Ecstasy: Dangers and Controversies

Jina V. Pham, Pharm.D., and Talia Puzantian, Pharm.D., from the School of Pharmacy (Dr. Pham) and the Department of Psychiatry, School of Medicine (Dr. Puzantian), University of California-San Francisco, and San Francisco General Hospital (Dr. Puzantian), San Francisco, California. Pharmacotherapy 21(12):1561-1565, 2001. © 2001 Pharmacotherapy Publications

Abstract

Ecstasy is a recreational drug that is increasing in popularity, particularly in young adolescents. Its appeal involves its euphoric effects and a feeling of empathy for others (hence the nickname "hug drug"). This appeal may be furthered by a misleading and anecdotal perception of safety. Cases of adverse effects, toxic reactions, and fatalities are increasingly being reported in the medical literature, as well as in the popular press. Adverse effects include hyperthermia, seizures, cardiac abnormalities, and hyponatremia. Long-term Ecstasy use may result in serotonin terminal degeneration and depletion, which may result in psychiatric and cognitive sequelae. Controversy surrounds the legalization of Ecstasy for medicinal purposes.

Introduction

Historically, 3,4-methylenedioxymethamphet-amine (MDMA) was synthesized in 1912 and patented in 1914 by Merck Pharmaceuticals in Germany, with the intent of marketing the compound as an appetite suppressant.[1, 2] It was indeed used for this purpose during World War I, being widely distributed to soldiers.[1] During the 1970s and 1980s, MDMA was administered to facilitate psychoanalysis by some psychologists and psychiatrists. Because of its recognized abuse potential, however, in 1985 the United States Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA) classified MDMA as a schedule I hallucinogen and therefore completely prohibited it for medicinal purposes.[3-8] Currently, MDMA is not manufactured by any pharmaceutical companies; thus, the sources of MDMA come from clandestine laboratories that synthesize MDMA by using different recipes. Of interest, often what is sold as "Ecstasy" may contain no MDMA, with caffeine and pseudoephedrine most often being misrepresented as MDMA. Structurally, the semisynthetic MDMA is derived from methamphetamine.[1] Its mechanism of action is not fully understood; however, evidence exists that MDMA exerts its action by interacting with serotonin reuptake receptors and thereby causes an increased release of serotonin primarily and possibly dopamine and norepinephrine secondarily.[9, 10] Long-term use of MDMA has been observed to cause serotonin terminal degeneration and serotonin depletion in primates, and preliminary human data suggest a possibility for similar neurologic effects in individuals who take Ecstasy.[11, 12]

Socially, MDMA has a high abuse potential. It is well known on the street as Ecstasy, X, XTC, ADAM, Clarity, and Lover's Speed. Other street names include Bean, Cloud 9, Doves, E, Eve, M, Rave Energy, and Roll. Ecstasy
comes in tablet, capsule, or powder form and can be ingested orally, snorted, injected intravenously or subcutaneously, or smoked.[1] (Images of Ecstasy tablets are available from the following Web sites: www.erowid.org/chemicals/mdma/mdma_images2.shtml, or www.meb.uni-bonn.de/giftzentrale/ xtcuebs3.html.) An Ecstasy pill contains from 50-150 mg of MDMA, depending on the brand.[1, 5, 6, 13] The effects from an orally ingested pill have an onset of 20-60 minutes and last 2-6 hours.[6] Once consumed, Ecstasy produces mild stimulant and psychedelic effects; in other words, MDMA is a pleasant combination of lysergic acid diethylamide (LSD)- and amphetamine-like effects.[3-7] Ecstasy is usually taken in a group setting; less commonly, an individual will take it when he or she is alone. The most common place where Ecstasy is taken is in "raves" or "trances," which are all-night underground clubs where drugs are overtly used. "Rave culture" originated in the United Kingdom and the Netherlands in the 1980s and spread to the U.S. in the early 1990s. Ecstasy quickly gained popularity among substance users owing to a misperception that it is a safer drug than other hallucinogens and psychostimulants, as Ecstasy has fewer psychologic adverse effects than do hallucinogens and a more tolerable "crash" compared with that of psychostimulants.[5-7]

A recent pharmacokinetic study in humans showed a nonlinear relationship between the dose and the maximum serum concentration of MDMA.[14] The study also disclosed the possibility of saturation of hepatic metabolism of MDMA at doses larger than 125 mg. The drug MDMA has a half-life of 6-8 hours.[14, 15] It is extensively metabolized by cytochrome P450 (CYP) 2D6 to 4-hydroxy-3-methoxymethamphetamine (HMMA) and to a lesser extent by CYP3A4 to 3,4-methylenedioxyamphetamine (MDA), a metabolite that exhibits some psychoactive properties. Cytochrome P450 2D6 is subject to genetic polymorphism; about 10% of the Caucasian population poorly metabolizes CYP2D6.[14]

