

BRIEF REPORT

Lasting Neuropsychiatric Sequelae of (±)Methylenedioxymethamphetamine ('Ecstasy') in Recreational Users

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Two persons are described who demonstrated prolonged neuropsychiatric syndromes after the ingestion of large doses of (±)-3,4-methylenedioxymethamphetamine (MDMA), a recreationally used amphetamine analog. These cases suggest that MDMA, known to be neurotoxic to serotonin neurons in several experimental animals, may also produce untoward effects in humans. In addition, they provide evidence that ingestion of large doses of MDMA can produce lasting adverse functional consequences in vulnerable persons.

(J Clin Psychopharmacol 1991;11:302-305)

"ECSTASY" ((±)-3,4-methylenedioxymethamphetamine [MDMA]), an amphetamine analog used recreationally by humans, has been found to damage CNS serotonin neurons in several experimental animals, including nonhuman primates.¹⁻⁶ Neurotoxic doses of MDMA in the monkey closely approach those typically ingested by humans.⁷ Consequently, there is question whether MDMA damages serotonin neurons in the human brain.⁸⁻¹⁰ Functional consequences of serotonergic neurotoxicity induced by MDMA have yet to be identified, in animals or humans. Given serotonin's implied role in mood, anxiety, sleep, pain, and appetite,¹¹⁻¹⁴ disturbances in these functional spheres might be anticipated. We report on two subjects who provide evidence that

MDMA can produce long-lasting psychiatric disturbance in predisposed persons.

Case 1

An 18-year-old female high school student with a psychiatric history of conduct disorder and major depression presented for neurologic and psychiatric consultations. She complained of persistent anxiety and depression after ingesting 500-700 mg of MDMA.

The patient first experimented with MDMA 2 years before her consultation. At that time, she ingested two MDMA capsules, each containing 100-125 mg of MDMA. These induced a sense of intensified pleasure, garrulousness, and bruxism. Although the overall experience was positive, she noted a brief period during which she felt "panicky," which resolved in minutes without further complication. A second MDMA exposure took place approximately 1 year later, when she again ingested two MDMA capsules. This exposure was also pleasurable and caused her to "crave" more drug to prolong the experience. Her third and final MDMA exposure took place 4 months before her consultations, when she ingested six to seven capsules (600-875 mg) at a party. Acute subjective effects were excitement, a euphoric sense of well being, jaw clenching, colorful visual hallucinations, visual illusions, and later, anxiety and insomnia. For 2 days after MDMA ingestion, she felt fatigued and lethargic, with a depressed mood severe enough to keep her from attending school. The week after MDMA ingestion, her mood became increasingly anxious, and she developed a somatic delusion that "someone was pumping something

Received July 3, 1990 and accepted May 13, 1991.

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through her system." Her anxiety increased to the point of "constant panic," with persistent symptoms of a panic attack (shortness of breath, dizziness, nausea, tachycardia, trembling, diaphoresis, depersonalization, fear of going crazy). These symptoms were present for the majority of her waking hours for approximately 5 weeks. During this time, even when not experiencing panic symptoms, she was never without the sense of impending panic. She was disabled by her symptoms, causing her to quit her part-time job. Although she continued to attend classes, her school performance declined. She withdrew from all social activities, restricting her interactions to those with her boyfriend or her mother. She developed a severely depressed mood, had frequent crying spells, and felt unable to go anywhere unaccompanied. Even at night she was unable to be alone, and began sharing a bed with her mother. Over this 5- to 6-week period she lost 15 pounds, developed insomnia with nightmares, and had feelings that she was losing her mind and would never recover.

Six weeks after her last dose of MDMA, the patient describes what she refers to as her first "normalcy attack," when for the first time since the ingestion of MDMA, she had a discrete 2-hour period without unpleasant psychiatric symptoms. Over the next 3 months, symptoms of panic and depression decreased, and periods of normalcy increased, although panic attacks could be precipitated by thinking about her "MDMA experience," or by traveling near the home where she had taken MDMA. At the time of her psychiatric consultation, approximately 4½ months after her last MDMA ingestion, she was anxious, emotionally labile, and tearful when describing her recent history. She still experienced occasional panic attacks, and reported experiencing one while walking through the halls of the hospital with the consulting neurologist.

