NATIONAL INSTITUTE ON DRUG ABUSE

Research Report SERIES

MDMA (Ecstasy) *Abuse*

from the director

The so-called "club drug" MDMA continues to be used by millions of Americans across the country, despite evidence of its potential harmful effects. 3,4-methylenedioxymethamphetamine (MDMA, or ecstasy) has gained a deceptive reputation as a "safe" drug among its users. This illegal drug, which has both stimulant and psychedelic properties, is often taken for the feelings of well-being, stimulation, and the distortions in time and sensory perceptions that it produces. MDMA first became popular in the "rave" and all-night party scene, but its use has now spread to a wide range of settings and demographic subgroups. According to the 2004 National Survey on Drug Use and Health, more than 11 million people have tried MDMA at least once.

Myths abound about both the acute effects and long-term consequences of this drug, often called ecstasy or "X." Indeed, one reason for the rapid rise in the drug's popularity is that many young people believe that MDMA is a new safe drug. But MDMA is not new to the scientific community, as many laboratories began investigating this drug in the 1980s, and the picture emerging from their efforts is of a drug that is far from benign. For example, MDMA can cause a dangerous increase in body temperature that can lead to kidney failure. MDMA can also increase heart rate, blood pressure, and heart wall stress. Animal studies show that MDMA can damage specific neurons in the brain. In humans, the research is not conclusive at this time; however, a number of studies show that long-term, heavy MDMA users suffer cognitive deficits, including problems with memory.

NIDA-supported research is developing a clearer picture of the potential dangers of MDMA, and this Research Report *summarizes the latest findings. We hope that this compilation of scientific information will inform readers and help the public recognize the risks of MDMA use.*

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse

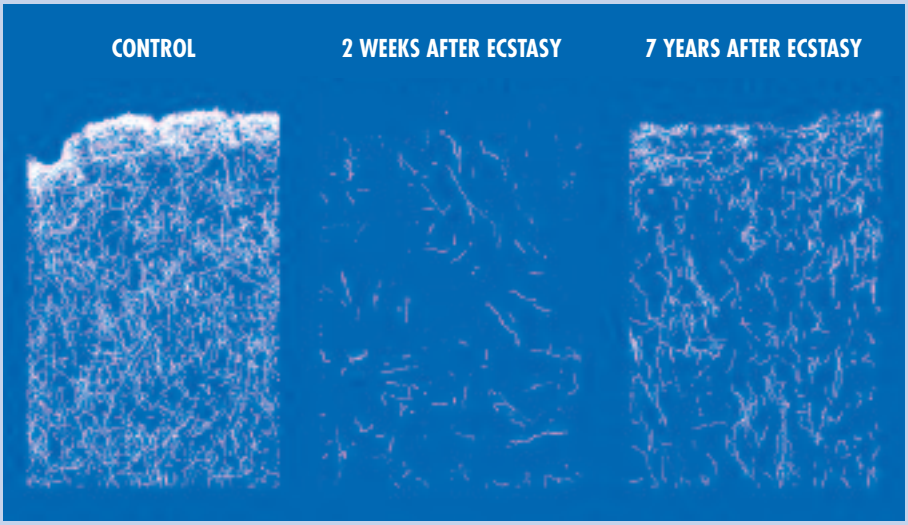
What is MDMA?

MDMA is an illegal drug that acts as both a stimulant and psychedelic, producing an energizing effect, as well as distortions in time and perception and enhanced enjoyment from tactile experiences. Typically, MDMA (an acronym for its chemical name 3,4-methylenedioxymethamphetamine) is taken orally, usually in a tablet or capsule, and its effects last approximately 3 to 6 hours. The average reported dose is one to two tablets, with each tablet typically containing between 60 and 120 milligrams of MDMA. It is not uncommon for users to take a second dose of the drug as the effects of the first dose begin to fade.

