MDMA ("Ecstasy") Abuse: Psychopathological Features and Craving for Chocolate: A Case Series

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Introduction

The amphetamine analog 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") is a drug of abuse which combines the effects of amphetamines and lysergic acid diethylamide (LSD). MDMA has become increasingly popular in northern Italy, but its use has been associated with lasting adverse neuropsychiatric sequelae in humans who have taken repeated doses (and in one case even after a single dose; McCann and Ricaurte 1992). These adverse effects include anxiety, panic attacks, insomnia, flashbacks, chronic psychoses (McGuire and Fahy 1991), recurrent acute paranoid psychosis, cognitive abnormalities, and depression with suicidal behavior (Benazzi and Mazzoli 1991; Creighton et al 1991; McCann and Ricaurte 1991; Pallanti and Mazzi 1992; Krystal and Price 1992). It has been suggested (Henry 1992) that it will take many years to understand fully the real contribution of MDMA abuse to the onset of psychiatric disturbances. In the last 24 months, 50 consecutive MDMA abusers presented to the Addiction Treatment Unit in Padova and one or more of the above-described psychopathological features were found in 16 of them (data not shown here; Schifano 1994). The present report focuses on seven patients (one has been the subject of another communication; Schifano 1991) whose psychopathological disturbances included a craving for chocolate (a symptom which, to the best of our knowledge, had not been observed previously in MDMA abusers).

Case 1

A 24-year-old man had been taking what he believed to be MDMA for 4 years and reported using it about 150 times. The typical daily dose was 200 mg (about 2.8 mg/kg BW), at intervals ranging from 1–14 days. He reported sporadic use of other drugs (alcohol, benzodiazepines, cannabis, cocaine). His family psychiatric history was negative. He had not complained of any psychological disturbances until starting to use MDMA, but in the last 3 years he had suffered from paranoid delusions (he was convinced he was being stared at and ridiculed by people when he went out of doors). He also suffered from high levels of anxiety; delusions of bodily change (he believed his brain had been stolen, his eyes were not his own); changes of mood (which never met DSM-III-R diagnostic criteria for an affective disorder); inverted sleeping-waking patterns; aggressive outbursts; and loss of appetite accompanied by striking weight loss (10 kg) despite no dieting (his original weight was 70 kg). Over the last 2 years, for the first time in his life, he had been having intermittent episodes of craving for foods containing chocolate; the frequent, usually twice-weekly, chocolate binge-eating episodes were associated with loss of appetite for other foods. During such episodes, he would ingest an estimated 1500 kcal. The patient was unable to explain why this happened; he had no history of bulimic episodes, and there was no clear temporal relationship between his MDMA intake and binge-eating episodes. Routine blood tests and computed tomography (CT) of the brain were normal. A chronic, atypical psychosis was diagnosed according to DSM-III-R criteria. Neuroleptic therapy (haloperidol and promazine) was only partially beneficial.

Case 2

A 24-year-old man was referred to us 30 months after suspending MDMA, which he had taken for two 20-day periods, with a drug-free interval of 6 months. During these periods, he took what he believed to be MDMA every day or every other day, at a daily dose of 200–600 mg (about 2.6–7.9 mg/kg BW). He also reported sporadic use of cannabis prior to using MDMA. His family psychiatric history was negative. He had not complained of any psychological disturbances before using MDMA (this was confirmed by

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his parents) but, after the second period of MDMA intake, he gradually began to show depressive and/or dysphoric moods, difficulty in concentrating, recurrent thoughts of death, markedly diminished interest in almost all activities, hypersomnia alternating with insomnia, inverted sleeping-waking patterns, depersonalization, derealization, emotional overreaction to rejection, loss of interpersonal relationships, and severely impaired academic results (he was attending a university). For the first time in his life, he complained of several episodes of being afraid of losing his mind, together with nausea, ataxia, vertigo, fear of imminent death, tachycardia, hyperventilation. A panic disorder (without agoraphobia) was diagnosed, according to DSM-III-R criteria. A striking weight loss was observed (12 kg) despite no dieting, together with several reported episodes of craving for chocolate. A typical binge-eating episode was characterized by the ingestion of 30–40 chocolates (corresponding to about 1500–2000 kcal) within 20–30 minutes. He also showed loss of appetite or desire for other foods. He had never had bulimic episodes. Routine blood tests, EEG, and computed tomography (CT) of the brain were normal. A major depressive episode was diagnosed according to DSM-III-R criteria (scoring 32 on the Hamilton Depression Scale) with clearly atypical features. Fluoxetine therapy (60 mg/day) was implemented, with remission of all symptoms. After 6 months, the patient spontaneously suspended the medication ("I felt OK") but, after 20 days, the above-described features recurred (especially the depressive symptoms and cognitive disturbances). Fluoxetine therapy was begun, with remission of the psychopathological disturbances; the patient is still receiving treatment.

