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DRUG EXPERIENCE

Drug Safety 1996 Aug; 15 (2): 107-115
0114-5916/96/0008-0107/$04.50/0

Adverse Reactions with 3,4-Methylenedioxymethamphetamine (MDMA; 'Ecstasy')

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Contents

Summary

3,4-Methylenedioxymethamphetamine (MDMA; 'ecstasy') is an increasingly popular recreational drug in the US, Western Europe and Australia. In animals, including nonhuman primates, MDMA is known to damage brain serotonin (5-hydroxytryptamine; 5-HT) neurons. It is not known whether MDMA damages serotonin neurons in the human brain but there is some indication that it may. Although the large majority of individuals who have used MDMA recreationally do not develop acute complications, as the popularity of MDMA has increased, so have reports of adverse nonpsychiatric and psychiatric consequences associated with use of the drug. Further, since manifestations of MDMA-induced serotonin injury might only become apparent with age, or under periods of stress, it is possible that some individuals with no apparent abnormalities might develop complications over time.

3,4-Methylenedioxymethamphetamine (MDMA; 'ecstasy') is an amphetamine derivative that has gained significant popularity as a recreational drug in recent years. Though generally regarded as a relatively safe recreational drug, it has become increasingly apparent that MDMA use can be associated with adverse effects. The purpose of this manuscript is to review the English language medical literature regarding complications of MDMA use. To this end, a Medline search was performed, including publications from the years 1980 to 1995, restricting the search to articles in English

that mentioned both MDMA and humans. Further, in an effort to retrieve more recent publications, a similar literature search was performed using Current Contents (ISI, California) for the 3-month period previous to November 1995.

1. 3,4-Methylenedioxymethamphetamine (MDMA; 'Ecstasy') as a Drug of Abuse

Although originally synthesised in 1914, it was not until the late 1970s that MDMA first received attention in professional circles and in the illicit drug market. At that time, MDMA was advocated by some health professionals as a potentially useful medicinal adjunct to psychotherapy.[1-3] Shortly thereafter, some members of the general public began to use MDMA purely for its pleasurable subjective effects, and its use began to increase on the recreational drug scene.

In 1985, the US Drug Enforcement Administration (DEA) placed MDMA on Schedule I of Controlled Substances on an emergent basis.[4] This action was taken based on the perception that the popularity of MDMA was increasing, and also because a closely related drug, 3,4-methylenedioxyamphetamine (MDA), had been found to damage brain cells containing serotonin (5-hydroxytryptamine; 5-HT) in experimental animals.[5] Despite its Schedule I status, the use of MDMA has continued to rise, with particularly dramatic increases in use noted over the last 5 years, in the context of social gatherings known as 'raves' (all-night events attended by hundreds to thousands of party goers who dance to laser light shows and music known as 'techno' or 'house music').[6,7]

Since the arrival of the rave phenomenon, a new pattern of MDMA use has emerged. In particular, previously MDMA abusers typically reported ingesting doses of 75 to 150mg (1 to 2 tablets) once or twice per weekend, and no more often than twice monthly. However, in the setting of raves, it is not uncommon for an individual to take up to 8 MDMA tablets or capsules in one night, once a week.

Like its close structural relative MDA,[5] MDMA has been found to damage serotonin neurons in all experimental animals tested to date.[8-19] Further, in nonhuman primates, the neurotoxic properties of MDMA are more potent than those seen in rodents.[15] Since the neurotoxic dose of MDMA in primates is close to the dose used by humans (particularly when used, as described above, during raves),[20] there is concern that human MDMA users are at risk of serotonin neurotoxicity. Because serotonin neurotoxicity is difficult to diagnose in living humans, researchers who have tried to determine whether MDMA users have incurred serotonin neurotoxicity have had to rely on indirect measures such as assessments of serotonin metabolites in CSF[21] and evaluation of behavioural functions that are thought to be modulated by brain serotonin systems, such as sleep, impulse control and pain. Although it is far from clear whether or not MDMA damages brain serotonin neurons in humans, evidence from the one controlled study of MDMA abusers[22] suggests that MDMA may have this effect. Further, as will be discussed in detail in section 3, emerging data from case reports around the globe also indicate that MDMA can lead to neuropsychiatric difficulties, some of which may be secondary to neurotoxicity.

