CME

Psychopharmacology of MDMA (Ecstasy)

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Interest in 3,4-methylenedioxymethamphetamine (MDMA), better known as Ecstasy, has grown considerably since this drug was last discussed in *Psychiatric Annals*.[1] The use of Ecstasy by adolescents and young adults, generally at raves[2] and in nightclubs and more recently in private settings, is increasing despite accumulating evidence of the dangers of the drug. Although Ecstasy was once thought of as "safe," clinicians are now starting to see consequences of its use by their patients. This article provides an updated review of Ecstasy, including its epidemiology, pharmacology, short-term effects, and delayed and long-term effects.

EPIDEMIOLOGY

Ecstasy was originally developed as an experimental drug by the German division of Merck in 1914. In the 1970s, a small but vocal group of psychotherapists used Ecstasy in their practices, sometimes with their patients to feel more open and connected. They did so until the U.S. Drug Enforcement Agency placed Ecstasy on Schedule I in 1985.[3] Currently, Ecstasy is produced primarily in Europe, with U.S. basement laboratories being a relatively new phenomenon. Unlike some of the other "club drugs" (eg, flunitrazepam [roofies], gamma-hydroxybutyrate [GHB], and ketamine [special K]), which were originally manufactured for legitimate pharmaceutical purposes, Ecstasy production does not involve sterile precautions, quality control, or Food and Drug Administration–like supervision. Basement chemists have occasionally made bad versions of Ecstasy. Some of these chemically related compounds are even more dangerous than Ecstasy. Paramethoxyamphetamine (PMA), a substance sometimes sold as Ecstasy, caused multiple deaths in 2000.

The use of Ecstasy by adolescents and young adults has increased dramatically in recent years. The most recent results of the National Institute of Drug Abuse's Monitoring the Future Study suggest that 3.1% of 8th graders, 5.4% of 10th graders, and 8.2% of 12th graders have used Ecstasy in the past 12 months. Access to the drug has also increased, with 51% of high school seniors reporting that Ecstasy would be easy to get if wanted. The Monitoring the Future Study also found increases in the use of Ecstasy by those in their early to mid 20s. Another survey of teenagers, sponsored by the Partnership for a Drug-Free America, found that, unlike for other substances, the trial use of Ecstasy continues to increase, doubling from 5% in 1995 to 10% in 1999.[4] Another indicator of increased use of Ecstasy is the Drug Abuse Warning Network emergency department reports, which showed significant increases in the mention of Ecstasy between 1994 and 1999. The estimated number of mentions of Ecstasy more than doubled to 2,850 in 1999.[5]

PHARMACOLOGY

The pharmacology of Ecstasy, including its metabolism and pharmacokinetics, has been described in the literature.[2,6,7] Variable metabolism for Ecstasy is likely.[6] The time to maximum plasma concentration is usually approximately 2

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TABLE 1

Short-term Neuropsychiatric Effects of Ecstasy

Anxiety
Depression
Mental fatigue
"Emotional inflation"
Fear
Paranoia
Racing thoughts
Confusion
"Negative self talk"
Irritability
Defensiveness
Decreased libido
Inability to complete the sexual response cycle
Decreased desire to perform physical or mental tasks
Increased obsessiveness
Motor tics
Decreased ability to interact or be open with others
Altered time perception
Panic attacks
Psychosis
Irrational or impulsive behavior

hours after the administration of Ecstasy.[7] The subjective effects of Ecstasy usually emerge 20 to 40 minutes after intake. Often there is a "rush" similar to that experienced with amphetamines and then the effects plateau. The duration of action is approximately 4 hours.[2] A recent study found that the metabolism of Ecstasy shows nonlinear pharmacokinetics.[7] As the dose of Ecstasy is increased, concentrations of it do not rise proportionally.

SHORT-TERM EFFECTS

Subjective Effects

The two most commonly reported acute reinforcing subjective effects of Ecstasy are an intense feeling of attachment and connection to others and highly increased energy.[3] Ecstasy makes some users feel as if they could dance all night or for days at a time, depending on the amount ingested and the frequency of ingestion. Other "pleasurable" acute effects may include peacefulness, euphoria, altered time perception, heightened sensory perception, intensified feelings, and increased desire for sex. This desire often is not fulfilled because Ecstasy can also inhibit the ability to become aroused, reach orgasm, or both.[2] An indirect effect of Ecstasy may be increased risk of sexually transmitted diseases.