MDMA can affect the brain by altering the activity of chemical messengers, or neurotransmitters, which enable nerve cells in the brain to communicate with one another. Research in animals has shown that MDMA in moderate to high doses can be toxic to nerve cells that contain serotonin and can cause long-lasting damage to them. Furthermore, MDMA raises body temperature. On rare but largely unpredictable occasions, this has led to severe medical consequences, including death. Also, MDMA causes the release of another neurotransmitter, norepinephrine, which is likely the cause of the increase in heart rate and blood pressure that often accompanies MDMA use.

Although MDMA is known universally among users as ecstasy, researchers have determined that many ecstasy tablets contain not only MDMA but also a number of other drugs or drug combinations that can be harmful as well. Adulterants found in MDMA tablets purchased on the street include methamphetamine, caffeine, the over-the-counter cough suppressant dextromethorphan, the diet drug ephedrine, and cocaine. Also, as with many other drugs of abuse, MDMA is rarely used alone. It is not uncommon for users to mix MDMA with other substances, such as alcohol and marijuana.

Serotonin Present in Cerebral Cortex Neurons



Long-term effects in monkeys. 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.

A brief history of MDMA

MDMA was developed in Germany in the early 1900s as a parent compound to be used to synthesize other pharmaceuticals. During the 1970s, in the United States, some psychiatrists began using MDMA as a psychotherapeutic tool, despite the fact that the drug had never undergone formal clinical trials nor received approval from the U.S. Food and Drug Administration (FDA) for use in humans. In fact, it was only in late 2000 that the FDA approved the first small clinical trial for MDMA that will determine if the drug can be used safely with 2 sessions of ongoing psychotherapy under carefully monitored conditions to treat post-traumatic stress disorder. Nevertheless, the drug gained a small following among psychiatrists in the late 1970s and early 1980s, with some even calling it "penicillin for the soul" because it was perceived to enhance communication in patient sessions and reportedly allowed users to achieve insights about their problems. It was also during this time that MDMA first started becoming available on the street. In 1985, the U.S. Drug Enforcement Administration (DEA) banned the drug, placing it on its list of Schedule I drugs, corresponding to those substances with no proven therapeutic value.

What is the scope of MDMA abuse in the U.S.?

It is difficult to determine the exact scope of this problem because MDMA is often used in combination with other substances, and does not appear in some traditional data sources, such as treatment admission rates.

More than 11 million persons aged 12 or older reported using ecstasy at least once in their lifetimes, according to the 2004 National Survey on Drug Use and Health. The number of current (use in past month) users in 2004 was estimated to be 450,000.

The Drug Abuse Warning Network, maintained by the Substance Abuse and Mental

Health Services Administration, reported that mentions of MDMA in drug abuse-related cases in hospital emergency departments were 2,221 for the third and fourth quarters of 2003. The majority of patients who came to emergency departments mentioning MDMA as a factor in their admissions during that time were aged 18–20.

There is, however, some encouraging news from NIDA's Monitoring the Future (MTF) survey, an annual survey used to track drug abuse trends among adolescents in middle and high schools across the country. Between 2001 and 2005, annual ecstasy use decreased by 52 percent in 8th-graders, 58 percent in 10th-graders, and 67 percent in 12th-graders. Rates of lifetime MDMA use decreased significantly from 2004 to 2005 among 12th-graders.

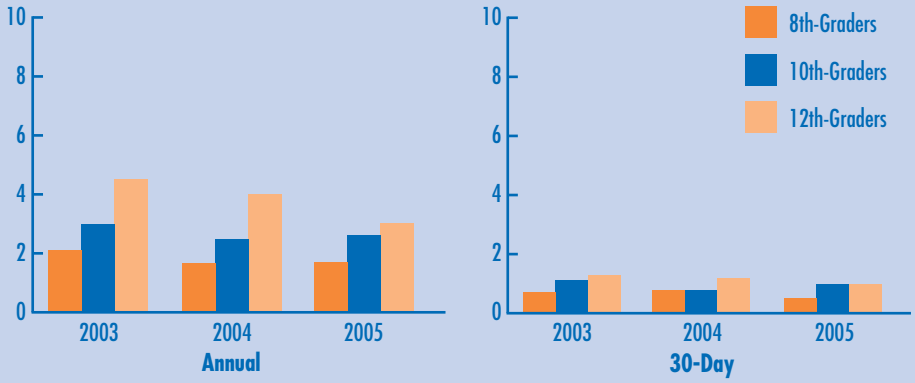
In 2005, 8th-graders reported a significant decrease in perceived harmfulness in using MDMA occasionally. The MTF data also show that MDMA use extends across many demographic subgroups. Among 12th-graders in 2005, for example, 3.9 percent of Whites, 3.0 percent of Hispanic students, and 1.4 percent of African-Americans reported using MDMA in the year prior to the survey.

