6% in 1998. Among eighth graders, Ecstasy use rose from 1.7% in 1999 to 3.1% in 2000.

The trend of MDMA use in increasing numbers of young people, coupled with concerns about the health effects of MDMA, have lead to studies investigating the pharmacology and the toxicity of this substance. In this article, the authors review the history and pharmacology of MDMA, as well as its potential physical and psychologic effects on humans. A discussion of the limitations of MDMA research in humans will also be presented.

Historical Perspectives

MDMA was first synthesized by the firm of Merck in 1912, and patented as an appetite suppressant in 1914 [2]. MDMA did not receive widespread use until the late 1970s and early 1980s, when a group of psychotherapists began using MDMA to treat patients [3,4]. Because of the reported ability of MDMA to enable its users to search within themselves to deal with difficult and not easily accessible emotional experiences, Nichols [5] proposed that MDMA be placed in a new class of substances, separate from stimulants and hallucinogens, called *entactogens*, a term meaning "producing or touching within."

Along with the reports of the therapeutic benefits of MDMA came information demonstrating its negative physiologic effects. In 1985, Ricaurte *et al.* [6] reported that high doses of the *N*-desmethyl parent compound of MDMA (MDA), caused degeneration of serotonin nerve terminals in rats. This demonstration of the neurotoxic effects of MDA in animal models led the US Drug Enforcement Agency (DEA) to list MDMA in its most restrictive category, schedule I [7].

Despite the legal limitations placed on MDMA, the use of this substance, sold as Ecstasy, flourished during the 1980s. All-night dance parties, fueled by rhythmic electronic music and the use of drugs such as Ecstasy, became popular in the Europe and the US [8–10]. These parties, called "raves," were often held in empty warehouses, basements, dilapidated schools, or open fields, and attracted thousands of young people every weekend [9–11]. By the late 1980s, the use and popularity of Ecstasy had grown so much that one study showed that 39% of a random, anonymous sample of 369 undergraduates enrolled at Stanford University had used Ecstasy at least once during their life [12]. More recently, Riley *et al.* [13•] reported that 82% of 122 subjects surveyed at three dance events in Edinburgh, Scotland had used Ecstasy in the previous year, with approximately one third of these individuals reporting weekly use.

Pharmacology

MDMA is often synthesized in illicit laboratories or home garages, and is most commonly ingested as a tablet or capsule, but has also been taken in a powder form that can be dissolved in water and injected, and as a suppository [14]. Ecstasy tablets contain an average 60 to 120 mg of

MDMA [15]. Once ingested, the effects of MDMA occur within 30 minutes and last approximately 5 hours [14].

MDMA is extensively metabolized in both animals and humans, and its metabolites are measurable in both blood and urine [16]. The detection of MDMA in human blood and urine has depended on the cross-reactivity of these metabolites with commercially available amphetamine and methamphetamine assays [17]. In general, MDMA cross-reacts poorly with these assays, leaving high-performance liquid chromotography (HPLC), gas chromotography-mass spectrometry (GCMS), and immunoassays as the main methods used to measure MDMA and its metabolites in body fluids. Using immunochemical strips as a potential means of rapid identification of MDMA in human sweat, Pacifici *et al.* [18•] were able to detect, in a controlled setting, MDMA and its metabolites in two Italian subjects between 2 and 12 hours after initial ingestion of MDMA. The authors suggested that this rapid means of MDMA detection has promise, but they also recognized that more studies on larger sample sizes are needed to evaluate the true efficacy of this test.

Once in the central nervous system (CNS) of both humans and animals, MDMA is thought to cause the release of serotonin (5-HT) stores from affected neurons [6,19–23]. MDMA is also believed to affect the dopamine (DA) systems in the animal brain, but to a lesser extent [21,24]. In animal models, MDMA is taken up into neurons by binding to 5-HT receptors, resulting in the release of 5-HT stores [25]. MDMA also blocks neuronal reuptake of 5-HT [26], and inhibits new synthesis of 5-HT by reducing tryptophan hydroxylase (TPH) activity in the animal brain [24,27,28].

Because 5-HT is involved in several physiologic functions, such as the regulation of mood, appetite, sleep, and body temperature [29], the effects of MDMA are associated with increased levels of CNS 5-HT. MDMA has been reported to cause increased positive emotions such as happiness, euphoria, exhilaration, friendliness, and warmth [30–33]. Additionally, MDMA users have reported heightened perception of sound, touch, and color, as well as enhanced communication, empathy, or understanding [30,32,33]. The reported physiologic effects of MDMA have included tachycardia, mydriasis, diaphoresis, dehydration, trismus, ataxia, and a subjective sense of increased body temperature [30,32,33]. During the post-MDMA period, users commonly report feelings of lethargy, irritability, depression, anxiety, and insomnia, which are likely to be caused by decreased 5-HT levels in the brain [30,33].

