National Institute on Drug Abuse
Advancing Addiction Science

Research Report
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MDMA (Ecstasy) Abuse Research Report

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MDMA (Ecstasy) Abuse Research Report

Describes the science behind MDMA (ecstasy) abuse, including what it does to the brain, whether it is addictive, and the latest research regarding prevention and treatment of MDMA.

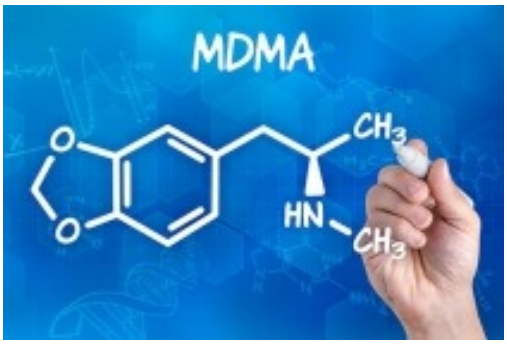
Introduction

3,4-methylenedioxymethamphetamine (MDMA), also known as Molly, Ecstasy, or X, continues to be used by millions of Americans across the country. This illegal drug is often taken for the feelings of well-being, stimulation, and distortions in time and sensory perceptions that it produces.[1,2] MDMA first became popular in the all-night party scene (e.g., “raves”),[3] but its use has now spread to a wide range of settings. According to the National Survey on Drug Use and Health, more than 18 million people in the United States have tried MDMA at least once in their lifetime.[4]

MDMA is a synthetic drug that became popular in the 1980s,[5] leading researchers to begin investigating its effects. Their efforts identified a number of potentially serious negative side effects. For example, MDMA can cause a dangerous increase in body temperature that can be fatal in some environments.[6]

MDMA can also stress the heart, increasing heart rate[7] and blood pressure,[8] and can damage the kidneys.[9] Animal studies show that MDMA may also damage specific neurons in the brain,[10–12] but research on MDMA’s effects on the human brain is not conclusive at this time.[13] However, a number of studies show that long-term, heavy MDMA use is associated with cognitive deficits, including problems with learning and memory.[14]

What is MDMA?



3,4-methylenedioxymethamphetamine (MDMA) is a derivative of amphetamine and a member of the phenethylamine family of chemicals that may act as stimulants, hallucinogens, and/or entactogens.

MDMA is a synthetic drug that acts as a stimulant and hallucinogen.[15–17] It produces an energizing effect, distortions in time and perception, and enhanced enjoyment from sensory experiences. It has also been described as an entactogen—a drug that can increase self-awareness and empathy.[1,2,18]

Ecstasy is often used to refer to MDMA in the tablet or capsule form, which is the most common way people take the drug.[17,19] Researchers have determined that many ecstasy tablets contain not only MDMA at different concentrations, but also a number of other drugs or drug combinations that can be harmful. Adulterants found in ecstasy tablets purchased on the street have included methamphetamine, the anesthetic ketamine, caffeine, the diet drug ephedrine,[20] the over-the-counter cough suppressant dextromethorphan,[21,22] heroin, phencyclidine (PCP), and cocaine.[22]

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Some people mistakenly believe that using Molly can avoid contaminants often found in ecstasy, not realizing that drugs sold as Molly may not be MDMA.

Molly—slang for “molecular”—refers to the crystalline powder form of MDMA, usually sold as powder or in capsules. Some people mistakenly believe that Molly does not contain contaminants often found in ecstasy. In fact, chemical analyses of drugs sold as Molly and seized by the U.S. Drug Enforcement Administration (DEA) have shown that they often contain other types of drugs and may not contain any MDMA.[23] For example, epidemiologists from Washington state and Florida reported in 2013 that substances being sold as Molly were actually methylone, a synthetic stimulant commonly found in “bath salts.”[24] In 2015, ethylone, a synthetic stimulant similar to methylone but with some differences in binding within the brain,[25] replaced methylone as the main substance marketed as Molly.[26] This underscores that people who take Molly often do not know what they are ingesting, and the substances sold as Molly may pose serious health risks.