For years, MDMA had the reputation of being a 'safe' drug, despite strong evidence in animals documenting its neurotoxic potential.[23,24] Indeed, given the large numbers of individuals who have used MDMA, it is striking that relatively little is known about its complications and adverse effects. Nevertheless, as the numbers of MDMA abusers have increased in recent years, so have reports of potential hazards of MDMA use. Taken in isolation, individual case studies might be perceived as anecdotal and can therefore be ignored or trivialised. However, taken together it is difficult to ignore the accumulating evidence that there are clear patterns of MDMA-related complications, some of which lead to a fatal outcome.

As indicated above, this paper reviews the English language medical literature regarding adverse effects of MDMA. For simplicity, MDMA-related complications have been categorised in sections 2 and 3 according to whether they occur and remit

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within 48 hours of MDMA ingestion (i.e. acute complications) or whether they persist beyond the 48-hour post-ingestion period (i.e. chronic complications). Further, within each category, complications are classified as either nonpsychiatric adverse effects (e.g. hepatitis) or psychiatric adverse effects (e.g. anxiety).

2. Acute Complications of MDMA

2.1 General Medical Adverse Effects

Before 1985, when MDMA was placed on Schedule I of Controlled Substances in the US, 2 prospective studies evaluated the effects of MDMA in a total of 50 healthy volunteers.[24,25] Study participants received single doses of MDMA ranging between 1.75 and 4.18 mg/kg in one study,[24] and doses between 75mg and 300mg in the second study.[25] Acute effects of MDMA reported that might be perceived as unwanted or unpleasant included nausea, vomiting, jaw clenching (trismus), teeth grinding (bruxism), hypertension, palpitations, headaches, hyperreflexia, difficulty walking, urinary urgency, diaphoresis, anorexia, muscle aches or tension, hot and cold flashes, jittery vision (nystagmus) and insomnia.

Three retrospective surveys of the effects of MDMA have also been conducted in a total of 265 individuals who reported having used MDMA.[26-28] The range of adverse effects seen in these studies was similar to those reported by in the two prospective studies;[24,25] however' several complications were reported in the retrospective studies that were not reported in the prospective studies. These additional complications included paraesthesias, dry mouth, motor tics, visual illusions or hallucinations, blurred vision, fainting and decreased respiration. Of interest, in one of the studies[28] only 5% of survey respondents who experienced MDMA-related adverse effects had ever sought medical attention for them.

Data regarding acute medical complications of MDMA use have also accumulated in the form of case reports, reports from poison centres and medical coroners. Although some of these complications were readily treatable, a number of them led to death, even with aggressive treatment in a medical setting. Serious, but treatable, complications of MDMA use that have been reported include corneal erosions secondary to prolonged corneal exposure,[29] urinary retention due to the α-adrenergic properties of MDMA,[30] pneumomediastinum secondary to severe vomiting,[31] and severe chest pain secondary to intercostal muscle spasm.[32] Three cases of acute seizures have been reported in individuals who developed hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) following MDMA ingestion.[33,34] All 3 individuals recovered after receiving medical attention. A potentially fatal case was reported in a 13-month-old child, who developed status epilepticus after accidental ingestion of 1 tablet of MDMA (probably between 75 and 125mg).[35] The child survived the incident due to aggressive inpatient medical care.

As indicated in section 1, several individuals who have developed acute MDMA-related medical complications have not survived. Fatal acute complications of MDMA have been secondary to cardiac abnormalities, massive neurological disturbances and multiple organ system failure. Each of these will be discussed in turn.

2.1.1 Cardiac Adverse Effects

Cardiac adverse effects reported following MDMA use have included fatal arrhythmias and asystole,[36,37] and cardiovascular collapse;[38] 13 fatalities were recorded in these 3 reports. MDMA can exacerbate the risk of fatal arrhythmias in patients with pre-existing cardiac conditions such as the Wolff-Parkinson-White syndrome. Exacerbation of fatal arrhythmias in a patient with Wolff-Parkinson-White syndrome appeared to be the cause of 1 of the deaths due to cardiac complications reported to date.[38] In the other fatal cases, however,[36,37] MDMA is thought to have induced *de novo* arrhythmias, although some of the individuals who died had also been taking other psychoactive drugs.