As noted above, this patient's psychiatric history was remarkable for conduct disorder from age 13–16. More specifically, after a "model childhood," at age 13 she changed peer groups, to one notorious for disruptive behavior. She experimented with alcohol and numerous street drugs, including marijuana, LSD, PCP, cocaine, opium, and benzodiazepines. In addition, she began to engage in numerous antisocial behaviors, such as shoplifting, on a regular basis. This behavior, although disturbing to her mother, was associated with no lingering psychiatric disturbance. At her mother's request, the patient received regular counseling from her school psychologist for a 3-year period, at which point her behavior improved to a level that was acceptable to both her mother and the psychologist. At age 17, after a break-up with a boyfriend, she became extremely depressed for a 1-month period. During this time, she had chronic fatigue, excessive somnolence, and crying spells. Although she had no

suicidal tendencies, she felt that life was not worth living. These symptoms were accompanied by a decreased appetite and a weight loss of approximately 10 pounds. Her exposure to a toxic dose of MDMA took place 10 months later.

Case 2

A 33-year-old neurolinguist with a history of depression contacted the neurology service to inquire about ongoing studies of MDMA neurotoxicity in humans. He complained of memory disturbance, perceptual distortions, depression, anxiety, and sleep disturbance after ingestion of a large cumulative dose of MDMA.

The patient described a 2½-year period during which he took increasing amounts of MDMA. Initially, the drug had been recommended to him by a friend who felt it would help him communicate. For the first 2 years that he used MDMA, he used it only on weekends, and usually at a dose between 0.2 and 0.3 g per weekend. With this use pattern, he found its effects to be beneficial. In particular, he noticed that two to three capsules helped him empathize with others and put him at ease in social situations. He indicated that these skills persisted even when not under the acute influence of the drug, and noted that several coworkers complimented him on his improvement professionally. During this 2½-year period, the only problem he associated with MDMA was the development of occasional word-finding difficulties.

Two years after first using MDMA, the patient lost his job, secondary to company lay-offs. In an attempt to self-medicate for depression over this loss, he began to enjoy "getting lost in the MDMA experience" for its own sake. He deliberately "chased the high," taking increasingly larger doses, (approximately 0.4–0.6 g per weekend). At these doses, he had difficulty getting along with his friends and began to note "cognitive problems." Specifically, he noted marked perseveration, and that he frequently repeated his own words as well as those of others. Despite these symptoms, he continued to increase his consumption of MDMA. His last MDMA dose, which caused him to cease further use, was followed by persistent cognitive and psychiatric disturbance. This last exposure was over a 2-day period, during which he consumed a total of 1 g of MDMA, in combination with hallucinogenic mushrooms. On the first day, the experience was pleasant. On the second day, he began to have unpleasant visual illusions, burning myalgias, and very poor long- and short-term recall.

Over the next 8 months, despite total cessation of MDMA use, he had hallucinations of "whispering, rushing feelings bordering on sound," visual and auditory perceptual distortions, extremely poor long- and short-term memory (he was unable to remember his mother's name

on one occasion), severe insomnia, and a persistent, severe frontal headache. He also developed cravings for foods high in carbohydrate content. He felt paranoid and anxious, and frequently sensed that he recognized persons that he had never met before (for example, he once was certain that a stranger on the street was his brother).

After unsuccessful treatment with amitriptyline, 75 mg/day for 18 months, his internist switched him to fluoxetine, 20 mg/day, which was later increased to 40 mg/day. During his first week on fluoxetine, he recalls feeling "restored." In a follow-up interview approximately 2 years after his MDMA ingestion, the patient reported that his internist had suggested that he discontinue fluoxetine, as side effects of long-term treatment were not known. Within 1 month of drug discontinuation, he developed recurrent symptoms of dysthymia. He saw a psychiatrist, who re-initiated fluoxetine treatment, which was successful in reversing his symptoms over a 1-month period. He continues to take fluoxetine, 40 mg/day orally, and has no psychiatric complaints.

As noted above, this patient's psychiatric history was remarkable for depression. Specifically, he recalls feeling chronically depressed, with symptoms of chronic fatigue and various somatic complaints, during college and graduate school. He viewed life with "grim acceptance," as something that must be endured. He constantly felt as though he was "spinning his wheels," and had an "irrational resentment" for those around him. Although not recognized at the time, the patient now feels that he had major depression during at least part of this period, and chronic dysthymia when not depressed. His drug history before using MDMA was remarkable for marijuana use, one to two times per month since age 16 and LSD use two times per year during the same period. This drug use was not associated with lasting psychiatric disturbance.

