Toxic Topic

Experiencing Ecstasy: Is it all the Rave?

Kevin C. Osterhoudt, MD

Case Presentation

A mother is concerned because her teenage daughter has had a recent change in behavior. The teenager's school performance is worsening; she has begun staying out late and goes out with fluorescent fingernail polish and jewelry. Perhaps more bizarre, although she denies being pregnant, she has a number of infant pacifiers around the house and on necklaces. The mother overheard one of her daughter's friends mentioning a "rave." The mother has seen news programs about raves, and wonders if her daughter could be abusing drugs such as "ecstasy."

▶ What is a rave?

Rave parties are an international phenomenon typified by continuous, late or all night dancing to repetitive, hypnotic electronically synthesized music. These parties carry a mystique among many teenagers and young adults and are often held in secretive locations within makeshift dance halls.[1] Recently, the rave scene has started to flourish in commercial venues. Rave attendees often claim to promote the "PLUR" ideology of peace, love, unity, and respect.[2] (Further information regarding the rave culture is readily available on the internet, at sites such as *www.hyperreal.org* [accessed 12/20/01].

Many attend and enjoy raves without abusing mind-altering drugs. Ethanol intoxication is uncommon at raves,[2] but use of various so-called club drugs is common. Cannabis, ecstasy, gamma-hydroxybutyrate (GHB), ketamine, dextromethorphan, and lysergic acid diethylamide (LSD) are some of the current popular drugs used at raves within the United States. Ecstasy may be the quintessential rave drug, because it is used to provide endurance for marathon dance sessions and to enhance sensory stimuli.

From the Section of Medical Toxicology, Division of Emergency Medicine, The Children's Hospital of Philadelphia; and the Poison Control Center, Philadelphia, PA.

Address correspondence to Kevin C. Osterhoudt, MD, Division of Emergency Medicine, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104-4399.
E-mail: osterhoudtk@email.chop.edu

▶ What is ecstasy?

Ecstasy is a lay term most commonly applied to the drug 3,4-methylenedioxymethamphetamine (MDMA). Although many drugs of abuse, such as cocaine, heroin, and marijuana, are plant-derived, MDMA is a synthetic derivative of methamphetamine that has sympathomimetic and hallucinogenic properties. MDMA is a crystalline powder in its native form, but is typically distributed in the form of pills or tablets containing 50–250 mg/tablet.[3] The United States government currently lists MDMA as a Schedule I drug, and its possession is illegal. To confuse matters, the term "liquid ecstasy" has been applied to another Schedule I drug, GHB, and the term "herbal ecstasy" has been attributed to currently legal preparations containing the stimulant ephedrine.

Because MDMA is not a pharmaceutical, quality control measures do not exist with regards to its manufacturing or distribution. Among ecstasy pill samples submitted for anonymous testing, 37% contained no MDMA.[4] Other chemicals commonly identified in pills sold as ecstasy were dextromethorphan (DXM), caffeine, ephedrine, pseudoephedrine, and salicylates. In addition, there are several chemically distinct "designer" amphetamines that often are sold as ecstasy. Clearly ecstasy users play an unfortunate game of Russian roulette with clandestine drug dealers.

The desired effects of low doses of MDMA include mood elevation, release of behavioral and emotional inhibition, sensory enhancement, and increased energy despite a feeling of relaxation. "Trip reports" offering detailed, and often glorified, descriptions of users' experiences with MDMA are abundant on the internet (for example, see *www.lycaeum.org* [accessed 12/20/01]). Unfortunately, abuse of ecstasy often has tragic consequences. The dangers of ecstasy abuse will be discussed below.

▶ Are the teenager's pacifiers a clue revealing ecstasy abuse?

Ecstasy use has a culture all its own, and unfamiliar observers of the rave scene often are surprised by the paraphernalia of the dancers. Although clothing is usually unpretentious, rave attendees often are glowing with fluorescent colors. MDMA has an illusory

effect on sensory perception, and dancers may carry luminescent "glow-sticks" or wear luminescent jewelry to create psychedelic imagery. Interestingly, many readers of this column may have noticed displays of these glow-sticks near the counters of their local hardware and convenience stores. Fluorescent tongue paints and nail polishes also are popular in some parts of the country. Jaw clenching is a common side effect of MDMA use, and, as a result, pacifiers and lollipops are often used for symptomatic relief. Pacifier necklaces, fluorescent fingernail polish, and luminescent jewelry now have become trendy, and parents should be reassured that for many teenagers it is a style statement and is not, by itself, indicative of drug use. However, such rave paraphernalia should be a nidus for open family discussion.