Case 3

A 28-year-old man had taken what he believed to be MDMA for 4 months up until 6 months prior to presentation; he reported using it on about 20 occasions. The typical daily dose was 300 mg (about 4.8 mg/kg BW) at intervals of 5–7 days. He also reported using opiates. His family psychiatric history was negative. He had not complained of any psychological disturbances until suspending the use of MDMA, however, in the last 6 months, he had suffered from changes of mood (which never met DSM-III-R criteria for an affective disorder), and he had ideas of reference of psychotic proportions (e.g., that others were taking particular notice of him) when he went out of doors, such meeting the DSM-III-R criteria for an atypical psychosis. In the last 4 months, though he had no history of bulimic episodes, he had been having intermittent episodes of craving for foods containing chocolate; several binges with chocolate (on average, once a week) were reported. On each occasion, he would ingest an estimated 1700 kcal. He showed no loss of appetite and he had not lost weight. Since he has recently "switched" to opiates, he has been administered methadone (together with antipsychotic medications).

Case 4

A 28-year-old man had been taking what he believed to be MDMA for 5 months, up until 6 months prior to presentation, and he reported using it on about 20 occasions. The typical daily dose was 250 mg (about 2.98 mg/kg BW), at intervals of 6–7 days. He also reported use of opiates, tetrahydrocannabinols, and alcohol. His family psychiatric history was negative. He showed no psychological suffering before suspending the use of MDMA, but he subsequently became gradually convinced that he was being stared at and ridiculed by people when he went out of doors; this was observed together with mnemic disturbances and a diminished ability to concentrate. Since the ideas of reference were of psychotic proportions, an atypical psychosis was diagnosed (according to DSM-III-R criteria); antipsychotic treatment was begun, with some beneficial effects. There were no bulimic episodes or eating preferences in his personal history but he had recently shown a strong craving for carbohydrates (and chocolate in particular), leading to a few (about 10 in 3 months) binge-eating episodes (during which he would ingest an estimated 1200 kcal of chocolate sweets). He is now attending a residential program in a therapeutic community.

Case 5

A 22-year-old man had been taking what he believed to be MDMA for 4 years, up until 15 days prior to presentation; he reported using it on about 35 occasions. The typical daily dose was 250 mg (about 3.7 mg/kg BW), at intervals ranging from 1–90 days. He also reported using other drugs (opiates, tetrahydrocannabinols). His family psychiatric history was negative. He had shown no psychological disturbances up until 8 months prior to our observation, when he had begun to suffer from depersonalization and derealization. In the last 5 months, a delusion had become evident: he was convinced that he was being stared at and ridiculed by people when he went out of doors. An atypical psychosis was diagnosed (according to DSM-III-R criteria), but a trial with antipsychotic medication produced poor results. In the last 4 months, he had lost 14 kg (his prior weight was 81 kg) due to a severe loss of appetite or desire for food together with a strong craving for chocolate (especially plain chocolate), with several binge-eating episodes (at least 12 in 2 months). He had never had this kind of eating habit previously. On each occasion, he ingested an estimated 1000 kcal of chocolate sweets and cakes. In the past months, a major depression (diagnosis being made according to DSM-III-R criteria) has become evident (the Hamilton Depression Scale score was 24), and the patient has been hospitalized.

Case 6

A 20-year-old woman had been taking what she believed to be MDMA for 1 year, up until 1 year prior to presentation, and reported using it on about 45 occasions. The typical daily dose was 150 mg (about 2.7 mg/kg BW), at intervals of 7 days. She also reported using other psychoactive substances (alcohol, tetrahydrocannabinols). Her family history was negative. She had shown no psychological disturbances up until 11 months previously, when she became convinced that she was being stared at and ridiculed by people when she attended disco-parties. In the past 3 months, she has shown depressive mood, recurrent thoughts of death, insomnia, anger, irritability, and difficulty in concentrating. She scored 28 on the Hamilton Depression Scale. In the same period, she has shown a strong craving for carbohydrates associated with a loss of

appetite or desire for other foods. She reported excessive consumption (corresponding to an estimated 500 kcal/day) of chocolate sweets and cakes. She has just been assessed, and a major depressive episode has been diagnosed according to DSM-III-R criteria; a trial with antidepressants is being implemented.