Adverse Medical Effects

Reports of deaths associated with overdoses of MDMA began appearing in the medical literature in the 1970s and 1980s [34–37]. Case reports of fatalities from MDMA cited physical complications including hyperpyrexia [38–40], rhabdomyolysis, disseminated intravascular coagulation, and renal failure [38,39,41]. MDMA is thought to alter thermoregulation by interfering with 5-HT pathways [39]; the resulted elevation in body temperature is exacerbated by the external heat generated by vigorous dancing and the elevated room temperatures at raves [10].

Case reports have also described nonfatal hepatitis [42,43], sometimes followed by tissue fibrosis [44], in otherwise healthy Ecstasy users. MDMA, or one of its metabolites, is most likely involved in hepatic cell damage [42–44]. Additionally, Ecstasy use has been associated with the development of subarachnoid hemorrhage [45], subcortical hemorrhage [46], aortic dissection [47], and sudden cardiac death [48]. Although the relationship between MDMA and these adverse events remains unclear, MDMA is known to cause hypertension that might lead to serious neurovascular and cardiovascular complications [45–48] particular when premorbid conditions are present [45,48].

Psychologic Effects

The psychologic effects of MDMA have been a focus of research because of the effects it may exert on CNS serotonergic neurons. Significant biochemical and neuroendocrine evidence suggests that abnormalities in 5-HT levels are correlated with depression and other mood disorders [29]. Reduced central serotonergic function has also been associated with self- and other-directed impulsive or aggressive behaviors in individuals with primary personality disorders, including schizotypal, paranoid, borderline, histrionic, and compulsive types [49]. Self-directed (*eg,* suicidal) behaviors have been associated with reduced 5-HT function in individuals with *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) diagnosed major affective disorders.

Depressed mood is a common symptom reported by individuals who use Ecstasy recreationally [12,30,33,50–56]. Negative mood states are often experienced in the days directly following use of Ecstasy—a period felt to be associated with 5-HT depletion [12,30,33,51,55]. In one study [55], Ecstasy users reported significantly more negative mood states, such as depression, sadness, unsociability, and unpleasantness for 2 days following a dance compared with a control group of non-MDMA users who reported other illicit drug use. Although moods were relatively stable in the control group during the week following the dance, those who used MDMA experienced fluctuations in mood states such as depression, sadness, calmness, pleasantness, and sociability [55].

In addition to depression, MDMA use has been associated with the development of psychotic symptoms [54,57–60,61•]. Recently, Vaiva [61•] described the case of one individual, with no previous history of psychopathology except moderate anxiety, who experienced an acute psychotic episode approximately 12 hours after unknowingly ingesting MDMA in an alcohol drink. The

psychotic symptoms he exhibited included severe violent behavior and delusions with supernatural and persecutory themes. Six months following MDMA use, the patient met criteria for mild major depressive disorder, and some psychotic symptoms were still present. Similar findings had been reported in a prior study in which 53% of a sample of 150 Ecstasy users reported one or more DSM-III-R psychiatric disorders; depression and psychotic disorders were reported most frequently [56].

Other studies have also examined the link between MDMA use and changes in behavior and personality. Parrott *et al.* [62••] used clinical symptom self-assessment scales to compare heavy MDMA users (MDMA use greater than 20 times, average use 371 times) with light MDMA users (MDMA use 20 times or less, average use 6.8 times) and to a non-MDMA using control group. Heavy MDMA users reported significantly increased levels of somatization, obsessional behavior, anxiety, phobic-anxiety, paranoid ideation, psychoticism, poor appetite, and disturbed sleep patterns compared with control individuals. Light MDMA users differed significantly from the control group only on the scales of paranoid ideation and psychoticism. A possible explanation for these results is that light MDMA users may have fewer psychiatric problems than heavy users. However, because the light users had intermediate scores on the majority of the self-assessment scales, it is more likely that increased paranoia and psychoticism are early signs of developing psychiatric problems that could occur with continued MDMA use. These findings support those of an earlier study [56] that found that MDMA users who had taken a larger cumulative median number of tablets, at an increased frequency, for a longer duration of time were at an increased risk for developing one or more psychopathologic disturbances.