MDMA often is mixed with other drugs to enhance its ability to alter the sensorium. DXM is a popular coingestant and may be evidenced by unusually excessive use of over-the-counter cough and cold medications. "Warming" topicals such as liniments or menthol inhalants also are frequently combined with MDMA abuse. Ecstasy often is taken in multiple doses over many hours at a rave, and users often are dancing continuously in a climate of high ambient temperatures. Bottled water is popular in such a setting. In the Philadelphia area, it is not uncommon for dance clubs to sell bottles of spring water to teenagers for as much as $6 per bottle on "underage" dance nights.

▶ How prevalent is ecstasy use among teenagers?

An epidemiologic review of drug abuse patterns among high school students from 36 countries, which did not examine caffeine or tobacco use, found that ecstasy was the fourth most commonly used drug trailing only alcohol, cannabis, and amphetamines.[5] According to a survey from the National Institute on Drug Abuse (NIDA), 5% of eighth grade students in the United States and 12% of high school seniors have tried ecstasy; with 3% of high school seniors reporting regular use (this information is available at *www.nida.nih.gov/infofax/hsyouthtrends.html* [accessed 12/20/01]).

▶ Will a urine drug screen detect ecstasy use?

Most hospital laboratories test urine for drugs-of-abuse with commercially produced immunoassays, but MDMA-specific immunoassays currently are not widely available. In some tests, MDMA in the urine may lead to a positive test for amphetamines, but the sensitivities of various commercial amphetamine immunoassays are variable with regard to MDMA.[6] In some circumstances, coingestant or contaminant drugs may be identified. Gas chromatography currently is the preferred test for detecting MDMA and is typically available only from a subset of reference laboratories.

▶ What are the dangers of ecstasy?

Typical of amphetamines, MDMA has indirect sympathomimetic activity mediated by the release of dopamine and norepinephrine at nerve terminals. However, much of the effect caused by MDMA on mood and behavior is thought to be the result of serotonergic receptor stimulation within the autonomic and central nervous systems.[7] MDMA blocks the transporter protein responsible for serotonin reuptake.[8]

Many internet sites promote the concept that MDMA is safe to the health of recreational users. Some even have supported the medical use of MDMA as an "entactogen" to enhance empathy and intimacy in the setting of psychotherapy.[1] The desired effects that MDMA is thought to cause include increased wakefulness and sense of energy, euphoria, loss of social inhibition, and enhanced sensory perception and illusion. The desire for physical stimuli has led to the use of another colloquialism for MDMA: "the hug drug." Based on the large prevalence of ecstasy abuse and the relative paucity of ecstasy users seeking emergent medical attention, life-threatening acute toxicity seems to be an uncommon event. However, a 1997 review[1] describing 53 deaths in the United Kingdom from acute MDMA toxicity suggests that MDMA is not nearly as safe as advertised. Kalant[8] has compiled an appendix summarizing the published cases of MDMA-associated fatality.

Common negative side effects of MDMA at low doses include nausea, anorexia, headache, insomnia, sweating, tremor, myoclonus, hypertension, and ataxia. Bruxism and muscle stiffness often occur. Undesired acute psychologic effects include panic attacks and frank psychosis.[9] At higher doses, negative side effects include hallucinations significant enough to lead to agitation or injury.[10] Difficulty concentrating, depression, and fatigue often occur as a "hangover" effect when sobering from MDMA use.[11]

The life-threatening effects of MDMA include hypertension, hyperthermia, hypoglycemia, hypo- or hypernatremia, myoglobinuric renal failure, hepatotoxicity, seizures, cerebral hemorrhage, and cerebral edema.[12] Several of these toxicities, as well as concerns for chronic behavioral and cognitive injury, will be specifically addressed below. Anecdotal evidence also suggests that ingestion of as little as a single MDMA pill can lead to myocardial infarction in young individuals without atherosclerotic coronary disease.[13] Indirect morbidity and mortality, such as unintended pregnancy or traumatic injury, may occur as a complication of impaired inhibition, judgment, or motor skills. As addressed above, there also is little assurance that ecstasy purchased from a dealer is MDMA and not another toxic drug.