Discussion

To our knowledge, there are no published reports of persistent neurobehavioral disturbance after MDMA ingestion. Whitaker-Azmitia and Aronson¹⁵ reported three cases of MDMA-induced panic after acute ingestion of MDMA. These cases, however, were short-lived and occurred only while the persons were under the drug's influence. The case studies presented here suggest that MDMA taken in high doses by susceptible persons can cause lasting dysfunction in behavioral domains thought to be modulated by CNS serotonin. Whether this dysfunction is secondary to serotonergic damage is not clear, but deserves further investigation.

One aspect of these case reports is notable. The fact that both of these people showed evidence of vulnerability to psychiatric disturbance before their use of MDMA

may point to an important factor in their subsequent development of MDMA-related neuropsychiatric syndromes. Indeed, given the reported popularity of MDMA,¹⁶ it is remarkable that there have been no previous reports of long-lasting adverse consequences of drug ingestion. It is possible that persons with fragile homeostatic neurotransmitter balance are most vulnerable to the negative behavioral consequences of MDMA neurotoxicity. Psychologically stable persons may enjoy a resiliency to neurochemical insult that those with a more fragile neurotransmitter milieu do not. In this regard, it is of interest to note that LSD, another serotonin-active drug, also had a propensity to cause lasting psychiatric disturbance in those with family histories of psychiatric problems.^{17, 18}

It could be argued that the two people reported upon here were psychiatrically unstable and might have developed their neuropsychiatric syndromes spontaneously, in the absence of MDMA exposure. Given the temporal relationship of both syndromes to the ingestion of large doses of MDMA, this is less likely. In case 1, it is also noteworthy that the patient had experienced a panic attack on a previous occasion, after the ingestion of MDMA. Furthermore, the time course of both syndromes and the variety of symptoms experienced by these patients would be atypical for idiopathic forms of psychiatric illnesses, such as depression and panic disorder.

Another common feature in both of the cases reported here is that MDMA was experienced as a highly reinforcing agent. This property led one to "chase the high," and the other to "have a craving" for MDMA. Such potent reinforcing properties are shared by other amphetamine analogs (e.g., methamphetamine ["speed"]), and are thought to be mediated by central dopamine systems. The combination of a potent reinforcing action and serotonin neurotoxic potential could be hazardous to those with a vulnerability to psychiatric illness.

Although the neurotoxic potential of MDMA in humans is not clear, there is neurochemical and anatomic evidence in several animal species that MDMA damages central serotonin neurons.¹⁻⁵ In rodents, it appears that structural damage is restricted to serotonin nerve terminals, and recovers over time, whereas recent evidence in the nonhuman primate indicates that MDMA can produce cell body damage and can produce lasting depletions of CNS serotonin.⁶ These findings raise the concern that when given in sufficiently high doses, MDMA may also produce lasting depletions of serotonin in humans.^{5, 19} Viewing the above cases in this light, there are at least three possible explanations for their gradual recovery over time. First, compensatory metabolic changes taking place within residual serotonin systems could underlie reversal of behavioral deficits. Alternatively, recovery could be related to regeneration of damaged serotonergic axons.^{20, 21} Fi-

nally, it is possible that nonserotonergic CNS systems compensate for serotonin deficits and that other CNS systems account for the observed improvement in neuropsychiatric symptoms.

As noted previously, serotonin is thought to play a role in a number of abnormalities in behavioral functions. Specifically, serotonergic imbalance has been postulated to underlie several psychiatric disorders, including depression, anxiety, panic disorder, and disorders of impulse control.^{11, 22-24} The cases reported here lend support to this view because MDMA is known to perturb serotonin systems. Whether the neuropsychiatric syndromes in these two people represent manifestations of CNS serotonin neurotoxicity is not certain. Unfortunately, current studies of the function of serotonin in the living human brain are limited to indirect measurements, such as cerebrospinal fluid 5-hydroxyindoleacetic acid concentrations and neuroendocrine challenges. Retrospective case reports such as those reported here underscore the importance of developing more direct methods for assessing serotonin function (e.g., positron emission tomography). Such methods would be useful in the detection of neurotoxicity and would also serve to increase knowledge regarding the role of serotonin in human behavior, in both health and disease.

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