2.1.2 Neurological Adverse Effects

MDMA, like other amphetamines, can lead to fatal neurological events. Types of potentially fatal neurological sequelae reported following MDMA use include subarachnoid haemorrhage,[39] intracranial haemorrhage or cerebral infarction[40-44] and cerebral venous sinus thrombosis.[45] There are at least 3 mechanisms by which MDMA might lead to haemorrhage and thrombosis. In some cases, MDMA could potentially lead to short term hypertensive surges and subsequently to disruption of cerebral blood vessels. This would be particularly dangerous in individuals with congenital arteriovenous malformations or cerebral angiomas.[39,42] Alternatively, cerebral angiitis (inflammation of the cranial blood vessels) is a well documented, though poorly understood, complication of amphetamine exposure, and it is possible that MDMA can also produce angiitis with subsequent thrombosis or haemorrhage. Finally, as will be described in section 2.1.3, individuals who use MDMA while engaging in strenuous physical activity can easily become dehydrated. In cases of severe dehydration, development of cerebral thromboses is possible.

There has only been one MDMA-related fatality in which neuropathological findings have been reported.[46] In that case, a 30-year-old man ingested MDMA in combination with diamorphine (heroin) and amphetamine and subsequently alcohol (ethanol) while he was at a rave. The man was found unconscious, and later he had a seizure and became comatose. He died 5 weeks later, having never gained consciousness. On neuropathological examination, he was found to have bilateral necrosis of the globus pallidus, as well as focal necrosis of brain white matter. Because this patient had ingested several drugs prior to his neurological event, it is difficult to know whether these brain abnormalities were secondary to MDMA in particular or whether the other drugs used by the patient and/or his complicated medical course played a role in the neuropathological findings.

2.1.3. Multiorgan Syndrome

One complication of MDMA appears to be much more prevalent in the setting of raves or crowded dance clubs. A clear cluster of symptoms involving multiple organ systems has been reported by numerous authors, and includes the following symptoms: dehydration, hyperthermia, seizures, rhabdomyolysis, disseminated intravascular coagulation, and acute renal failure.[47-57] Particular individuals may not exhibit each of the symptoms, since early treatment may prevent development of the full syndrome. This constellation of symptoms is thought to be secondary to extreme levels of physical exertion for extended periods of time in crowded conditions. Of interest, in animals, the hyperthermic effects of amphetamine are significantly enhanced by crowding, a phenomenon known as aggregation toxicity. It is possible that the crowded setting of raves contributes to the development of this potentially deadly syndrome which can occur after relatively small doses of MDMA (approximately 75 to 125mg) in the occasional user.

2.2 Neuropsychiatric Adverse Effects

Acute undesirable emotional effects reported by the 2 prospective studies in MDMA abusers[24,25] included anxiety, depression, mental fatigue, 'emotional inflation', fear, paranoia, racing thoughts, confusion, and 'negative self-talk'. In one of the studies,[24] 3 of 10 MDMA abusers had difficulty multiplying numbers and 4 of 10 MDMA abusers had impaired judgement, as determined by their idiosyncratic responses to hypothetical problems involving decision making. Similar symptoms were reported in 2 retrospective surveys of MDMA abusers,[26,27] in addition to other acute neuropsychiatric symptoms. These other symptoms included dizziness or vertigo, visual and tactile hallucinations, paraesthesias, irritability, defensiveness, decreased libido, decreased desire to perform mental or physical tasks, increased obsessiveness, motor tics, decreased ability to interact or be open with others, and altered time perception.

