

## Agony and ecstasy: a review of MDMA effects and toxicity

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**Summary – Background** – Ecstasy is a recreational drug with an anecdotal reputation for safety. However, reports of adverse effects and fatalities have increased in the medical and popular press.

**Method** – Literature search and review.

**Results** – Acute Ecstasy toxicity does not appear to be due to overdose and cannot be solely attributed to the nature of the usual ambient environment. Adverse effects include hyperthermia, seizures, cardiac arrhythmias, hepatotoxicity, hyponatraemia and many psychiatric disorders. Ecstasy causes serotonergic neurotoxicity in the brains of animals at doses close to those used by humans, but its long-term effect on the human brain is unknown.

**Conclusion** – Ecstasy toxicity should be considered in the differential diagnosis of a variety of medical and psychiatric conditions. Given its popularity, both the acute and the potential long-term effects are a cause for concern.

**ecstasy / genetic / MDMA / serotonin / toxicity**

### INTRODUCTION AND HISTORICAL ASPECTS OF MDMA USE

3,4-methylenedioxymethamphetamine (MDMA), known as “Ecstasy,” has become increasingly popular as a recreational drug [16, 33]. There has been an associated increase in reports in the medical and popular press of presumed Ecstasy-related fatalities and severe adverse effects. In a review of adverse reactions to MDMA, Henry et al. [21] concluded that the pattern of toxicity was not attributable to ‘overdose’. Some individuals can use the drug without immediate harm whilst others, taking similar amounts, have experienced severe toxicity, including death [61].

Tablets sold as Ecstasy primarily contain 3,4-methylenedioxymethamphetamine (MDMA),

although in some cases other structurally related analogues such as amphetamine and methylenedioxyethamphetamine (MDEA) are present [61]. Despite the fact that the manufacture of Ecstasy is uncontrolled, Henry et al. [21] concluded that there was no evidence that variation in the manufacturing process or an impurity in the tablets were responsible for the majority of cases of severe toxicity.

In addition to acute toxic effects, there is evidence from animal studies of MDMA-induced chronic brain serotonergic neurodegeneration. These effects occur at doses close to those ingested by humans [16]. There is therefore concern that chronic MDMA use may lead to serotonergic neurodegeneration in humans [16].

MDMA was first synthesised and patented by Merck in 1914 [11]. The drug was developed for use as an

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appetite suppressant, but it has never been used for that purpose. It was rediscovered in the 1960s [16], and there are reports of its use as an 'affective enhancer' as an adjunct to psychotherapy [11].

Recreational use of MDMA first appeared in the U.S.A. in the 1970s [55]. In the U.K., MDMA has been subject to control since 1977 under the generic definition of an 'amphetamine-like' compound in the Misuse of Drugs Act [16]. In the U.S.A., the Drugs Enforcement Agency placed MDMA on schedule I of controlled substances in 1985, thereby restricting its use [58]. This prohibition was based upon reports that the administration of a related analogue (itself one of the metabolites of MDMA), methylenedioxymphetamine (MDA), caused damage to serotonergic nerve terminals in rodent brains [58]. Subsequently MDMA was reported to produce similar findings [58]. A study in the U.S.A. in 1988 found that 39% of students on a college campus admitted to having taken the drug at least once in the previous year [44]. In the UK it is generally accepted that there has been a marked increase in MDMA use as part of the so-called 'rave' scene (i.e., at certain types of dance clubs and parties). There has been an associated rise in illicit Ecstasy manufacture in Europe [16]. Substances used in the manufacture of Ecstasy are now subject to legal control; however, many of these precursor substances are readily available for legitimate industrial uses, and synthesis of MDMA is relatively simple, [16, 18].

In recent years there has been considerable study devoted to clarifying the extent and pattern of Ecstasy use, discovering the causes of acute toxicity, and further investigating the possibility that MDMA causes a chronic brain serotonergic neurotoxicity.

## PHARMACOLOGY AND CHEMISTRY OF MDMA

MDMA is structurally related to MDA and MDEA, or "Eve". All three cause euphoria and are drugs of abuse similar to the stimulant methamphetamine and to the hallucinogen mescaline [10]. Four biotransformation pathways of MDMA have been identified in the rodent: N-demethylation, O-dealkylation, deamination and conjugation [28]. MDA may be formed by MDMA N-demethylation. Demethylenation of MDMA yields dihydroxymethylamphetamine (DHMA) [60]. This is a major metabolic pathway of MDMA metabolism and it is catalysed by cytochrome P450 in the liver and brain [23, 29]. The enzyme debrisoquine hydroxylase,

CYP2D6, is a major contributor to the human hepatic demethylenation of MDMA [60].