When MDMA is taken in tablet or capsule form, a person begins feeling the effects 45 minutes later, on average. These effects peak 15 to 30 minutes after they are first felt and last an average of 3 hours,[27] though side effects could be experienced up to days later.[17,28] People typically take one to two tablets on each occasion,[17,29,30] with each tablet generally containing between 50 and 150 milligrams of MDMA.[31] People often take a second dose of the drug as the effects of the first dose begin to fade,[32] increasing the risk of adverse side effects as doses combine.

MDMA seized in the United States is primarily synthesized in Canada and, to a lesser extent, the Netherlands. There are a small number of illegal MDMA labs operating in the United States.[19]

What is the history of MDMA?

MDMA was developed by a German pharmaceutical company in 1912. Originally known as "Methylsafrylaminc," it was intended as a parent compound to synthesize medications that control bleeding, not to control appetite as is often incorrectly cited.[33,34]

MDMA gained a small following among psychiatrists in the late 1970s and early 1980s, despite the fact that the drug had not undergone formal clinical trials nor received approval from the U.S. Food and Drug Administration (FDA) for use in humans. Some psychiatrists believed that it enhanced communication in patient sessions and allowed patients to achieve insights about their problems.[35] It was also during this time that MDMA started becoming more widely available on the street.[5,36]

In 1985, the DEA declared an emergency ban on MDMA, placing it on the list of Schedule I drugs, defined as substances with no currently accepted medical use and a high potential for abuse. MDMA has remained a Schedule I substance since then, with the exception of a brief period of time between 1987 and 1988.[37,38]

Does MDMA Have Therapeutic Value?

The evidence on MDMA's therapeutic effects is limited thus far,[39] although research is ongoing in this area. Proponents of MDMA-assisted therapy recommend that it only be used for reactive disorders such as post-traumatic stress disorder because it can worsen some psychiatric conditions.[40]

In the early 1990s, the FDA approved the first human trial exploring whether MDMA could help relieve pain in terminally ill patients, as well as serve as an adjunct to psychotherapy.[41] Results from this study have not been published; however, these early studies helped establish safety parameters for administering MDMA to human participants in controlled, clinical settings.[42] Clinical trials are ongoing

to explore whether MDMA has therapeutic potential in the treatment of post-traumatic stress disorder and anxiety in autistic adults and patients with a terminal illness such as cancer.

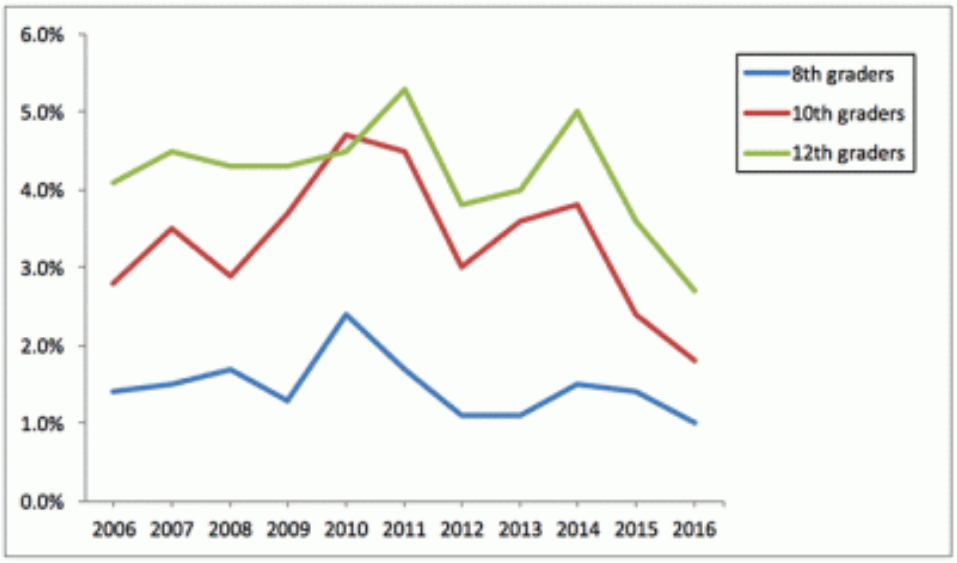
What is the scope of MDMA use in the United States?