Neuropsychiatric Effects

Several short-term neuropsychiatric effects of Ecstasy have been reported.[8] These effects are listed in Table 1. Severe psychosis is the effect for which users are most likely to seek psychiatric care during the acute phase of drug intoxication.[1]

Medical Effects

Ecstasy can produce adverse effects that range from unpleasant to life-threatening and fatal.[2,3,8,9] Unpleasant effects often worsen as dose and frequency increase. The acute medical effects of Ecstasy are presented in Table 2. Side effects may cause an individual to discontinue using the drug or, alternatively, to find methods for managing them (eg, sucking on a baby pacifier to relieve bruxism, dancing until insomnia and restlessness subside, or taking other drugs to counteract these effects). Much more complex and only partially understood are the deadly physiologic changes that can occur with the use of Ecstasy. Fatal and potentially fatal complications are listed in Table 3.

Another area of great concern is acute liver damage following the ingestion of Ecstasy. In a review of patients admitted from 1994 through 1996 to an intensive care unit for acute liver failure, 8% (5 of 62) of the admissions were related to the use of Ecstasy, without evidence of other possible etiologies. For patients younger than 25 years, Ecstasy was the second leading cause of liver failure.[10] An earlier report described 8 cases of acute liver damage related to the ingestion of Ecstasy, with all of the tests for other etiologies having negative results.[9] In all of these cases, there was no correlation between the amount of Ecstasy consumed or the frequency of consumption and the severity of illness. A potentially fatal syndrome of mental status changes, convulsions, autonomic instability, hyperthermia, tachycardia, mydriasis, muscle rigidity, coagulopathy, and rhabdomyolysis has also been described in several cases following the ingestion of Ecstasy.[11]

TABLE 2

Common Short-term Medical Effects of Ecstasy

Nausea
Vomiting
Trismus
Bruxism
Hypertension
Palpitations
Headache
Hyperreflexia
Difficulty walking
Urinary urgency
Diaphoresis
Anorexia
Muscle aches
Muscle tension
Hot flashes
Cold flashes
Nystagmus
Insomnia
Blurred vision
Illusions
Visual hallucinations
Motor tics
Dry mouth
Corneal erosions
Urinary retention
Paresthesias
Fainting
Decreased respiratory rate

Similar to the cases of hepatic injury, in these cases the amount ingested did not correlate with the severity of symptoms.

Etiologies of Short-term Effects

The etiologies of short-term effects are often multifactorial. Factors such as a preexisting condition in the user, hot environment, continuous activity, combining drugs, and changes to the serotonergic system in the brain may all play a role. Researchers continue to study the neurobiology that underlies the effects of Ecstasy. Animal studies have laid the groundwork, and human studies are increasing. Short-term neuropsychiatric effects of the ingestion of Ecstasy appear to be mediated by an acute release of serotonin (5-HT) and a simultaneous blockade of its reuptake in the brain.[12]

TABLE 3

Fatal and Potentially Fatal Short-term Medical Effects of Ecstasy

Pneumomediastinum
Severe chest pain
Seizures
Status epilepticus
Syndrome of inappropriate secretion of antidiuretic hormone
Cardiac arrhythmias
Asystole
Subarachnoid hemorrhage
Cerebral venous sinus thrombosis
Hyperpyrexia
Failure of multiple organ systems
Intracerebral hemorrhage
Liver damage and failure

DELAYED AND LONG-TERM EFFECTS

Delayed Neuropsychiatric Effects

Ecstasy is neurotoxic to both animals and humans. Researchers from a variety of disciplines have documented several neuropsychiatric effects that appear to result from Ecstasy. These effects may persist or new ones may emerge. It appears that Ecstasy can exacerbate existing conditions, contribute to relapse, or actually be responsible for changes that lead to a new condition. Numerous long-term symptoms have been reported (Table 4). Parrott et al. reported increased impulsiveness among heavy users of Ecstasy, who were also significantly more likely than light users and control subjects to have high scores for several psychiatric symptoms (Table 5).[13] The most common conditions for which individuals seek treatment during the chronic phase of drug intoxication are depression, anxiety, and panic attacks.[1] Some Ecstasy-related changes in the brain appear to be permanent.