## ANIMAL STUDIES

Many of the animal studies of MDMA concern its toxic effect on brain neurones. It causes a dose-related decrease in the concentration of serotonin (5 hydroxytryptamine, 5-HT), and its metabolite, 5 hydroxyindolacetic acid (5-HIAA), in the brain [58]. It causes 5-HT release from brain neurones and inhibits 5-HT reuptake [61]. To a lesser extent it also causes dopamine release [58]. Administration of MDMA to animals results in 'acute' and 'long-term' effects [18].

## ACUTE PHASE

In the acute phase hyperthermia, locomotor hyperactivity, salivation, mydriasis and piloerection occur: this is consistent with a sympathomimetic response [58]. Ataxia and abnormal limb movements are also seen and at higher doses seizures may occur. This phase is characterised biochemically by marked depletion of serotonin, which returns to normal within 24 hours [18]. The hyperthermic response depends on the ambient temperature and can be attenuated by the addition of certain drugs (e.g., chlormethiazole, haloperidol), or by transferring the animal to a lower ambient temperature [18]. It is interesting to note here that periods of 'rest' and rehydration have been recommended for those who dance at 'rave' events, in order to reduce the risk of hyperthermia. The hyperthermia and the locomotor hyperactivity are considered to be related to altered serotonergic function [18], and many of these features resemble the 'serotonin syndrome' noted in humans [59]. The most frequent clinical features of this syndrome are changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor.

A dose of 5 mg/kg can produce hyperthermia in rodents [18]. The estimated human recreational dose of MDMA is 3–5mg/kg and even higher doses have been recorded [18].

## CHRONIC PHASE

MDMA causes brain serotonergic neurotoxicity in animals in the long term. Studies indicate that MDMA may also be toxic to dopaminergic systems but to a lesser extent [58]. The long-term reduction in serotonin is associated with immunocytochemical evidence of

neurodegeneration, reduced tryptophan hydroxylase activity, (an enzyme involved in serotonin synthesis) and a decreased density in serotonin reuptake sites. Scheffel et al. [50] used positron emission tomography to examine the short- and long-term effects of MDMA administration on the serotonin system in the living baboon brain. Using a 5HT transporter ligand, they found short- and long-term decreases in ligand binding. These results were suggestive of MDMA-induced neurotoxicity. Areas of the brain rich in serotonergic nerve terminals appear to be particularly vulnerable, with selective damage noted to the dorsal raphe nuclei [58].

In rodents there is some evidence of serotonergic neurone regeneration [49], although this is often abnormal [13]. In primates, however, the neurodegeneration may be permanent [46]. Hatzidimitiou et al. studied the serotonin system in the brains of primates previously treated with MDMA [20]. They found that abnormal brain 5HT innervation patterns were present seven years after the initial administration of MDMA. Long-term neurotoxicity in rats and non-human primates can occur after a large single dose (20 mg/kg), or after repeated smaller doses (5 mg/kg) [19]. Multiple doses of MDMA were noted to be more effective in producing long-term neurodegeneration but it has also been noted to occur following a single dose of 5 mg/kg of MDMA given either subcutaneously or orally [47].

The mechanism of MDMA-associated neurotoxicity is not yet known. There are several theories under investigation, including the possibility that metabolites formed from demethylenation of MDMA might themselves be toxic [60]. Free radicals produced by oxidation of metabolites of MDMA have also been implicated in vitro [19]. The free radical theory of MDMA-induced neurodegeneration is supported by recent in vivo work by Colado et al. [6]. In a study of the MDMA-induced generation of reactive oxygen species, Shankaran et al. [54] found that this relied in part on the activation of the 5HT transporter. The metabolite theory is also supported by the work of Paris and Cunningham [43], which suggested that MDMA injected directly into the brain was not neurotoxic. Some studies have shown an attenuation of MDMA-induced serotonergic neurotoxicity by serotonin precursors tryptophan and 5 hydroxytryptophan [57] and by dopamine receptor blockade (e.g., with haloperidol) [52], suggesting that serotonin depletion and dopamine receptor activity are key elements in the process.

Schmidt [51] found that the addition of a selective serotonin reuptake inhibitor (SSRI) soon after MDMA administration protected against long-term serotonergic neurodegeneration in animals. However, 12 hours after MDMA administration, the addition of the SSRI no longer has this effect. The author inferred that the protective effect of the SSRI might be due to the inhibition of neuronal uptake of a hypothesised toxic metabolite of MDMA.