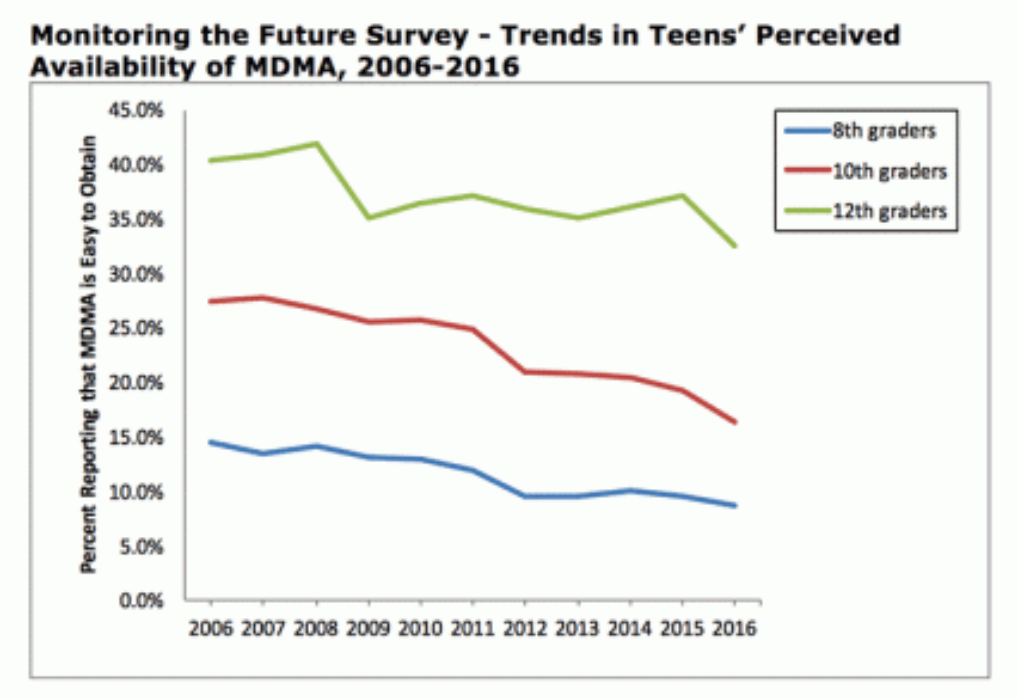
> In 2015, changes were made to the NSDUH questionnaire and data collection procedures for hallucinogens and other substances that do not allow comparisons of 2015 and 2016 with previous years for a number of outcomes.

The National Survey on Drug Use and Health, found that in 2014 more than 17 million persons aged 12 or older reported using MDMA at least once in their lifetimes.[43] This is an increase from 11 million reported 10 years prior.[44] In 2014, the number of people who used in the past month was estimated to be 660,000,[43] up from 450,000 in 2004.[44]

In 2016, NIDA's annual survey on teen drug use, the Monitoring the Future (MTF) Survey, found that past-year MDMA use was reported by 2.7 percent of 12th graders, 1.8 percent of 10th graders, and 1 percent of 8th graders. A downward trend in perceived availability indicates that teens across all grade levels believe that MDMA is harder to obtain than it was a decade ago.[45] According to an analysis of MTF data from 2007 to 2012, use was higher among males as well as specific groups of teens, including those living in the city, with a weekly income, or with lifetime use of other substances.[46]

Monitoring the Future Survey - Trends in Past-Year Use of MDMA in Teens, 2006-2016





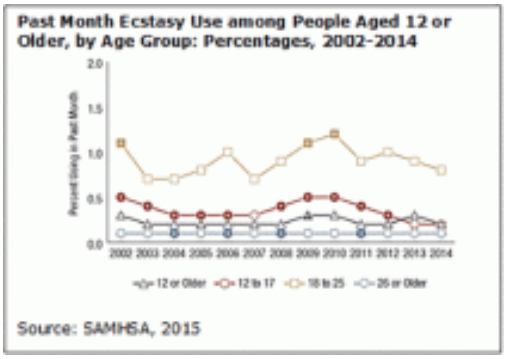
Note: These data are from the 2016 Monitoring the Future survey, funded by the National Institute on Drug Abuse, and conducted annually by the University of Michigan's Institute for Social Research. "Annual" refers to use at least once during the year preceding the survey.