Long-term Cognitive and Behavioral Changes

Evidence of long-term cognitive and behavioral changes in Ecstasy users is also accumulating. The results of a controlled study of cognitive performance showed that, compared with

TABLE 4

Long-term Symptoms Reported After the Use of Ecstasy

Panic disorder psychosis
Aggressive outbursts
Flashbacks
Major depressive disorder
Suicidal thinking
Memory deficits
Cognitive disturbances
Anxiety and panic attacks
Carbohydrate or chocolate cravings
Sleep disorders
Anorexia
Other eating disorders
Long-term fears

TABLE 5

Psychiatric Symptoms Resulting From Heavy Use of Ecstasy

Depression
Paranoid ideation
Somatization
Psychoticism
Anxiety
Obsessionality
Hostility
Insomnia
Restless sleep
Altered appetite
Phobic anxiety

nonusers, drug-free Ecstasy users had deficits on specific tasks involving sustained attention, complex attention, combined incidental learning, short-term memory, and semantic recognition combined with verbal reasoning.[14]

Etiologies of Delayed and Long-term Effects

Decreased Levels of 5-HT. Studies of rats, guinea pigs, and monkeys given Ecstasy have shown long-term decreases in the levels of 5-HT in their brains. Recent research indicated that anterograde transport of labeled material in ascending 5-HT pathways from raphe nuclei to the forebrain was reduced in rats treated with Ecstasy 2 weeks earlier. The same results were obtained when rats were pretreated with a documented 5-HT neurotoxin, dihydroxytryptamine. Thus, it may be concluded that Ecstasy itself is also a 5-HT neurotoxin.[15]

5-HT Axon Recovery. There is also evidence that 5-HT axons try to recover after the administration of Ecstasy ceases. Sometimes 5-HT axons regenerate, but in an altered pattern. In a 7-year study of monkeys, persistent 5-HT abnormalities were found in their brains. Recovery was noted in some regions; however, in other areas, recovery did not occur or was only partial.[16] A study in which positron emission tomography was used to assess the brains of baboons given Ecstasy provided further evidence of short- and long-term neuroanatomic changes induced by the drug. Nine to 13 months after the administration of Ecstasy, specific regions of the brain, the hypothalamus, and the midbrain showed recovery of transporter density; however, production over baseline also occurred, indicating abnormal recovery.[17]

Long-Lasting Changes in 5-HT. Studies of humans provide further evidence of long-term alterations in 5-HT. Studies in which positron emission tomography was used to compare Ecstasy users who abstained for at least 3 weeks with nonusers showed significantly decreased 5-HT transporter sites in the brains of users that correlated positively with the amount of Ecstasy ingestion and the frequency of ingestion that they reported.[18] Studies in which single photon emission computed tomography was used have revealed a correlation between memory impairment and Ecstasy-related 5-HT neuronal injury.[19]

Changes in Cerebral Blood Flow. Cerebral blood flow also appears to be affected by the use of Ecstasy. The vascular system is partially regulated by 5-HT, with 5-HT having vasoconstrictive effects. In a study of magnetic resonance images of the brain, regional cerebral blood flow was found to be lower in users of Ecstasy than in control subjects.[20] The regions most affected were the parietal and dorsolateral frontal areas, which are related to the serotonergic system. Larger decreases in cerebral blood flow were found in those who had used Ecstasy more recently and in those who had taken higher doses. After periods of abstinence, cerebral blood flow is thought to

potentially recover. Due to postulated aberrantly located or excessive regrowth of serotonergic terminals, cerebral blood flow may even increase over baseline.

In another study, single photon emission computed tomography was used to measure receptor density and dynamic magnetic resonance imaging was used to assess cerebral blood volumes in current and former Ecstasy users and in nonusers.[21] Current Ecstasy users were found to have significantly lower mean cortical receptor binding compared with former Ecstasy users and nonusers, implying that downregulation of 5-HT_{2A} receptors may occur as a compensatory mechanism following massive 5-HT release induced by Ecstasy. Data of the current Ecstasy users showed a significant positive correlation between 5-HT_{2A} receptor binding and regional cerebral blood volume in the globus pallidus and occipital cortex; lower receptor densities were associated with lower blood vessel volumes. Interestingly, the former Ecstasy users were found to have higher receptor densities, possibly due to upregulation of receptors caused by serotonergic depletion after the repeated use of Ecstasy. Furthermore, regional cerebral blood volume was higher in former users, indicating vasodilation. These data provide evidence that Ecstasy affects 5-HT_{2A} receptors and, in turn, cerebral blood vessel volumes.