Interestingly, the acute and chronic phases of serotonin depletion are differentiated by their stereoselectivity; both stereoisomers of MDMA are associated with the acute serotonin depletion; however, only the (+) stereoisomer is associated with the long-term neurotoxicity [51]. This suggests that the chronic neurotoxic effect may occur independently of the acute depletion of serotonin and that the acute phase involves a reversible change in neurotransmitter turnover.

## CELLULAR CHANGES

Simantov and Tauber [56] investigated MDMA toxicity at the cellular level using the human placental serotonergic cell line JAR. They found that MDMA altered the cell cycle and induced DNA fragmentation, producing apoptosis. They proposed, from this study and a review of similar studies, that serotonin activates MDMA neurotoxicity by enhancing dopamine release and that dopamine interacts with MDMA at the cellular level.

## MDMA AND HUMANS

It has been estimated that recreational use of MDMA involves oral ingestion of a dose of 75–150 mg [58]. Accurate measurement of doses is problematic [18] and many studies rely on self-reports; however, these have been found to correlate well with the results of urine screening [4]. Acute effects occur within 30 to 60 minutes after ingestion and last for several hours [16]. Some users will take a further 'booster' dose several hours later [58], usually inducing more marked adverse effects but not necessarily an elevation in mood [18]. MDMA is also taken intravenously [14]; Siegel [55] noted this as far back as 1986, in his report on "MDMA non-medical use and intoxication." Some individuals report an increase in the frequency of MDMA use in order to attain the original psychological effect, suggesting a degree of tolerance [58].

## EFFECTS IN NORMAL VOLUNTEERS

The effects of MDMA have been studied in normal volunteers with previous experience of MDMA use [11]. Symptoms similar to other stimulants were produced, including increased heart rate, hypertension, reduced appetite, a dry mouth, dilated pupils, mood elevation and a subjective sense of increased energy. In one study of ten such individuals, jaw clenching occurred in six, nystagmus in eight, various degrees of ataxia in seven and increased deep tendon reflexes occurred in eight. Nausea was noted in just one case and dilation of pupils was seen in all subjects. Psychological experiences included euphoria and, in four cases, impaired judgement (with idiosyncratic answers noted in response to problems requiring decision-making). The author concluded that his findings supported "the general impression among knowledgeable professionals that MDMA is reasonably safe." However, he did admit to the possibility of a bias existing in the process of subject selection, as those who had experienced a more positive reaction to MDMA use in the past may have been more likely to volunteer. He also noted that a drug that caused ataxia, hypertension and tachycardia could be "unsafe." Another study describing those who had ingested MDMA, (in this case during clinical psychotherapeutic sessions), noted that these individuals described the experience of "an expanded mental perspective" and "improved self-examination" [61]. One of these patients developed chronic intermittent panic attacks.

When the cardiovascular and neuroendocrine effects of MDMA on human volunteers were examined in a clinical trial significant increases in systolic blood pressure and heart rate were found [31]. The authors noted that these increases of 40 mmHg in systolic blood pressure and 30 beats per minute in heart rate could be clinically relevant in terms of toxicity in 'real-life conditions'.

## TOXIC EFFECTS

In interpreting the relevance of the results of animal studies, it is important to take into account the different drug sensitivities which rodents, primates and humans may exhibit. The primate has been found to be four to eight times as sensitive to the toxic effects of MDMA compared to the rodent [48]. In general, humans are regarded as being more sensitive than non-human primates to the toxic effects of drugs [48].

As the use of MDMA has increased, reports of associated adverse medical and psychiatric sequelae and death have appeared in the literature. In many of these cases the identity and dose of the substance taken is not known; however, in some cases only MDMA was identified on testing [3, 21]. The acute adverse effects associated with MDMA use include cardiac arrhythmia, hyperthermia, cerebral haemorrhage, rhabdomyolysis, acute renal failure, hepatotoxicity [12, 21, 24, 38] and acute and chronic psychiatric symptoms and syndromes [34, 36, 37].