Who is abusing MDMA?

MDMA first gained popularity among adolescents and young adults in the nightclub scene or weekend-long dance parties known as raves. However, the profile of the typical MDMA user has been changing. Community-level data from NIDA's Community Epidemiology Work Group (CEWG), continued to report that use of MDMA has spread among populations outside the nightclub scene.

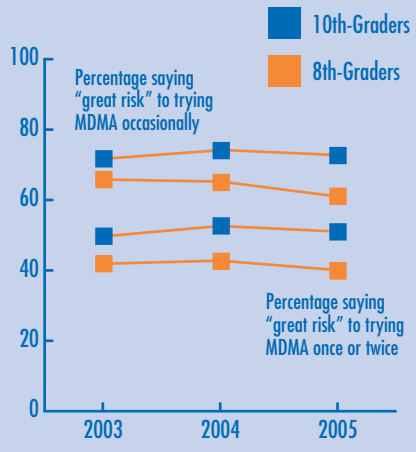
Reports also indicate that use is spreading beyond predominantly White youth to a broader range of ethnic groups. In Chicago, the drug continues to be predominantly used by White youth, but there are increasing reports of its use by African-American adults in their twenties and thirties. Also, indicators in New York suggest that both the distribution and use of club drugs are becoming more common in non-White communities.

Monitoring the Future Survey* Trends in MDMA Prevalence, 2003–2005



*These data are from the 2005 Monitoring the Future survey, funded by the National Institute on Drug Abuse, National Institutes of Health, DHHS, and conducted annually by the University of Michigan's Institute for Social Research. "Annual" refers to use at least once during the year preceding an individual's response to the survey. "30-day" refers to use at least once during the 30 days preceding an individual's response to the survey.

Trends in Perceived Harmfulness of MDMA Use



Perceived risk associated with MDMA use in selected categories.

Other NIDA research shows that MDMA has also become a popular drug among urban gay males. Reports have shown that some gay and bisexual men take MDMA and other club drugs in myriad venues. This is concerning given that the use of club drugs has been linked to high-risk sexual behaviors that may lead to HIV or other sexually transmitted diseases. Many gay males in big cities report using MDMA as part of a multiple-drug experience that includes marijuana, cocaine, methamphetamine, ketamine, and other legal and illegal substances.

What are the effects of MDMA?

MDMA has become a popular drug, in part because of the positive effects that a person may experience within an hour or so after taking a single dose. Those effects include feelings of mental stimulation, emotional warmth, empathy toward others, a general sense of well being, and decreased anxiety. In addition, users report enhanced sensory perception as a hallmark of the MDMA experience. Because of the drug's stimulant properties, when used in club or dance settings, MDMA can also enable users to dance for extended periods. However, there are some users who report undesirable effects immediately, including anxiety, agitation, and recklessness.

As noted, MDMA is not a benign drug. MDMA can produce a variety of adverse health effects, including nausea, chills, sweating, involuntary teeth clenching, muscle cramping, and blurred vision. MDMA overdose can also occur—the symptoms can include high blood pressure, faintness, panic attacks, and in severe cases, a loss of consciousness and seizures.

Because of its stimulant properties and the environments in which it is often taken, MDMA is associated with vigorous physical activity for extended periods. This can lead to one of the most significant, although rare, acute adverse effects—a marked rise in body temperature (hyperthermia). Treatment of hyperthermia requires prompt medical attention, as it can rapidly lead to muscle breakdown, which can in turn result in kidney failure. In addition, dehydration, hypertension, and heart failure may occur in susceptible individuals. MDMA can also reduce the pumping efficiency of the heart, of particular concern during periods of increased physical activity, further complicating these problems.