MDMA use has also been associated with increased levels of anxiety and panic disorder [53–56,62••,63]. One study [54] described 13 cases in which psychotic symptoms and panic attacks began after short-term use of MDMA. With the exception of one individual who was adopted, 50% of the sample (six of 12) had a positive family history of psychiatric problems, including depression, personality disorder, schizophrenia, and drug and alcohol abuse. The presence of a family history of psychiatric disturbances in these subjects appeared to represent a significant risk factor for experiencing psychiatric problems from recreational MDMA use. McCann and Ricaurte [53] have also suggested that individuals with an existing history of psychiatric disturbances might be most at risk for negative behavioral consequences of MDMA use.

Certain personality characteristics appear to be more common in MDMA users compared with those who use substances other than MDMA and those who do not use substances at all. For example, higher levels of impulsivity have been associated with MDMA use [56,62••,65•]. In a study comparing a group of MDMA users with two control groups (one non-MDMA using group with similar drug and personal histories to the MDMA group, and one group with no history of illicit drug use), the MDMA group demonstrated significantly higher levels of impulsiveness on the Impulsiveness, Venturesomeness, and Empathy scale (IVE) compared with the control groups [65•]. However, the MDMA group and the control drug groups did not differ significantly on any of these measures. Similarly, Parrott *et al.* [62••] used the IVE to assess personality differences and found that heavy MDMA use (greater than 20 times with a mean use of 371 times) was associated with significantly higher impulsivity scores. No differences were found, however, on venturesomeness or empathy scales. One contradictory study, however, found that MDMA users had decreased impulsivity, decreased hostility scores, and increased harm avoidance [22]. These findings, however, like those regarding psychiatric disorders in MDMA users, do not suggest a causal relationship between MDMA use and mood disorders or personality changes. More research will be needed to further elucidate the changes in affect and personality associated with MDMA use in humans.

Neurotoxicity

Studies in animals

Concerns about the neurotoxicity of MDMA in the CNS began with the report of long-lasting reductions in 5-HT and degeneration of serotonin nerve terminals in rats that were repeatedly injected with MDA, an analogue of MDMA [6]. Subsequent studies examining the effects of MDMA on the rat brain replicated these results and introduced new findings. Long-term reductions in concentrations of 5-HT [19,66,67,24,28], reductions in the primary 5-HT metabolite, 5-hydroxyindole acetic acid (5-HIAA) [19,24,28], reductions in the activity of the rate-limiting enzyme in the synthesis of 5-HT, tryptophan hydroxylase (TPH) [24,28,67], and reductions in 5-HT reuptake into nerve terminals [19,26,67] have been reported in rats who were frequently injected with MDMA. Degeneration of 5-HT nerve terminals in the cerebral cortex of the rat after treatment with MDMA has also been reported [19,20,66]. These findings are difficult to apply to humans however, because the animals did not ingest MDMA as humans would, and the doses of MDMA used in the rodent studies were higher than humans would consume [4].

Studies of the effect of MDMA on nonhuman primates have sought to assess its potential neurotoxicity in a species more closely related to human beings. Ricaurte *et al.* [68] found reductions in 5-HT and 5-HIAA as well as 5-HT nerve terminal damage in the cerebral cortex of monkeys who received repeated subcutaneous injections of high-dose MDMA over a 4-day period when compared with control nonhuman primates. These findings are similar to the neurologic changes seen in rodents [19,20,66]. The long-term effects of MDMA on nonhuman primates were demonstrated by lasting changes in

serotonin nerve terminals measured by only partial recovery of 5-HT and 5-HIAA at periods ranging from 14 to 18 weeks post-treatment [69,70]. Finally, monkeys treated with repeated oral doses of MDMA [21] or a single dose of MDMA approximating the amount that would be taken by humans [68] also had reduced levels of presynaptic markers of 5-HT function in various brain regions several weeks after initial treatment.

Studies in humans

The initial studies of the neurotoxic effects of MDMA used indirect means, such as measuring cerebrospinal fluid (CSF) concentrations of 5-HIAA, to demonstrate changes in CNS 5-HT function [22,71,72]. Although one study [71] did not find changes in CSF concentrations of 5-HIAA in a small sample of regular Ecstasy users, two studies [22,72] using larger sample sizes of frequent, long-term Ecstasy users demonstrated lower levels of CSF 5-HIAA when study subjects were compared with control individuals not using Ecstasy. Other studies of neuroendocrine function measured 5-HT by assessing prolactin response to an intravenous challenge of *L*-tryptophan [22,73] and serum prolactin and cortisol response to an intravenous dexfenfluramine challenge [74]. Blunted responses of prolactin and cortisol were reported in two studies [73,74], respectively, but no significant change in prolactin response was seen in another study [22].