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Acute psychiatric complications of MDMA that have appeared in case reports include panic attacks[58-60] and psychosis.[61-63] Also, in several MDMA abusers acute effects of MDMA were reported to lead to irrational and impulsive behaviour such as dangerous driving or 'car surfing', with subsequent severe medical consequences or death.[36,64-66]

3. Chronic Complications of MDMA

3.1 General Medical Adverse Effects

As was the case with acute medical complications of MDMA use, chronic medical complications of use can be minor and treatable or potentially fatal. A relatively minor effect of chronic MDMA use is the development of temporomandibular joint syndrome (TMJ), dental erosion and myofacial pain.[67] These adverse effects are secondary to the acute effect of MDMA to induce bruxism (teeth grinding) and trismus (jaw clenching) [see section 2.1]. While these syndromes are relatively minor themselves, the treatment for idiopathic TMJ syndrome and myofacial pain in MDMA abusers could lead to fatal complications. In particular, monoamine oxidase inhibitors (MAOIs) are often used to treat TMJ syndrome. In combination with MDMA or other amphetamines, MAOIs can produce a fatal syndrome characterised by severe hypertension, confusion and tachycardia ultimately leading to coma and death.[68]

A serious chronic complication of MDMA is aplastic anaemia. Two cases of aplastic anaemia were reported in individuals who used MDMA.[69] Both individuals had used MDMA on more than one occasion, the last time of use being 1 week and 1 month prior to diagnosis with aplastic anaemia. One individual required repeated platelet transfusions prior to recovery, while the second patient recovered spontaneously over 7 to 9 weeks.

To date, hepatotoxicity has been reported in 14 MDMA abusers.[37,51,70-73] While the majority of these individuals recovered, 2 required liver transplantation, and 1 died. Given the illicit source of MDMA in all of these case reports, it is possible that contaminants in the MDMA taken by these individuals played a role in the pathogenesis of the hepatotoxicity. Nevertheless, hepatotoxicity should be recognised as a potential complication of MDMA use.

3.2 Neuropsychiatric Adverse Effects

Chronic neuropsychiatric difficulties seen following MDMA abuse include panic disorder,[59,60,74-76] psychosis,[62,74-79] aggressive outbursts,[75] flashbacks,[62,75,76] major depressive disorder[75,80,81] and memory or cognitive disturbance.[75,80] Also, although not typically considered an adverse effect, a series of MDMA abusers were reported who developed a modification of appetite preferences following MDMA use.[75] In particular, these individuals developed carbohydrate or chocolate cravings, a phenomenon the authors postulated might be secondary to changes in serotonin function.

While describing each of these neuropsychiatric case reports in detail is beyond the scope of this review, it is important to underscore 2 points made by a number of their authors. First, in some cases it appears that either a genetic predisposition for neuropsychiatric illness or a personal history of a previous psychiatric problem increases the likelihood for the development of MDMA-related neuropsychiatric difficulties.[76,80] Secondly, although a number of the cases described involved individuals who used repeated or high doses of MDMA, some individuals develop neuropsychiatric difficulties with only a single 'typical' dose of MDMA.[59]

3.3 Neurotoxicity

3.3.1 Neurotoxicity in Preclinical Trials

It is not known at this time whether MDMA damages serotonin neurons in humans. However, there is significant cause for concern that humans who abuse MDMA, particularly those who use high doses repeatedly, are at risk of incurring brain serotonin injury. These concerns stem from the findings of preclinical studies as well as findings in humans who have abused MDMA.

In preclinical studies, MDMA has produced serotonin neurotoxicity in every animal species studied to date, including several nonhuman primate species. When given at high dosages, MDMA has also been found to lead to lasting depletions of brain dopamine in rats[9] and mice.[82,83] Further, in nonhuman primates MDMA-induced serotonin neurotoxicity is prolonged[16] and possibly permanent.[84] Finally, as mentioned in section 1, the dose of MDMA that damages serotonin neurons in monkeys[15] is close to that typically taken by recreational users,[23] and smaller than that taken by some MDMA abusers in the setting of raves. Taken together, the data from preclinical studies suggest that some human MDMA abusers are at risk of injury to brain serotonin neurons. In addition, individuals who use repeated high doses of MDMA might also be at risk for damage to brain dopamine neurones.

3.3.2 Neurotoxicity in Clinical Studies

There have been 2 uncontrolled clinical studies and 1 controlled clinical study that have used lumbar CSF 5-hydroxyindoleacetic acid (5-HIAA; the major metabolite of serotonin) measurements to screen for possible MDMA-induced neurotoxicity in humans. One of the uncontrolled studies reported reductions in CSF 5-HIAA[85] while the other did not.[86] Given the large number of factors which are known to influence CSF 5-HIAA (e.g. diet, activity, height, size of the sample), it is not surprising that data from these 2 studies do not concur.