MDMA is rapidly absorbed into the human bloodstream, but once in the body, MDMA metabolites interfere with the body's ability to metabolize, or break down, the drug. As a result,

Effects of MDMA

Reported Undesirable Effects
(up to 1 week post-MDMA, or longer):

- Anxiety
- Restlessness
- Irritability
- Sadness
- Impulsiveness
- Aggression
- Sleep disturbances
- Lack of appetite
- Thirst
- Reduced interest in and pleasure from sex
- Significant reductions in mental abilities

Potential Adverse Health Effects:

- Nausea
- Chills
- Sweating
- Involuntary jaw clenching and teeth grinding
- Muscle cramping
- Blurred vision
- Marked rise in body temperature (hyperthermia)
- Dehydration
- High blood pressure
- Heart failure
- Kidney failure
- Arrhythmia

Symptoms of MDMA Overdose:

- High blood pressure
- Faintness
- Panic attacks
- Loss of consciousness
- Seizures

additional doses of MDMA can produce unexpectedly high blood levels, which could worsen the cardiovascular and other toxic effects of this drug. MDMA also interferes with the metabolism of other drugs, including some of the adulterants that may be found in MDMA tablets.

In the hours after taking the drug, MDMA produces significant reductions in mental abilities. These changes, particularly those affecting memory, can last for up to a week, and possibly longer in regular users. The fact that MDMA markedly impairs information processing emphasizes the potential dangers of performing complex or skilled activities, such as driving a car, while under the influence of this drug.

Over the course of a week following moderate use of the drug, many MDMA users report feeling a range of emotions, including anxiety, restlessness, irritability, and sadness that in some individuals can be as severe as true clinical depression. Similarly, elevated anxiety, impulsiveness, and aggression, as well as sleep disturbances, lack of appetite, and reduced interest in and pleasure from sex have been observed in regular MDMA users. 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 or marijuana, or to adulterants commonly found in MDMA tablets.

The Neurobiology of Ecstasy (MDMA)

MDMA alters brain chemistry by binding to serotonin transporters.

What does MDMA do to the brain?

MDMA affects the brain by increasing the activity of at least three neurotransmitters (the chemical messengers of brain cells): serotonin, dopamine, and norepinephrine. Like other amphetamines, MDMA causes these neurotransmitters to be released from their storage sites in neurons, resulting in increased neurotransmitter activity. Compared to the very potent stimulant, methamphetamine, MDMA causes greater serotonin release and somewhat lesser dopamine release. 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 experienced by MDMA users. However, by releasing large amounts of serotonin, MDMA causes the brain to become significantly depleted of this important neurotransmitter, contributing to the negative behavioral aftereffects that users often experience for several days after taking MDMA.

Numerous studies in animals have demonstrated that MDMA can damage serotonin-containing neurons; some of these studies have shown these effects to be long lasting. This suggests that such damage may occur in humans as well; however, measuring serotonin damage in humans is more difficult. Studies have shown that some heavy MDMA users experience long-lasting confusion, depression, and selective impairment of working memory and attention processes. Such memory impairments have

been associated with a decrease in serotonin metabolites or other markers of serotonin function. Imaging studies in MDMA users have shown changes in brain activity in regions involved in cognition, emotion, and motor function. However, improved imaging technologies and more research are needed to confirm these findings and to elucidate the exact nature of the effects of MDMA on the human brain.