The use of neuroimaging studies such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) to evaluate structural and functional changes in neurons exposed to MDMA has been a helpful complement to neuroendocrine studies. Coupled with a powerful serotonin transporter ligand, SPECT showed decreased binding to cortical 5-HT transporters in long-term Ecstasy users compared with control subjects who used substances other than Ecstasy [75•]. Glucose metabolism, a marker of neuronal activity, measured by PET and 2-[18F]-fluoro-2-deoxy-d-glucose, was decreased in the hippocampus, amygdala, and cingulate of Ecstasy users 2 to 16 months following the last use of MDMA [76••]. A similar PET study demonstrated changes in serotonin transporters in the brains of Ecstasy users who had not used Ecstasy for at least 3 weeks [23]. Those subjects who had used Ecstasy more frequently showed greater decreases in serotonin transporters.

Finally, long-term Ecstasy use has been correlated with reductions in glucose metabolism in specific human brain regions measured by PET scanning [••77]. Ninety-three Ecstasy users who ingested, on average, 483 Ecstasy tablets for 19.5 years (last ingestion approximately 6.5 months prior to the study) were compared with a control group of 27 oncology patients who did not use substances. Uptake of 2-[18F]-fluoro-2-deoxy-d-glucose was reduced in the striatum, cingulate, amygdala, cortex, and hippocampus bilaterally in Ecstasy users compared with the control individuals, findings similar to those previously reported by Obrocki *et al*. [76••]. Those subjects who first used Ecstasy before age 18 had greater reductions in 2-[18F]-fluoro-2-deoxy-d-glucose uptake than did those who initiated Ecstasy use later in life.

Methodologic problems in studies of MDMA as a human neurotoxin

Curran [78] examined methodologic and ethical issues in studies of the neurotoxic effects of MDMA in humans. One significant problem is the lack of certainty regarding what is contained in tablets sold as *Ecstasy*, and what the effects of varying amounts of MDMA and other compounds may have on the human brain. Because Ecstasy production is not under quality control, tablets sold as *Ecstasy* may contain varying (if any) amounts of MDMA, with or without adulterants [79•,80•].

Additional limitations in these studies include reports of other substance use in both study subjects and control individuals, reliance on self-report of MDMA and other substance use in recruited subjects, baseline sociodemographic differences in MDMA users and control individuals, and selection of patients from psychiatric and substance abuse treatment centers.

Conclusions

The growing popularity of Ecstasy as a recreational drug has led to increasing concerns about the effect of MDMA on the human brain. Studies in rodents and nonhuman primates treated typically with high-dose MDMA have demonstrated short- and long-term CNS neuronal damage with attendant reductions in the serotonin. Human studies of Ecstasy users have demonstrated structural and functional changes in serotonergic neurons and associated changes in human behavior. Many confounding factors in human studies, however, lead to questions about the true causes of neurotoxicity seen in subjects who consume Ecstasy and other substances. Controlled clinical trials would elucidate these confounders but legal, ethical, and clinical complications could prevent or limit human studies of MDMA. The best course of future study of MDMA might be a focus on rapid detection of the substance, community education regarding the dangers of MDMA to prevent initial Ecstasy use, and specific treatments for MDMA abuse and associated problems.

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This case study presented one individual who experienced an acute episode of psychosis characterized by delusions and violent behavior 12 hours after ingesting MDMA. Although he had no previously known psychiatric history, he met criteria for mild major depression with some psychotic symptoms 6 months after taking MDMA.

62.•• Parrott A, Sisk E, Turner J: **Psychobiological problems in heavy 'Ecstasy' (MDMA) polydrug users.** *Drug Alcohol Depend* 2000, **60:**105-110.

In this study using clinical symptoms self-assessment scales to compare a group of heavy MDMA users with a non-MDMA using control group, heavy users had significantly greater levels of anxiety, paranoid ideation, anorexia, somatization, obsessionality, psychoticism, and disturbed sleep patterns than did controls. Light MDMA users had intermediate symptom on the majority of self-assessment scores when compared with controls except on measures of paranoid ideation and psychoticism. The authors suggest those early indicators (psychoticism and paranoia) of developing psychiatric disorders present in light users may continue with continued MDMA use.