Hyperpyrexia From MDMA

Hyperthermia is, perhaps, the most common form of severe toxicity encountered after MDMA abuse. Serotonin and dopamine are important modulators of brainstem thermoregulation. MDMA-exposed animals develop significant elevations in body temperature when exposed to only modest elevations in environmental temperature.[14] This has important ramifications on rave attendees who often subject themselves to prolonged exertion in the hot environment of a rave setting. Complications of hyperpyrexia include rhabdomyolysis and myoglobinuric renal injury, disseminated intravascular coagulation, and multiorgan failure.[8]

Hepatotoxicity From MDMA

Acute hepatitis has been observed in many cases of MDMA intoxication, and one series of patients admitted to the hospital found that ecstasy abuse was the second most common cause of clinically significant hepatotoxicity among teenagers and adults younger than 25 years of age.[15] Proposed mechanisms for such hepatotoxicity have included allergic reaction, toxic contaminants, hyperpyrexia, and MDMA-induced glutathione depletion.[8] Several cases of liver transplantation and/or death have been reported after ecstasy-associated fulminant liver failure.[16]

Hyponatremia From MDMA

Hypernatremia is sometimes seen among patients with MDMA intoxication and is attributed to dehydration from sympathomimetic metabolic stimulation combined with intense physical activity. Interestingly, hyponatremia is a complicating feature of many severe cases of ecstasy toxicity. One proposal for such hyponatremia has been excessive water drinking in response to sodium-laden fluid loss from sweating.[8] Cases of hyponatremia, in the absence of water intoxication, have led to consideration that MDMA might produce the syndrome of inappropriate antidiuretic hormone (SIADH).[17] Further evidence for the role of SIADH in ecstasy-associated hyponatremia was provided by Henry's observation that a single low dose of MDMA given to healthy volunteer subjects resulted in increased serum vasopressin and decreased natremia.[18]

Cerebral Injury From MDMA

Cerebral edema and cerebral hemorrhage have been encountered in association with ecstasy toxicity. Cerebral edema is believed to result from a multifactorial cascade including hyponatremia, hyperthermia, hypertension, and convulsions. Recent arteriographic studies suggest that cerebral hemorrhage most often occurs as a response to intracranial hypertension among users with previously clinically silent vascular malformations.[19]

Detrimental Effects of MDMA on Long-term Mood and Cognition

There is significant concern that MDMA abuse can lead to long-term deficits in mood and cognition. These concerns arise from animal models of toxicity and from human studies. Among animal studies, reductions in serotonin-related neurochemicals have been demonstrated in many MDMA-exposed animal species including non-human primates.[20] Furthermore, evidence of injury to serotonergic nerve axons has been noted to persist for at least 7 years in monkey models.[21]

Among humans, neurochemical, anatomic, cognitive, and behavioral evidence of injury has been demonstrated. Recent positron emission tomography studies have documented decreased activity at serotonin receptors among abstinent human ecstasy users.[22] In addition, human studies have shown that long-term MDMA users have abnormally low levels of serotonin in the cerebrospinal fluid, reduced numbers of serotonin transporter molecules, electroencephalographic abnormalities similar to those seen in dementia, and alterations in cerebral glucose metabolism and blood flow.[8] Results from single photon emission computed tomography evaluation of neuroanatomic changes and from functional memory tests demonstrate that MDMA-induced neurotoxicity can be persistent in human MDMA users who have been abstinent for more than 1 year.[23] Clinically, a comprehensive cognitive test battery has been applied to compare abstinent recreational abusers of MDMA and marijuana with control groups who did or did not use recreational marijuana. Ecstasy users performed worse in tests of attention, memory, and learning.[24] Finally, chronic use of MDMA has been associated with a persistent psychosis, panic disorder, and depression.[25]

Skeptics of the neurotoxicity of MDMA point out that most animal studies have been performed with doses higher than typical among recreational users, and that gliosis as a marker of neuronal injury has not been seen.[3] In addition, many human studies of MDMA toxicity have used imperfect control groups and have been subject to considerable selection bias and confounding. Many human studies rely on self-reporting of MDMA use and, as discussed above, most MDMA users are unaware of the dose or drug that they are actually consuming. In addition, the majority of MDMA users also abuse other drugs with the potential for neurologic insult. At this time, cause and effect between MDMA and neurologic decline have not been proven conclusively, but an association is certain to exist.