## PSYCHIATRIC SYMPTOMS AND SYNDROMES AND SEROTONERGIC FUNCTION IN HUMANS

Evidence from animal studies suggests that repeated MDMA administration brings about a lasting reduction in 5HT activity in the central nervous system [39]. The effect of MDMA on human 5HT neurotransmission and human behaviour remains unclear [15]. 5HT has been implicated in the regulation of mood, impulsivity, cognition and sleep in humans [1, 40]. Abnormalities in serotonin neurotransmission have been implicated in many neuropsychiatric illnesses such as depression and anxiety [35]. Research into the effects of MDMA on the human brain has included descriptions of neuropsychiatric symptoms and syndromes found in association with MDMA use [34, 36, 37] and the study of serotonergic neurotransmission in humans with a history of MDMA use [15, 33]. Studies of serotonergic neurotransmission in humans have relied upon indirect methods such as the measurement of serotonin metabolites in cerebrospinal fluid (CSF), or the use of neuroendocrine challenge tests such as the D-fenfluramine and L-tryptophan challenge tests [15, 33]. Recent advances in neuroimaging techniques have been accompanied by the application of these techniques to the study of the serotonin system in the brains of humans with a history of MDMA use [35, 42, 53]. These techniques seem likely to provide increasingly useful information on the possible toxic effect of MDMA on human brains.

In the acute phase, MDMA ingestion results in euphoria; unlike mescaline, however, it is not typically hallucinogenic [58]. MDMA use has been associated with a wide diversity of psychopathology including panic disorder, depression and chronic paranoid psychosis [34, 36, 37]. As these syndromes may occur independently of MDMA use, it would be difficult to prove causality, but it has been suggested that some

individuals may be more vulnerable to MDMA-induced psychiatric disorder [58].

McGuire et al. in 1994 described a series of 13 psychiatric cases thought to be associated with MDMA use [37]. Eight of these cases had psychotic syndromes, two had visual illusions and hallucinations, one individual suffered from panic attacks, one individual suffered from depression and one had chronic depersonalisation and derealisation. In a prospective study of weekend MDMA users compared to weekend alcohol users, the MDMA group showed a significantly lower mood midweek, with impairment of an attentional/working memory task suggesting, according to the authors, a temporary depletion of serotonin [8]. Studies comparing cognitive function in MDMA users and control groups have revealed that MDMA use is associated with selective impairments in memory [27, 41]. The results of neuropsychological testing indicated that this was not explained by attentional deficits or poor motivation [27]. Neuropsychological testing has demonstrated differences between MDMA users and controls on measures of impulsivity [33, 40]. It has also been shown that MDMA use alters sleep duration and pattern with reduced non-REM sleep (in particular stage two), compared to age- and sex-matched controls [1].

McCann et al. [33] reported a reduction in the serotonin metabolite 5-hydroxyindoleacetic acid in the CSF of those with a history of MDMA use compared to controls, but no difference in prolactin response to L-tryptophan. Gerra et al. [15] used neuroendocrine tests, clinical psychobehavioural evaluation and tests of personality characteristics to compare a group of MDMA users with a control group. There was evidence of significant biological and psychological differences between the groups. The authors noted that their results suggested an association between MDMA use and impairment of the serotonin system in humans [15]. The former is not necessarily causative, however, as noted by the authors.

In 1998 McCann and colleagues reported the results of a study applying neuroimaging techniques to the study of brain serotonin neurons in humans who had a history of MDMA use [35]. In this study, using positron emission tomography (PET), those with a history of MDMA use were compared to a control group. The former group had decreased global and regional brain binding of a ligand selective for the 5HT transporter [35]. The authors concluded that this demonstrated direct evidence of a reduction in a structural compo-

nent of brain 5HT neurons in human MDMA users [35]. Neuroimaging studies by Obrocki et al. [42] using PET and Semple et al. [53] using single photon emission computed tomography (SPECT) compared MDMA users with control groups and found results suggestive of MDMA-associated neurotoxicity in humans.

Limitations of studies of human MDMA users include the reliance on the participants' own estimates of the extent of MDMA use [45] and uncertainty regarding the exact contents of the substance taken [25]. Another problem is the difficulty in interpreting the significance of the finding of reduced serotonin transporter ligand binding in MDMA users. Morgan noted that MDMA users may differ from controls in terms of personality characteristics which may be associated with preexisting serotonin system abnormalities [39].

## NON-PSYCHIATRIC TOXIC EFFECTS

In 1987 Dowling et al. reported on five deaths associated with the use of MDMA and MDEA [10]. In one of the cases MDMA was considered to be the immediate cause of death. In three of the cases MDMA and/ or MDEA were postulated to have contributed to death by inducing a fatal arrhythmia in predisposed individuals (i.e., those with underlying disease). Henry et al. [21] described a series of seven cases of MDMA-related fatalities and a series of cases of complications from MDMA ingestion. The presence of MDMA was confirmed analytically in all of these cases. MDA and amphetamine were also detected in a minority of the samples, although as MDA is a metabolite of MDMA it may or may not have been ingested. Prior to death, pyrexia and in most cases convulsions and tachycardia were present. Symptoms and signs in the severely affected non-fatal group include agitation, pyrexia, tachycardia and one confirmed subarachnoid haemorrhage. Of interest in the series reported by Henry et al., the number of tablets ingested, according to the histories, did not differ between the fatal cases and the non-fatal cases.