The one controlled study of human MDMA abusers[22] suggests that human MDMA abusers, like MDMA-treated animals, may incur lasting damage to brain serotonin neurons. In that study, 24 MDMA abusers (who had used MDMA at least 25 times) were compared with age- and sex-matched controls who had never used MDMA, using several indirect measures of brain serotonin function. Compared with controls, MDMA abusers were found to have lower levels of 5-HIAA in their CSF. Female MDMA users were also found to have lower levels of CSF homovanillic acid (HVA, the major metabolite of dopamine). Since 5-HIAA has been shown to be a marker of MDMA-induced neurotoxicity in monkeys,[87] this finding suggests that lower levels of CSF 5-HIAA in MDMA users are a reflection of serotonin neuronal injury. Lower levels of CSF HVA seen in female MDMA users could be a reflection of decreased brain dopamine levels in that group, possibly as a consequence of higher MDMA exposure. Women in the study reported taking similar MDMA dosages to men, but more often. Further, women in the study weighed less and, therefore, took higher dosages on a milligram per kilogram basis.

MDMA users in the study were also found to have alterations in their sleep architecture, i.e. they reported less total and stage 2 sleep,[88] and less hostility and impulsive personality tendencies than controls.[22] Since sleep and impulse control are thought to be modulated by brain serotonin systems, these data could be considered preliminary evidence for alterations in brain serotonin function in human MDMA abusers. However, since the precise role of serotonin in these behaviours is not known, further research is needed to confirm and extend these observations.

Other evidence for possible MDMA-induced neurotoxicity in humans comes from case reports (see section 2.1). Specifically, since brain serotonin is thought to be an important modulator of mood, anxiety, cognition and impulse control, it is possible that some of the aforementioned case reports involving these behavioural functions might have been examples of MDMA-induced brain serotonin neuron damage. In particular, individuals who developed disturbances in mood, anxiety or cognition following high or repeated doses of MDMA may have had these symptoms secondary to brain serotonin injury. In contrast, individuals who developed symptoms after relatively small doses of MDMA used on rare occasions would not be expected to have lasting serotonin injury. In those cases, it is more likely that a predisposition or preexisting vulnerability to psychiatric disturbance in combination with a drug that interacts with brain serotonin and catecholamine systems resulted in psychiatric difficulties.

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4. Conclusions

As the use of MDMA has increased over recent years, so have reports of adverse nonpsychiatric and psychiatric effects following MDMA ingestion. Some MDMA-related complications, such as fatal cardiac arrhythmias and cerebral infarctions, are related to the acute pharmacological properties of MDMA that are shared by a number of amphetamines. Other complications, such as severe hyperthermia with rhabdomyolysis, renal failure and disseminated intravascular coagulation, are more probably related to the use of MDMA in raves, where individuals participate in extreme physical activity for prolonged periods in a hot, crowded setting. Repeated use of high doses of MDMA, such as those used by regular ravers, may lead to brain serotonin neurotoxicity and neuropsychiatric sequelae such as major depression, cognitive disturbance and anxiety disorders.

Although reports of adverse nonpsychiatric and psychiatric effects associated with MDMA are relatively small in number, when compared with the large numbers of MDMA users, it can be assumed (as was found in one study[28]) that the number of cases of MDMA-related adverse effects reported falls far short of the actual number of cases that occur. It should also be recognised, particularly in cases of MDMA-induced neurotoxicity, that symptoms might not be obvious acutely after MDMA ingestion. Since serotonin is known to be involved in a number of normal behavioural functions, including mood, anxiety, sleep, cognition, appetite and impulse control, disturbances in these behavioural spheres might be subtle, and their association with MDMA use could easily be missed even when symptoms are recognised. Until the risks of MDMA are fully understood, it will be important for health providers to consider MDMA use in the differential diagnosis of new onset neuropsychiatric illness, as well as the wide array of adverse effects reviewed in sections 2 and 3.

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