The Drug Abuse Warning Network, maintained until 2011 by the Substance Abuse and Mental Health Services Administration (SAMHSA), reported that mentions of MDMA in drug-related hospital emergency departments visits were 22,498 for 2011, equating to approximately 1.8 percent of all drug-related emergency department visits. The majority of patients who came to emergency departments with recent MDMA use as a factor in their admissions during that time were aged 18 to 20.[47] In addition, of those seeking treatment for a substance use disorder in 2015, 3,510 people reported MDMA as a factor.[48]

Who is using MDMA?

MDMA first gained popularity among adolescents and young adults in the nightclub scene and at dance parties known as raves.[3] However, the profile of the typical person who uses MDMA has been

changing. Beginning in 1999, community-level data from NIDA's Community Epidemiology Work Group began to report that use of MDMA had spread among populations outside the nightclub scene.[49]



MDMA is predominantly used by males between the ages of 18 and 25.[43,50] Most use typically begins at 21 years of age.[51]

NIDA-funded research shows that sexual orientation also influences MDMA usage rates. For example, gay or bisexual men and women are more likely than their heterosexual counterparts to have used MDMA within the last 30 days and to report harm associated with MDMA use.[52]

What are the effects of MDMA?

Acute Effects

A person may experience the intoxicating effects of MDMA within 45 minutes or so after taking a single dose. Those effects include an enhanced sense of well-being,[28,53] increased extroversion,[27,53] emotional warmth, empathy toward others,[54] and a willingness to discuss emotionally-charged memories.[55] In addition, people report enhanced sensory perception as a hallmark of the MDMA experience.[27,28]

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Use of even moderate doses of MDMA in crowded, warm environments—or during periods of vigorous, extended physical activity—can dramatically increase body temperature, with potential deadly consequences.

However, MDMA can also cause a number of acute adverse health effects. For example, while fatal overdoses on MDMA are rare, they can potentially be life threatening—with symptoms including high blood pressure (hypertension), faintness,[8,56] panic attacks,[57] and in severe cases, a loss of consciousness and seizures.[58]

Because of its stimulant properties and the situations in which it is often taken, MDMA is associated with vigorous physical activity for extended periods in warm environments. This can lead to one of the most significant, although rare, acute adverse effects—a marked rise in body temperature (hyperthermia).[59–61] Research in rats shows that even moderate doses of MDMA interfere with the body's ability to regulate temperature, potentially leading to deadly consequences in warm environments.[6] Treatment of hyperthermia requires prompt medical attention, as it can rapidly lead to muscle breakdown or an electrolyte (sodium) imbalance, which can in turn produce kidney failure[9] or fatal swelling of the brain, especially in women.[62] MDMA use in combination with vigorous exercise causes dehydration,[56,57] leading some people to drink large amounts of liquids. However, this could increase the risk of electrolyte imbalance or brain swelling because MDMA causes the body to retain water.[63,64] One modest dose of MDMA can also reduce the pumping efficiency of the heart in people who use regularly,[65] which is of particular concern during periods of increased physical activity.