The following quote from a recent editorial serves as a fitting summary of the evidence for MDMA neurotoxicity: "although many have vigorously contested the applicability of [ecstasy studies] to the human condition, a growing body of data is sufficient to raise legitimate concern that negative consequences of exposure to MDMA . . . might develop into major deficits over longer periods of time."[26]

REFERENCES

1. Schwartz RH, Miller NS. MDMA (ecstasy) and the rave: a review. Pediatrics 1997;100:705–708.
2. Weir E. Raves: a review of the culture, the drugs, and the prevention of harm. CMAJ 2000;162:1843–1848.
3. Doyon S. The many faces of ecstasy. Curr Opin Pediatr 2001;13:170–176.
4. Baggot M, Heifets B, Jones RT, et al. Chemical analysis of ecstasy pills. JAMA 2000;284:2190.
5. Smart RG, Ogborne AC. Drug use and drinking among students in 36 countries. Addict Behav 2000;25:455–460.
6. Zhao H, Brenneisen R, Scholer A, et al. Profiles of urine samples taken from ecstasy users at Rave parties: analysis by immunoassays, HPLC, and GC-MS. J Analytic Toxicol 2001;25:258–269.
7. Bankson MG, Cunningham KA. 3,4-methylenedioxymethamphetamine (MDMA) as a unique model of serotonin receptor function and serotonin-dopamine interactions. J Pharmacol Experiment Ther 2001;297:846–852.
8. Kalant H. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. CMAJ 2001;165:917–928.
9. McGuire PK, Cope H, Fahy TA. Diversity of psychopathology associated with use of 3,4-methylenedioxymethamphetamine. Br J Psychiatry 1994;165:391–395.
10. Hayner GN, McKinney H. MDMA-the dark side of ecstasy. J Psychoactive Drugs 1986;18:341–347.
11. Cohen RS. Subjective reports on the effects of the MDMA experience in humans. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:1137–1145.
12. Shannon M. Methylenedioxymethamphetamine (MDMA, "Ecstasy). Pediatr Emerg Care 2000;16:377–380.
13. Qasim A, Townend J, Davies MK. Ecstasy induced acute myocardial infarction. Heart 2001;85:e10.
14. Malberg JE, Seiden LS. Small changes in ambient temperature cause large changes in MDMA-induced serotonin neurotoxicity and core body temperature in the rat. J Neurosci 1998;18:5086–5094.
15. Andreu V, Mas A, Brugera M, et al. Ecstasy: a common cause of severe acute hepatotoxicity. J Hepatol 1998; 29:394–397.
16. Brauer RB, Heidecke CD, Nathrath W, et al. Liver transplantation for the treatment of fulminant hepatic failure induced by the ingestion of ecstasy. Transpl Int 1997;10:229–233.
17. Gomez-Balaguer M, Pena H, Morillas C, et al. Syndrome of inappropriate antidiuretic hormone secretion and "designer drugs" (ecstasy). J Pediatr Endocrin Metab 2000;13:437–438.
18. Henry JA, Fallon JK, Kieman AT, et al. Low dose MDMA ("ecstasy") induces vasopressin secretion. Lancet 1998;38:454–458.
19. McEvoy AW, Kitchen ND, Thomas DG. Intracerebral hemorrhage and drug abuse in young adults. Br J Neurosurg 2000;14:449–454.
20. Ricuarte GA, Martello AL, Katz JL, et al. Lasting effects of MDMA on central serotonergic neurons in nonhuman primates: neurochemical observations. J Pharmacol Exp Ther 1992;261:616–622.
21. Hatzidimitriou G, McCann DU, Ricuarte G. Altered serotonin innervation patterns in the forebrain of monkeys treated with 3,4-methylenedioxymethamphetamine seven years previously: factors influencing recovery. J Neurosci 1999;19:5096–5107.
22. McCann DU, Szabo Z, Scheffel U, et al. Positron emission tomographic evidence of toxic effects of MDMA (ecstasy) on brain serotonin neurons in human beings. Lancet 1998;352:1433–1437.
23. Reneman L, Lavalaye J, Schmand B, et al. Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine: preliminary findings. Arch General Psychiatr 2001;58:901–906.
24. Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, et al. Impaired cognitive performance in drug free users of recreational ecstasy. Neurology Neurosurg Psychiatr 2000;68:719–725.
25. McCann UD, Slate SO, Ricuarte GA. Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA: "ecstasy"). Drug Saf 1996;15:107–115.
26. Kelly PAT. Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). J Neurology Neurosurg Psychiatr 2000;68:690.

Dr. Osterhoudt welcomes your suggestions of ideas for future "Toxic Topics." Clinical questions in pediatric toxicology can be submitted via e-mail to osterhoudtk@email.chop.edu