**Adverse Effects**

A "trip" of Ecstasy starts with desirable effects such as euphoria, empathy for others, emotional openness, and ability to gain insights into self. During the rush, however, undesired effects could occur; those who have taken Ecstasy describe these effects as dizziness, vertigo, muscle tension, trismus, bruxism, nausea, blurred vision, rapid eye movement, chills, sweating, and faintness.[4, 5] Shortly after the rush is the crash or the "comedown" when individuals could experience severe anxiety, paranoia, sleep problems, and vivid nightmares for days to weeks.[5-7]

The inevitable problem with Ecstasy is psychologic dependency. One author described three cases in which individuals experienced seizures, severe depression, and sleep disturbances induced by Ecstasy, yet these individuals could not stop taking the drug despite knowing the complications.[16] They clearly exhibited features of dependency such as tolerance ("loss of magic"), mood disturbances, and desire to continue taking the drug to avoid a withdrawal state or to elevate mood.
Those who take Ecstasy commonly experience rapid tolerance to the drug, which usually compels them to escalate the dose in the hope of reaching the first-time euphoria. Typically, they begin with weekend binges and sometimes progress to high daily doses, with variations often depending on incomes. A high dose or an overdose of Ecstasy poses the risks of acute delirium, acute anxiety reactions, malignant hyperthermia, rhabdomyolysis, acute kidney failure, syndrome of inappropriate antidiuretic hormone, bilateral sixth nerve palsy, cardiovascular abnormalities, seizure, cerebral edema, coma, and death.

Of all the acute complications, hyperthermia is particularly important since it could lead to seizure and coma. Factors that induce hyperthermia include dehydration, alcohol consumption, physical exertion, and heat, all of which are present at rave clubs. Therefore, individuals with long-term experience taking Ecstasy recommend frequent breaks and adequate hydration; however, this could lead to overhydration -- another potential risk of taking Ecstasy. In two studies, the authors reported cases of hyponatremia-induced cerebral edema and syndrome of inappropriate antidiuretic hormone, respectively, that were linked to overhydration.

Whereas acute adverse effects could be associated with a single dose, long-term use of Ecstasy could result in functional incapacity and decreased quality of life when those who take the drug develop psychiatric disturbances, cognitive impairment, and memory deficits. Described psychiatric disturbances include paranoid psychosis, palinopsia (abnormal recurring visual hallucinations), panic attacks, depression, anxiety, and anorexia. These conditions can appear a few weeks after the last dose of Ecstasy and can last up to 6 months during the abstinence period. Individuals who take Ecstasy are at a greater risk if they have a first-degree relative with a psychiatric condition.

A hallmark investigation of cognitive impairment was performed in individuals who had repeatedly taken Ecstasy. The study participants had taken Ecstasy on at least 25 occasions but had abstained from it for at least 3 weeks before the study. The authors used the Walter Reed Army Institute of Research Performance Assessment Battery to measure cognitive performance in study subjects. The results revealed that those taking only Ecstasy, compared with individuals taking many substances but who had never taken Ecstasy, had impairment of "sustained attention task, task requiring visual discrimination and working memory, a short-term memory task, and a task of semantic recognition and verbal reasoning." Furthermore, the Ecstasy group had lower levels of cerebrospinal fluid 5-hydroxyindoleacetic acid (a metabolite of serotonin), which was interpreted by the authors as a marker for serotonin terminal degeneration. The authors believe that cognitive deficits in those who repeatedly took Ecstasy were caused by serotonin and catecholamine alterations and were associated with the extent of use rather than the amount of Ecstasy taken each time.

One author investigated memory deficits in individuals taking Ecstasy, individuals taking many substances but not Ecstasy, and individuals who did not take drugs. The Ecstasy group took at least 20 tablets in their
lifetime and had abstained for at least 1 month before the study. To assess memory effects, the author used the Rivermead Behavioral Memory Test followed by a battery of neuropsychologic tests. The results showed statistically significant impairment in both immediate recall performance and delayed recall performance in the Ecstasy group compared with those measures in the other two groups, and delayed recall performance was considerably more impaired than immediate recall performance. The author found a correlation between immediate recall impairment with a composite of average amount used per section and duration of use, but no correlation was found for delayed recall impairment. The demographics of the groups were not well matched, resulting in a few confounders, one of which was a significant difference in duration of LSD use in the two groups of illicit drug users.[9]

In another study,[10] the authors reported a case of idiosyncratic Parkinson's disease in an individual who took Ecstasy 10 times within a year and who was not responding to levodopa and pramipexole. The authors hypothesized that the case was a result of a delayed neurotoxic effect to serotonergic neurons in the striatum and substantia nigra.