Case 7

A 23-year-old man was referred to us 24 months after having suspended ecstasy tablets, which he had taken for two periods, with a drug-free interval of 2 years. In the first period, which lasted 2 years, he took what he believed to be MDMA at a daily dose of about 600–1500 mg (about 12.8–32.0 mg/kg BW) at intervals ranging from 2–15 days. After the drug-free period of 24 months (when he had been charged with illegal possession of high quantities of MDMA), he took about 200 MDMA tablets (in a time-span of a few months), arriving at a total estimated amount of 2000 MDMA tablets ingested in his life-time. He also reported sporadic use of benzodiazepines and opiates. His family psychiatric history was negative. He had not complained of any psychological disturbances before using MDMA (this was confirmed by his parents), but, after the first period of MDMA intake, he gradually began to show depressive moods, difficulty in concentrating, recurrent suicidal thoughts, insomnia, irritability and outbursts of temper, and severely impaired academics results (he was attending a high school). For the first time in his life, he complained of several episodes of being afraid of losing his mind, together with dizziness, fear of imminent death, tachycardia, and hyperventilation. He was also convinced that he was being ridiculed by people when he attended public places. In the last 4 years, a slight tremor (especially at the extremities) had become evident and, for 2 years after the first MDMA intake, a few flashbacks occurred. During the first MDMA intake, the patient suffered from loss of appetite, accompanied by striking weight loss (11 kg) despite no dieting. On the other hand, over the last 2 years, for the first time in his life, he has been having intermittent episodes of craving for carbohydrates, especially foods containing chocolate. During the frequent, usually twice weekly, chocolate binge-eating episodes, he would ingest an estimated amount of 1000 kcal. The patient has just been referred to us; the results of blood tests and neurological examination are not known at the time of this writing. Both a major depressive disorder and a panic disorder (without agoraphobia) have been diagnosed, according to DSM-III-R criteria. A fluoxetine therapy has just begun, together with methadone administration (since he has recently "switched" to opiates).

Comment

One might question the reliability of these patients' reported drug use; i.e. whether it was really MDMA that the patients took and how the dosage of ecstasy had been estimated. In the United Kingdom, most tablets sold as ecstasy contain MDMA as the active ingredient, but some contain LSD, amphetamine sulfate, or methylenedioxyamphetamine (MDA, the major metabolite of MDMA) (Woods and Henry 1992). However, sources from local forensic toxicological laboratories suggest that about 90% of "ecstasy" tablets seized in this area of Italy contain MDMA as the active ingredient, at a dosage of 100–150 mg per tablet, thus confirming other reports (Solowij 1992). MDA is usually found in the remaining 10% of tablets, though methylenedioxyethamphetamine (MDEA), a drug with effects similar to those of MDMA (Dowling et al 1987), has occasionally been observed.

In animals, including primates, MDMA causes initial release of serotonin (5-HT) followed by degeneration of 5-HT projections; the fine axons of dorsal raphe, associated with 5-HT_2 receptors, are especially vulnerable. Neurotoxic effects depend on the release of dopamine induced by MDMA. While it is not clear why this concomitant effect is necessary to produce 5-HT degeneration, it has been demonstrated that drugs interfering with dopamine release can prevent or reduce the effects of MDMA on the 5-HT system (Stone et al 1988; Cowen 1991). The lowest effective dose of MDMA capable of producing a long-term depletion of cortical 5-HT in primates is 2.5 mg/kg (Finnegan and Schuster 1989). The concentration of 5-HIAA (the metabolite of 5-HT) in lumbar cerebrospinal fluid (CSF) is substantially lower (Ricaurte et al 1990) and serum prolactin response to L-tryptophan challenge is blunted (Price et al 1989) in people with a history of MDMA use. It may be that the various psychopathological features observed were expedited by lasting or intensive use of MDMA and/or by sporadic use of other drugs, but we feel that MDMA may have induced the clinical syndromes described "de novo" (possibly via dopaminergic and/or serotonergic pathways). In this sense, since the psychiatric symptoms observed were all subsequent to the ingestion of MDMA, according to DSM-III-R criteria, the major disorders observed in this case series (depressive episodes, panic disorders, atypical psychoses) could be more suitably diagnosed as organic mental disorders (respectively: organic mood disorders, organic anxiety disorders, organic delusional disorders).

The psychopathological features that we have described (Table 1) are generally consistent with the findings of most authors (for a review, see Henry 1992), with the possible exception of the presence of depressive symptoms. In fact, Krystal et al (1992) described nine individuals with lengthy histories of MDMA abuse, none of whom met the clinical criteria for an affective disorder at the time of testing. The reason for the possible incongruence between the present series (four major depressive cases among seven patients) and Krystal's report may lie in the small numbers involved in both studies and in the possible differences in recruitment methods. Our patients were selected, as already mentioned, from a consecutive series of outpatients who presented spontaneously at the Public Health Unit with problems that they perceived to be linked in some way to their chronic MDMA use; so, to some extent, this sample should be considered "biased" by the severity of the disturbances. Nonetheless, other authors (Peroutka et al 1988) found depression to be one of the most frequent subacute symptoms (21%) after MDMA use in a series of 100 recreational users. We have been intrigued by the presence of the "fear of being ridiculed" symptom described in all cases except case 2. The symptom was of psychotic proportions in cases 1, 3, 4, and 5 (such as described elsewhere; McGuire and Fahy 1991). In cases 6 and 7, however, this psychopathological feature was neither psychotic nor a mood-congruent part of depression. Consequently, although the patients showed no avoidant behavior interfering with their usual activities, the clinical picture may resemble, at least to some extent, the DSM-III-R description of social phobia. If confirmed