MDMA can also produce other adverse health effects, including involuntary jaw clenching,[53] lack of appetite,[28,53] mild detachment from oneself (depersonalization), illogical or disorganized thoughts, restless legs,[28] nausea,[56,57,66] hot flashes or chills,[8,56] headache, sweating,[8,57] and muscle or joint stiffness.[66]

In the hours after taking the drug, MDMA produces significant reductions in perceiving and predicting motion—for example, the ability to judge whether a driver is in danger of colliding with another car. This emphasizes the potential dangers of performing complex or skilled activities, such as driving a car, while under the influence of this drug.[67]

Once MDMA is metabolized, or broken down in the body, its byproducts interfere with the body's ability to metabolize MDMA.[68] As a result, additional doses of MDMA can produce unexpectedly high blood levels, which could worsen the toxic effects of this drug.[69] In addition, combining MDMA with other substances, such as caffeine,[70] amphetamines,[71] the amphetamine-like mephedrone,[72] marijuana,[73] or alcohol,[74,75] may increase the risk of adverse health effects associated with MDMA.[29]

Sub-acute Effects

Recreational use of MDMA is often characterized by repeated drug taking over a number of days (binges), followed by periods of no drug taking. In one animal study, this pattern of use produced irregular heartbeat (arrhythmia) and heart damage.[76] In the week following use of the drug, many people report depression, impaired attention and memory,[77–79] anxiety, aggression,[80] and irritability.[78]

Effects of Regular MDMA Use

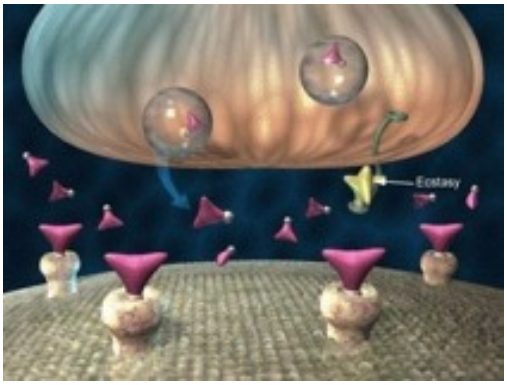
Sleep disturbances, lack of appetite, concentration difficulties, depression,[79] heart disease,[81,82] and impulsivity[83] have been associated with regular use of MDMA. In addition, heavy MDMA use over a 2-year period of time is associated with decreased cognitive function.[84] Some of these disturbances may not be directly attributable to MDMA, but may be related to some of the other drugs often used in combination with MDMA, such as cocaine, alcohol, or marijuana, or to adulterants commonly found in MDMA tablets. More research is needed to understand the specific effects of regular MDMA use.

Risk-taking in People who Use MDMA

Various studies have found that MDMA use is associated with risky sexual behaviors. For example, both males and females who use MDMA are more likely than alcohol-drinking controls to engage in risky sexual behaviors (e.g., without a condom).[85] MDMA use within the past 6 months is associated with initiating sex before age 14 and having two or more partners in the past 2 months.[86] In addition, people who use heavily report more sexual risk taking than those who use less often. People who use heavily are also more likely to have been tested for HIV, though they believe they are at low risk for contracting the disease.[87]

Homosexuals and bisexuals who use MDMA, both male and female, reported more sexual partners and more injection drug use—but did not have higher rates of unprotected sex and needle sharing—compared to heterosexuals who use MDMA.[88]

What are MDMA's effects on the brain?

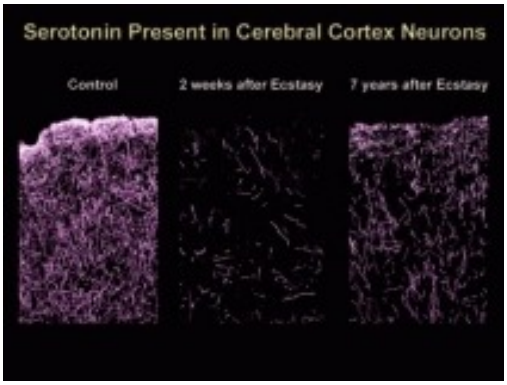


MDMA's Effects on Serotonin, Dopamine and Norepinephrine. MDMA increases levels of these neurotransmitters within the synapse by enhancing their release from nerve endings and/or inhibiting their reuptake.