Finally, Ecstasy was reported to cause cardiovascular and musculoskeletal malformations in babies born to mothers who took Ecstasy during pregnancy.[22] The authors conducted a prospective follow-up of 136 babies who were exposed to Ecstasy prenatally. When exposed to Ecstasy alone, the abnormalities were largely musculoskeletal. However, cardiovascular malformations were more predominant when pregnant mothers took Ecstasy along with amphetamines, g-hydroxybutyric acid, or alcohol.

**Legalization of Ecstasy for Medicinal Purposes**

The Multidisciplinary Association for Psychedelic Studies (MAPS) is an organization that was established in 1985.[4] This organization has been advocating the legitimization of MDMA, psilocin, and marijuana for medicinal purposes. In particular, MAPS has been seeking FDA approval for MDMA in psychoanalysis (e.g., in patients who have been abused or raped or in those with posttraumatic stress disorder) and in cancer therapy (for pain control and stress reduction[1]). The organization argues that MDMA is not harmful for nonrepeated administration or when monitored by a therapist. The organization also questions the validity of studies on cognitive and memory impairment because of their methodology (e.g., confounding factors, unmatched subject groups, nonuniform Ecstasy sources, built-in subjective bias). In 1999, the founder of MAPS and two colleagues had a conference with FDA officials on the matter; however, the FDA rejected MDMA for medicinal purposes on the grounds of possible cognitive and memory impairment.[1] Despite the first unsuccessful attempt, MAPS will continue to gather information and reintroduce the issue in the future.[4]
Pharmacologic Implications

Evidence exists of a neuroprotective role of selective serotonin reuptake inhibitors (SSRIs) when taken concomitantly with Ecstasy. Two individuals who had been taking citalopram and paroxetine for trichotillomania for several months reported not having the "rush" when they took Ecstasy at a rave.[23] However, when the second individual stopped taking paroxetine, she did experience euphoria with Ecstasy.

Drug interactions have been reported between Ecstasy and ritonavir, fluoxetine, and monoamine oxidase inhibitors. The drug MDMA is primarily metabolized by CYP2D6, and ritonavir, fluoxetine, and paroxetine are potent inhibitors of this enzyme. When individuals concurrently take Ecstasy and fluoxetine or paroxetine, they may be at risk for acute complications caused by accumulation of Ecstasy. Also, concomitant use of monoamine oxidase inhibitors and Ecstasy places these individuals at risk for serotonin syndrome. Finally, a case of lethality in an individual who took Ecstasy and ritonavir was reported.[3, 7]

Conclusion

Although, MDMA has been available for almost a century, the battle against it has just recently begun. Owing to ethical issues, large-scale prospective studies with human subjects have been prohibited. Therefore, the information gathered so far is useful but not definitive.

The legalization of MDMA for medicinal purposes is controversial. First, although MDMA could induce emotional openness, which is an invaluable tool in psychoanalysis, it poses a risk of flashbacks in victims of rape, child abuse, or posttraumatic stress disorder that could create suicidal ideations in these patients. Second, introducing a drug-naive individual to MDMA might initiate a desire to take Ecstasy and/or other illicit drugs. thus, the line between use and misuse of MDMA is rather blurred.

Further research needs to be conducted to explore whether the long-term cognitive and memory deficits are permanent or partially or fully reversible, and to elucidate the mechanism of action and dosage of SSRIs in blocking the action of Ecstasy. The latter may be promising for the administration of SSRIs in managing Ecstasy dependence and associated neurodegeneration.

Recognizing the elevated abuse (> 500% increase since 1994) and toxic sequelae of Ecstasy, the DEA has substantially increased its operations against Ecstasy trafficking and smuggling, mainly from Western Europe. The DEA also has been active in cleaning up drug use at rave parties.[8] It may be time to increase educational efforts directed toward young adolescents and their parents about the detrimental effects of Ecstasy. Short-term as well as long-term dangers should be emphasized. Equally important are the possible teratogenic effects caused by Ecstasy. This point
is critical because of the increase in teen pregnancies in the last decade and because most women who take ecstasy are of childbearing age. Finally, further clinical research on the effects of MDMA is needed to provide answers to important questions that remain.

References

17. Alciati A, Scaramelli B, Fusi A, Butteri E, Cattaneo ML, Mellado C.
Address reprint requests to Talia Puzantian, Pharm.D., San Francisco General Hospital, 1001 Potrero Avenue, Suite 7M, San Francisco, CA 94110.