Effects of Ecstasy When Pretreatments Are Used. Further evidence of 5-HT_{2A} receptor involvement was obtained when healthy humans were pretreated with the 5-HT_2 antagonist ketanserin prior to the administration of Ecstasy.[22] Compared with pretreatment with placebo, pretreatment with ketanserin attenuated several common effects of Ecstasy such as perceptual changes, emotional excitation, and acute adverse responses. Perceptual changes included a moderate intensification of visual, acoustic, and tactile perception and a changed experience of the environment; there were no hallucinations. The effect of ketanserin on emotional excitability is particularly significant given other data indicating that a D_2 antagonist (haloperidol) and a 5-HT reuptake inhibitor (citalopram) did not produce similar changes.[23] Ketanserin did not appear to have a significant effect on positive mood, well-being, and extroversion commonly induced by Ecstasy.

Liechti et al. found that pretreatment with citalopram did reduce several acute psychological effects by approximately 60%. These effects included positive mood, de-realization, depersonalization, thought disorder, and loss of thought and body control. Thus, the 5-HT reuptake site appears to have a significant role in the mechanism of action of Ecstasy.[24]

Autopsy Findings. The results of an autopsy of the brain of an Ecstasy user were described in one report. An analysis of blood and brain tissue revealed that the individual had used Ecstasy just prior to death; a forensic analysis of hair revealed that the individual had used the drug chronically. In the striatum, concentrations of 5-HT and its major metabolite, 5-HIAA, were decreased 50% to 80% compared with those of control subjects. Dopamine and its metabolites were also measured throughout the brain. Dopamine was found to be approximately 47% reduced in the nucleus accumbens, and homovanillic acid, a major dopamine metabolite, was increased by 45% in the putamen.[25]

Abuse of Other Substances. Many individuals who use Ecstasy use other drugs of abuse, such as alcohol, tobacco, marijuana, other club drugs, or all of these. Sometimes it is not clear whether reported effects are the result of Ecstasy, another drug, the frequency of ingestion and the amount ingested, a combination of drugs, or preexisting differences between users. Because both marijuana use and Ecstasy use have been associated with memory impairment, in one study individuals in each of these groups were compared with control subjects who had no history of use of illicit substances.[26] Significant impairment of verbal memory was found for the two groups of drug users. When compared with the other two groups, Ecstasy users had significant impairment of delayed memory.

CONCLUSION

It is clear that Ecstasy has a multitude of acute, delayed, and sometimes permanent adverse effects. Ecstasy can produce a major psychiatric disorder that can persist and can become a lifelong disease in its own right. Although acute tox-

icity is usually medical and can lead to visits to the emergency department and medical crises, different problems emerge over time. Difficulty sleeping through the night, anorexia, fears and phobias, depression, and difficulties thinking and remembering new material can appear after the use of Ecstasy and can persist. These effects can occur during the intoxication phase or may evolve months after use. Persistent depression, memory and learning dysfunction, sleep disorders, anxiety and panic, and eating disorders may soon be linked to Ecstasy-related 5-HT damage in the brain.

For many years, Ecstasy was viewed as safe; however, now we are seeing, as we did with cocaine, that it can be extremely harmful. We do not understand all of the factors that relate to neurotoxic risk, but it does appear that female gender is one such factor due to high levels of estrogen.[27] New research suggests that ascorbic acid may prevent Ecstasy-related brain damage in rats, but it remains to be seen whether the same protective effect exists in humans.[28] Also, it has recently been reported that temperature may affect methamphetamine-induced dopamine neurotoxicity. Hyperthermia is now believed to exacerbate and hypothermia to attenuate dopamine neurotoxic effects.[29] Unfortunately, we still do not know what all of the potential long-term effects might be for current and former users of Ecstasy.

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