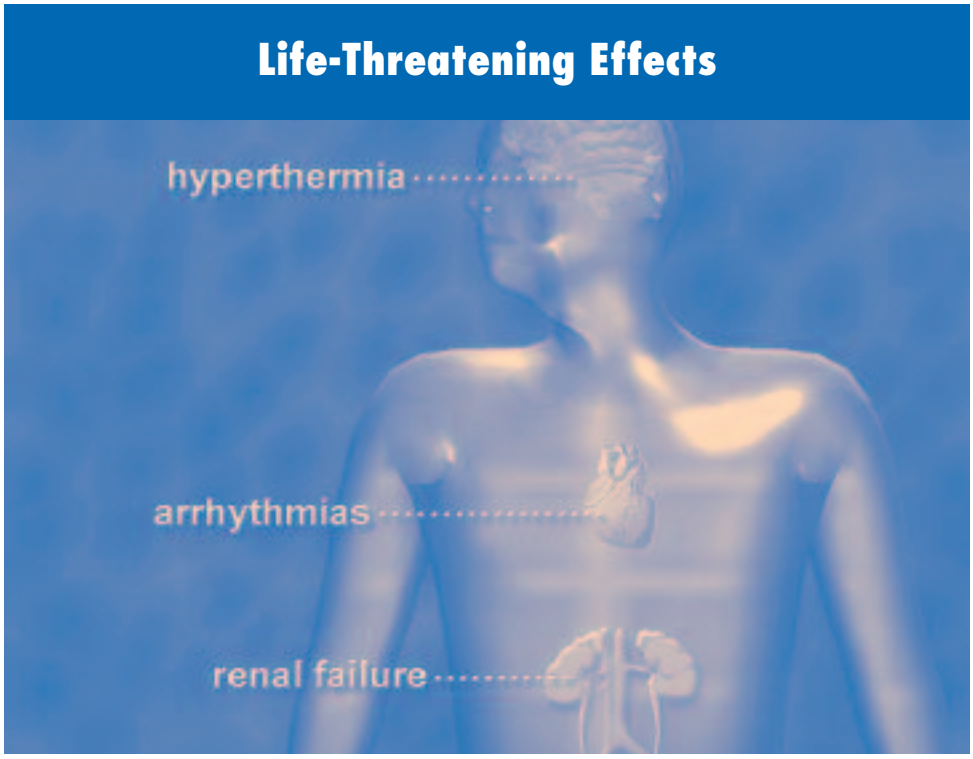
It is also important to keep in mind that many users of ecstasy may unknowingly be taking other drugs that are sold as ecstasy, and/or they may intentionally use other drugs, such as marijuana, which could contribute to these behavioral effects. Additionally, most studies in people do not have behavioral measures from before the users began taking drugs, making it difficult to rule out pre-existing conditions. Factors such as gender, dosage, frequency and intensity of use, age at which use began, the use of other drugs, as well as genetic and environmental factors all may play a role in some of the cognitive deficits that result from MDMA use and should be taken into consideration when studying the effects of MDMA in humans.

Given that most MDMA users are young and in their reproductive years, it is possible that some female users may be pregnant when they take MDMA, either inadvertently or intentionally because of the misperception that it is a safe drug. The potential adverse effects of MDMA on the developing fetus are of great concern. Behavioral studies in animals have found significant adverse effects on tests of learning and memory from exposure to MDMA during a developmental period equivalent to the third trimester in humans. However, the effects of MDMA on animals earlier in development are unclear; therefore, more research is needed to determine what the effects of MDMA are on the developing human nervous system.

Is MDMA addictive?

For some people, MDMA can be addictive. A survey of young adult and adolescent MDMA users found that 43 percent of those who reported ecstasy use met the accepted diagnostic criteria for dependence, as evidenced by continued use despite knowledge of physical or psychological harm, withdrawal effects, and tolerance (or diminished response), and 34 percent met the criteria for drug abuse. Almost 60 percent of people who use MDMA report withdrawal symptoms, including fatigue, loss of appetite, depressed feelings, and trouble concentrating.

MDMA affects many of the same neurotransmitter systems in the brain that are targeted by other addictive drugs. Experiments have shown that animals prefer MDMA, much like they do cocaine, over other pleasurable stimuli, another hallmark of most addictive drugs.



What do we know about preventing MDMA abuse?

Because social context and networks seem to be an important component of MDMA use, the use of peer-led advocacy and drug prevention programs may be a promising approach to reduce MDMA use among adolescents and young adults. High schools and colleges can serve as important venues for delivering messages about the effects of MDMA use. Providing accurate scientific information regarding the effects of MDMA is important if we hope to reduce the damaging effects of this drug. Education is one of the most important tools for use in preventing MDMA abuse.