MDMA affects the brain by increasing the activity of at least three neurotransmitters (the chemical messengers of brain cells): serotonin,[89,90] dopamine, and norepinephrine.[91] Like other amphetamines, MDMA enhances release of these neurotransmitters[89–92] and/or blocks their reuptake,[93,94] resulting in increased neurotransmitter levels within the synaptic cleft (the space between the neurons at a synapse).

MDMA causes greater release of serotonin and norepinephrine than of dopamine.[91] Serotonin is a neurotransmitter that plays an important role in the regulation of mood, sleep, pain, appetite, and other behaviors. The excess release of serotonin by MDMA likely causes the mood-elevating effects people experience.

However, by releasing large amounts of serotonin, MDMA causes the brain to become significantly depleted of this important neurotransmitter, contributing to the negative psychological aftereffects that people may experience for several days after taking MDMA.[95,96]



Source: Hatzidimitriou G, et al. J Neurosci Off J Soc Neurosci. 1999

Reduced Serotonin in Cerebral Cortex Neurons Following Long-term MDMA Exposure
The left panel is brain tissue from a normal monkey. The middle and right panels illustrate the loss of serotonin-containing nerve endings following MDMA exposure.

Research in rodents and primates has shown that moderate to high doses of MDMA, given twice daily for four days, damages nerve cells that contain serotonin.[10,12] MDMA-exposed primates showed reduced numbers of serotonergic neurons 7 years later, indicating that some of MDMA's effect on the brain can be long lasting.[11] MDMA has additional effects on the serotonin system. For example, 1 to 2 weeks following binge-dosing with MDMA (three or four low doses in one day), rats showed decreased expression of the serotonin transporter,[13,97] a protein that allows cells to take up and recycle released serotonin. The rats also showed changes in the expression of genes that regulate tryptophan hydroxylase, an enzyme involved in serotonin synthesis.

Low serotonin is associated with poor memory and depressed mood,[98] thus these findings are consistent with studies in humans that have shown that some people who use MDMA regularly experience confusion,[30] depression,[30,99] anxiety, paranoia,[30,100] and impairment of memory[83,101,102] and attention processes.[79] In addition, studies have found that the extent of MDMA use in humans correlates with a decrease in serotonin metabolites and other markers of serotonin function and the degree of memory impairment.[95,101] In addition, MDMA's effects on norepinephrine contribute to the cognitive impairment,[94] emotional excitation, and euphoria that accompanies MDMA use.[7]

Positron emission tomography (PET) brain imaging studies of people who have stopped using MDMA have shown decreases in brain activity at rest in prefrontal, parietal, and mediotemporal cortices as well as in the amygdala, cingulate, and hippocampus. These are brain regions involved in learning, memory, and emotion formation and processing.[103,104] PET imaging also showed that one low dose of MDMA increased cerebral blood in the ventromedial frontal and occipital cortex and inferior temporal lobe and cerebellum. It decreased cerebral blood flow in the motor and somatosensory cortex, amygdala, cingulate cortex, insula, and thalamus. These are brain regions involved in emotion formation and processing, behavioral learning, and sensory and motor function.[53] Few imaging studies have explored the effects of moderate MDMA use on the human brain, and results that do exist are inconsistent due to methodological differences across studies.[105] More studies are needed to determine whether the observed changes in brain activity in people who use MDMA are caused by MDMA, other drug use, or other common risk factors that predispose people to use MDMA.

Additionally, most studies in people do not have behavioral measures from before MDMA use started, making it difficult to rule out pre-existing differences or common underlying risk factors across groups that are separate from MDMA use.[83,106,107] Factors such as gender, dosage, frequency and intensity

of use, age at which use began, and the use of other drugs, as well as genetic and environmental factors all may play a role in some of the cognitive deficits associated with MDMA use and should be taken into consideration when studying the effects of MDMA in humans.