63. Pallanti S, Mazzi D: **MDMA (Ecstasy) precipitation of panic disorder.** *Biol Psychiatry* 1992, **32:**91–95.
64. Whitaker-Azmitia P, Aronson T: **Ecstasy (MDMA)-induced panic.** *Am J Psychiatry* 1989, **146:**119.
65.• Morgan M: **Recreational use of Ecstasy (MDMA) is associated with elevated impulsivity.** *Neuropsychopharmacology* 1998, **19:**252–264.

A group of 16 MDMA users was compared with 1) a group of 12 non-MDMA users with substance use and personal histories comparable to the MDMA users, and 2) a group of 16 non-substance-using controls. Using the Impulsiveness, Venturesomeness, and Empathy Scale (IVE), a significant difference between the MDMA group and the other groups was seen on measures of impulsiveness but no significant differences were reported on other scale measures.

66. Commins D, Vosmer G, Virus R, *et al.*: **Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain.** *J Pharmacol Exp Ther* 1987, **241:**338–345.
67. Schmidt C: **Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine.** *J Pharmacol Exp Ther* 1987, **240:**1–7.
68. Ricaurte G, Forno L, Wilson M, *et al.*: **(+/-) 3,4-methylenedioxymethamphetmine selectively damages central serotonergic neurons in nonhuman primates.** *JAMA* 1988, **260:**51–55.
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73. Price L, Ricaurte G, Krystal J, Heninger G: **Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methylenedioxymethamphetamine (MDMA) users.** *Arch Gen Psychiatry* 1989, **46:**20–22.
74. Verkes R, Gijsman H, Pieters M, *et al.*: **Cognitive performance and serotonergic function in users of Ecstasy.** *Psychopharmacology* 2001, **153:**196–202.
75.• Semple D, Ebmeier K, Glabus M, *et al.*: **Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA (Ecstasy) users.** *Br J Psychiatry* 1999, **175:**63–69.

In this study, 10 long-term Ecstasy users and 10 non-Ecstasy using but substance using controls were administered a serotonin transporter ligand before undergoing neuroimaging with single photon emission computed tomography (SPECT). Diminished binding to cortical serotonin transporters was found in long-term Ecstasy users compared with controls that used substances other than Ecstasy.

76.•• Obrocki J, Buchert R, Vaterlein O, *et al.*: **Ecstasy-long-term effects on the human central nervous system revealed by positron emission tomography.** *Br J Psychiatry* 1999, **175:**186–188.

This neuroimaging study used positron emission tomography (PET) and 2-[18F]-fluoro-2-deoxy-d-glucose to examine glucose metabolism, an indicator of neuronal activity, in seven Ecstasy users who had not used the substance for 2 to 16 months and seven non-substance using controls. Decreased glucose metabolism in the neurons of the hippocampus, amygdala, and cingulate was seen in the abstinent Ecstasy users compared with the non-substance using controls.

77.•• Buchert R, Obrocki J, Thomasius R, *et al.*: **Long-term effects of Ecstasy abuse on the human brain studied by FDG PET.** *Nucl Med Commun* 2001, **22:**889–897.

In this study using PET, 93 Ecstasy users who had taken approximately 483 Ecstasy tablets for approximately 20 years (last use 6.5 months prior to the study) demonstrated decreased FDG uptake in the striatum, cingulate, amygdala, cortex, and hippocampus, bilaterally when compared with 27 non-substance using controls. Greater reductions in 2-[18F]-fluoro-2-deoxy-d-glucose uptake were seen in those began using Ecstasy before the age of 18.

78. Curren H: **Is MDMA neurotoxic in humans? An overview of evidence and of methodological problems in research.** *Neuropsychobiology* 2000, **42:**34-41.

79.• Baggott M, Heifets B, Jones R, *et al.*: **Chemical analysis of Ecstasy pills.** *JAMA* 2000, **284:**2190.

In this study 107 Ecstasy tablets were examined for their content by GCMS. MDMA or its analogues, MDEA and MDA, were found in 67 tablets although 31 tablets contained no MDMA, but other identifiable substances including dextromethorphan, caffeine, ephedrine, pseudoephedrine, and salicylates. Nine tablets contained no identifiable drug at all.

80.• Sherlock K, Wolff K, Hay A, Conner M: **Analysis of illicit Ecstasy tablets: implications for clinical management in the accident and emergency departments.** *J Accid Emerg Med* 1999, **16:**194-197.

Twenty-five Ecstasy tablets were analyzed for content by gas chromatography. Of the 25 tablets, 12 tablets contained MDMA, four tablets contained MDEA, and the other 9 contained no MDMA, but instead contained varying amounts of caffeine, amphetamine, ephedrine, ketamine, and paracetamol.