Are there effective treatments for MDMA abuse?

There are no specific treatments for MDMA abuse. The most effective treatments for drug abuse and addiction 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. Drug abuse recovery support groups may be effective in combination with behavioral interventions to support long-term, drug-free recovery. There are currently no pharmacological treatments for dependence on MDMA.

Where can I get more scientific information on MDMA?

To learn more about MDMA and other drugs of abuse, contact the National Clearinghouse for Alcohol and Drug Information (NCADI) at 800–729–6686. Information specialists are available to help you locate information and resources.

Fact sheets, including *InfoFacts,* on the health effects of MDMA, other drugs of abuse, and other drug abuse topics are available on the NIDA Web site (www.drugabuse.gov), and can be ordered free of charge in English and Spanish from NCADI at www.health.org.

Access information on the Internet

- What's new on the NIDA Web site
- Information on drugs of abuse
- Publications and communications (including *NIDA NOTES*)
- Calendar of events
- Links to NIDA organizational units
- Funding information (including program announcements and deadlines)
- International activities
- Links to related Web sites (access to Web sites of many other organizations in the field)

NIDA Web Sites
drugabuse.gov
marijuana-info.org
steroidabuse.org
clubdrugs.org
inhalant.drugabuse.gov
hiv.drugabuse.gov
smoking.drugabuse.gov

NCADI
Web site: health.org
Phone no.: 800–729–6686

References

Bolla, K.I.; McCann, U.D.; and Ricaurte, G.A. Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* 51:1532–1537 (1998).

Broening, H.W.; Morford, L.L.; Inman-Wood, S.L.; Fukumura, M.; and Vorhees, C.V. 3,4-Methylenedioxymethamphetamine (Ecstasy)-induced learning and memory impairments depend on the age of exposure during early development. *The Journal of Neuroscience* 21:3228–3235 (2001).

Colado, M.I.; O'Shea, E.; Granados, R.; Misra, A.; Murray, T.K.; and Green, A.R.; A study of the neurotoxic effect of MDMA ('ecstasy') on 5-HT neurons in the brains of mothers and neonates following administration of the drug during pregnancy. *British Journal of Pharmacology* 121:827–833 (1997).

Community Epidemiology Work Group. *Epidemiologic Trends in Drug Abuse: Volume I.* Bethesda, MD. June 2005.

Cottler, L.B.; Womack, S.B.; Compton, W.M.; and Ben-Abdallah, A. Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria. *Human Psychopharmacology* 16:599–606 (2001).

Curran, H.V.; and Travill, R.A. Mood and cognitive effects of ±3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. *Addiction* 92:821–831 (1997).

Dafters, R.I.; and Lynch, E. Persistent loss of thermoregulation in the rate induced by 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy") but not by fenfluramine. *Psychopharmacology* 138:207–212 (1998).

Kish, S.J.; Furukawa, Y.; Ang, L.; Vorce, S.P.; and Kalasinsky, K.S. Striatal serotonin is depleted in brain of a human MDMA (Ecstasy) user. *Neurology* 55:294–296 (2000).

Koprich, J.B.; Chen, E.-Y.; Kanaan, N.M.; Campbell, N.G.; Kordower, J.H.; and Lipton, J.W. Prenatal 3,4-methylenedioxymethamphetamine (ecstasy) alters exploratory behavior, reduces monoamine metabolism, and increases forebrain tyrosine hydroxylase fiber density of juvenile rats. *Neurotoxicology and Teratology* 25: 509–517 (2003).

Lester, S.J.; Baggott, M.; Welm, S.; Schiller, N.B.; Jones, R.T.; Foster, E.; and Mendelson, J. Cardiovascular effects of 3,4-methylenedioxymethamphetamine: a double-blind, placebo-controlled trial. *Annals of Internal Medicine* 133:969–973 (2000).

Liechti, M.E.; and Vollenweider, F.X. Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. *Human Psychopharmacology* 16:589–598 (2001).