Effects of MDMA

Potential Acute Adverse Health Effects:

- Marked rise in body temperature (hyperthermia)
- Dehydration
- Electrolyte (sodium) imbalance
- High blood pressure (hypertension)
- Involuntary jaw clenching and teeth grinding
- Muscle or joint stiffness
- Lack of appetite
- Illogical or disorganized thoughts
- Restless legs
- Nausea
- Hot flashes or chills
- Headache
- Sweating
- Faintness
- Panic attacks
- Loss of consciousness
- Seizures
- Kidney failure
- Swelling of the brain

Potential Longer Term Health Effects (including those observed days or weeks post-MDMA use):

- Arrythmia (irregular heart beat) and heart damage
- Irritability
- Depression
- Impulsivity
- Impaired attention and memory
- Anxiety
- Aggression
- Sleep disturbances
- Concentration difficulties
- Lack of appetite
- Heart disease
- Decreased cognitive function

Can MDMA use during pregnancy harm the baby?

Given that most people who use MDMA are young and in their reproductive years,[50] some females may use MDMA when pregnant. Research suggests that MDMA may have adverse effects on the developing fetus. One study in humans showed that prenatal MDMA exposure was associated with motor delays in the offspring up to 2 years after birth. More research is needed to determine if these delays persist later in life.[108] Behavioral studies in animals have found significant adverse effects on tests of learning and memory following exposure to MDMA during a developmental period equivalent to the latter portion of the third trimester in humans.[109] These changes are paralleled by long-lasting changes in brain regions underlying learning and memory.[110] There is less research into the effects of MDMA on animals earlier in development—that is, during the period equivalent to the first trimester in humans.[109,111] One study showed that MDMA exposure during this developmental period produces

increased motor activity and changes in serotonin and dopamine function in rodents.[112] In addition, rats prenatally exposed to MDMA and alcohol showed decreased exploratory activity, impaired working memory, and impaired neuronal development into adulthood, although the contribution of MDMA alone was not determined.[113]

Is MDMA Addictive?

Research hasn't definitively answered whether MDMA is addictive, although it affects many of the same neurotransmitter systems in the brain that are targeted by other addictive drugs. Experiments have shown that animals will self-administer MDMA—an important indicator of a drug's addictive potential—although the degree of self-administration is less than some other addictive drugs, such as cocaine.[114,115]

Data from both humans and animals suggest that regular MDMA use produces adaptations in the serotonin and dopamine systems that are associated with substance use disorder and related behaviors, such as increased impulsivity.[116] Few studies have attempted to assess MDMA addiction or dependency among people with a history of use in the general population. Studies that have been conducted have shown widely varying results, likely because of the different population samples and different types of measures used. Some people who use MDMA do report symptoms of addiction, including continued use despite negative physical or psychological consequences, tolerance, withdrawal,[117,118] and craving.[119]

How can MDMA use be prevented?

Providing accurate scientific information regarding the effects of MDMA is important for reducing the negative health effects associated with use of this drug. Young adults who use MDMA report that friends, substance use disorder treatment programs, and physicians are their most trusted sources of information about MDMA. Many also report that the internet is an important source of information, suggesting that prevention websites should be designed to be responsive to the needs of this population.[120] In addition, the use of peer-led advocacy and drug prevention programs may be a

promising approach to reduce MDMA use among adolescents and young adults.

New technologies could also help in delivering messages to high school and college students about the effects of MDMA use. For example, one study showed that an online school-based prevention program reduced students' intentions to use MDMA and other drugs.[121]

More information on preventing drug use among children and teens can be found in NIDA's *Preventing Drug Use among Children and Adolescents (In Brief)*.

How are MDMA use disorders treated?

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Cognitive Behavioral Therapy helps patients recognize, avoid, and cope with the situations in which they are most likely to abuse drugs.

The most effective current treatments for patients with an MDMA use disorder are cognitive behavioral interventions that are designed to help modify the patient's thinking, expectancies, and behaviors, and to increase skills in coping with life's stressors. Recovery support groups may be effective in combination with behavioral interventions to support long-term recovery.

Although there are currently a number of medication targets that show promise in animal models[122–124] and in some eary clinical trials,[125,126] there are currently no FDA-approved medications to treat MDMA use disorder.

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