Table 1. Succinct Clinical Data of 7 MDMA Abusers Who Showed Different Psychiatric Complications

Case	Age/Sex	Typical daily dose in mg/kg BW (interval in days between MDMA administrations)	Estimated cumulative No. of ingested MDMA tablets	Psychopathological features	Weight Change
1	24/M	2.8 (1–14)	150	aggressive outbursts, atypical psychosis, chocolate craving	lost 10 kg
2	24/M	2.6–7.9 (1–2)	50	major depression, panic disorder, cognitive disturbances, chocolate craving	lost 12 kg
3	28/M	4.8 (5–7)	40	atypical psychosis, chocolate craving	/
4	28/M	2.98 (6–7)	65	atypical psychosis, cognitive disturbances, carbohydrate + chocolate craving	/
5	22/M	3.7 (1–90)	40	atypical psychosis, major depression, chocolate craving	lost 14 kg
6	20/F	2.7 (7)	45	major depression, "fear of being riduculed," cognitive disturbances, carbohydrate + chocolate craving	/
7	23/M	12.8–32 (1–15)	2000	major depression, cognitive disturbances, outbursts of temper, panic disorder "fear of being ridiculed," tremor, flashbacks, carbohydrate + chocolate craving	lost 11 kg

MDMA = 3, 4-methylenedioxymethamphetamine ("ecstasy").

by future studies, these data are possibly relevant to the pathophysiology of this clinical syndrome.

It is worth noting that all seven patients in this series showed striking changes in appetite and food preferences. A decreased central 5-HT function may contribute to the onset or persistence of binge-eating episodes in patients with bulimia nervosa, including low-weight anorexic patients with bulimic symptoms (Jimerson et al 1990); binge frequency is inversely correlated with serum prolactin response to the serotonergic agent m-chlorophenylpiperazine (mCPP) (Brewerton et al 1992). The ingestion of carbohydrates (especially chocolate; Apfeldorfer 1991) has been shown to selectively increase tryptophan uptake by the brain and consequently to increase CNS levels of 5-HT (Kaye et al 1984); it may be that eating chocolate was an attempt to raise brain 5-HT and was therefore a form of self-medication. This view is supported by findings in animals: drugs which increase 5-HT at postsynaptic receptors cause a reduced carbohydrate intake; 8-OH-DPAT (which decreases 5-HT at these sites) has the opposite effect, increasing carbohydrate intake in rats presented with a choice between carbohydrates and proteins (Curzon 1990). Together with selective binge-eating behavior, our patients generally presented with decreased appetite and weight loss, frequently with major depression. A possible causal relationship between the mood disturbances and the loss of both appetite and weight cannot be overruled; however, the amphetamine-like, appetite-suppressant properties of MDMA (Krystal et al 1992) could also be responsible for such symptoms, which helps to explain why these patients showed weight loss instead of weight gain together with their binge-eating behavior. In fact, a central 5-HT deficiency would be expected to result in decreased postingestion sense of repletion and weight gain (Jimerson et al 1990; Samanin and Garattini 1989). It is more difficult to understand why these patients tended to show a specific preference for chocolate rather than for a wider range of high-carbohydrate binge foods (found only in patients 4, 6, and 7), as might be expected with a deficiency in central 5-HT. Some speculative explanations for this particular eating attitude may lie in the fact that, apart from tryptophan, chocolate is high in phenylalanine and tyrosine, both of which are norepinephrine (NE) and dopamine (DA) precursors (Koch et al 1987). DA system toxicity is not found in MDMA-treated animals (Seiden 1990), and one could argue that any increase in CNS dopamine due to binge-eating episodes may, at best, have contributed to the pleasure linked with the ingestion of chocolate (central DA activity may play a role in abnormal hedonistic reactions to food; Jimerson et al 1992). As for the possible role of an increased NE after ingesting chocolate, it has been suggested that bulimic patients have a decreased sympathetic nervous system activity (Jimerson et al 1987).

Lastly, chocolate also contains phenylethylamine (one of the endogenous amines with amphetamine-like properties; Preziosi 1992) and theobromine (a caffeine-like substance), which might be useful in these patients in counteracting their blunted effect.

Though the link between MDMA and the psychopathological picture described in our series is somewhat speculative (given that these are only anecdotal clinical observations), these findings nonetheless raise serious doubts as to the image (in Italy, at least) of MDMA as a "safe" drug. The potential implications of our observations are obvious and deserve further study.

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