Lyles, J.; and Cadet, J.L. Methylenedioxymethamphetamine (MDMA, Ecstasy) neurotoxicity: cellular and molecular mechanisms. *Brain Research Reviews* 42:155–168 (2003).

McCann, U.D.; Eligulashvili, V.; and Ricaurte, G.A. (±)3,4-Methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: clinical studies. *Neuropsychobiology* 42:11–16 (2000).

Morgan, M.J. Ecstasy (MDMA): a review of its possible persistent psychological effects. *Psychopharmacology* 152:230–248 (2000).

Morgan, M.J. Memory deficits associated with recreational use of "ecstasy" (MDMA). *Psychopharmacology* 141:30–36 (1999).

National Institute on Drug Abuse. *Monitoring the Future: National Results on Adolescent Drug Use 2005.*

Obrocki, J.; Buchert, R.; Väterlein, O.; Thomasius, R.; Beyer, W.; and Schiemann, T. Ecstasy – long-term effects on the human central nervous system revealed by positron emission tomography. *British Journal of Psychiatry* 175:186–188 (1999).

Parrott, A.C.; and Lasky, J. Ecstasy (MDMA) effect upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology* 139:261–268 (1998).

Reneman, L.; Booij, J.; Schmand, B.; van den Brink, W.; and Gunning, B. Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin neurotransmission. *Psychopharmacology* 148:322–324 (2000).

Schenk, S.; Gittings, D.; Johnstone, M.; and Daniela, E. Development, maintenance and temporal pattern of self-administration maintained by ecstasy (MDMA) in rats. *Psychopharmacology* 169:21–27 (2003).

Sherlock, K.; Wolff, K.; Hay, A.W.; and Conner, M. Analysis of illicit ecstasy tablets. *Journal of Accident and Emergency Medicine* 16:194–197 (1999).

Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *Drug Abuse Warning Network, 2003: Interim National Estimates of Drug-Related Emergency Department Visits.* DAWN Series D-26, DHHS Publication No. (SMA) 04-3972. Rockville, MD (2004).

Thompson, M.R., Li, K.M., Clemens, K.J., Gurtman, C.G., Hunt, G.E., Cornish, J.L., and McGregor, I.S. Chronic fluoxetine treatment partly attenuates the long-term anxiety and depressive symptoms induced by MDMA ('Ecstasy') in rats. *Neuropsychopharmacology* 29(40):694–704, 2004.

Verkes, R.J.; Gijsman, H.J.; Pieters, M.S.M.; Schoemaker, R.C.; de Visser, S.; Kuijpers, M.; Pennings, E.J.M.; de Bruin, D.; Van de Wijngaart, G.; Van Gerven, J.M.A.; and Cohen, A.F. Cognitive performance and serotonergic function in users of ecstasy. *Psychopharmacology* 153:196–202 (2001).

Wareing, M.; Fisk, J.E.; and Murphy, P.N. Working memory deficits in current and previous users of MDMA ('ecstasy'). *British Journal of Psychology* 91:181–188 (2000).

Glossary

Addiction: A chronic, relapsing disease characterized by compulsive drug seeking and use.

Adulterant: A substance, either a biologically active material such as another drug or an inert material, added to a drug when it is formed into a tablet or capsule.

Cardiovascular system: The heart and blood vessels.

Dopamine: A neurotransmitter present in regions of the brain that regulate movement, emotion, motivation, and the feeling of pleasure.

Ecstasy: Common street name for MDMA.

Gastrointestinal system: The stomach and intestines.

Hyperthermia: A potentially dangerous rise in body temperature.

MDMA: Common chemical name for 3,4-methylenedioxymethamphetamine.

Neurotransmitter: A chemical that acts as a messenger to carry signals or information from one nerve cell to another.

Norepinephrine: A neurotransmitter present in regions of the brain that affect heart rate and blood pressure.

Serotonin: A neurotransmitter present in widespread parts of the brain that is involved in sleep, movement, and emotions.

Tolerance: A decrease in the effect of a drug that occurs with repeated administration.

NIDA
NATIONAL INSTITUTE ON DRUG ABUSE

NIH Publication Number 06-4728
Printed March 2006