Milroy et al. [38] reported on postmortem studies of MDMA- and MDEA-related fatalities, finding damage to hepatic, myocardial and brain tissues. It has been suggested that MDMA-associated rhabdomyolysis and other organ damage occurs as a consequence of hyperthermia [18], although Ellis et al. [12] reported eight cases of MDMA-associated liver damage, four of whom

had not been hyperthermic. In a review article in 1999, Jones and Simpson noted that recreational use of MDMA was a significant but often concealed cause of liver damage [26]. Cases of hyponatraemia, catatonic stupor [32] and aplastic anaemia [30] have also been reported.

## AMBIENT ENVIRONMENT

Many authors have noted that overheated and crowded conditions, the typical circumstance of MDMA use, may contribute to toxicity [21]. In animals the hyperthermia produced by amphetamine is increased by aggregation, (i.e., when the drug is administered to animals housed in groups rather than singly) [18]. Hyperthermia may occur in the absence of overcrowded conditions, however, as observed in the case of a baby aged 13 months, after accidental MDMA ingestion [18]. Attempts have been made to reduce the risk of hyperthermia by increasing fluid intake among those attending 'rave' parties, but this has resulted in water intoxication in some cases [32].

## GENETIC FACTORS

Genetically determined differences in drug metabolism have also been implicated. As noted previously, the enzyme CYP2D6 is involved in the metabolism of MDMA. CYP2D6 is polymorphic and a functioning enzyme is absent in 5–9% of Caucasians as a result of autosomal recessive gene inheritance [17]. An individual lacking a functioning enzyme is termed a 'poor metaboliser'; this phenotypic status can be determined by administering a test compound such as debrisoquine and measuring the metabolites and the parent compound in an eight-hour urine collection. It has been postulated by Tucker et al. [60] that 'poor metabolisers' at the enzyme CYP2D6 may be at increased risk of acute MDMA toxicity. Animal studies support this hypothesis. The female dark Agouti (DA) rat, a model for the human CYP2D6 poor metaboliser phenotype, was more susceptible to the acute hyperthermic effect of MDMA ingestion than the male DA rat (the male DA rat exhibits a more rapid debrisoquine metabolism) [5]. The enzyme CYP2D6 is also involved in the metabolism of many common medications including many antidepressants and antipsychotics [2]. There is, therefore, a theoretical possibility that adverse MDMA reactions might occur due to an interaction with those drugs. Some compounds, especially SSRI antidepressants,

are competitive inhibitors of CYP2D6 converting an individual with a normal CYP2D6 genotype into, phenotypically, a 'poor metaboliser'. In 1997, the *New Scientist* reported on the death of an individual who had taken MDMA and was also taking the prescribed medication ritonavir, a CYP2D6 antagonist [7]. The measured level of MDMA was high although collateral history indicated that no overdose had been taken (the recorded cause of death was MDMA overdose). Henry and Hill described the clinical features, necropsy findings and toxicology results of a case of fatal intoxication between ritonavir and MDMA [22]. The plasma concentration of MDMA was much higher than expected. The authors noted that ritonavir is a potent inhibitor of CYP2D6 and proposed that a drug interaction possibly combined with poor metabolism of MDMA may have been responsible for the fatality. Referring to that report, de la Torre et al. described a clinical trial demonstrating that MDMA pharmacokinetics is nonlinear [9]. Consequently, as noted by the authors, a small increase in the dose of MDMA ingested could result in a disproportionate increase in plasma concentration of MDMA as in the case described by Henry and Hill. There have been reports of people taking fluoxetine with MDMA to combat post-MDMA depression [7], thus potentially increasing the risk of acute adverse effects.

## CONCLUSIONS

MDMA use has undoubtedly increased in recent years and has been claimed to be a relatively 'safe' drug, although it has been associated with serious medical and psychiatric sequelae including death. MDMA toxicity should be considered in the differential diagnosis of a patient presenting with a hyperpyrexia, seizures, marked sympathomimetic symptoms, panic attacks, acute psychosis, altered consciousness or unexplained jaundice. The specific cause or causes of toxicity remain unknown but it does not appear to be related to intentional overdose, or to an impurity in the tablet [21], and has occurred in the absence of the overcrowded and overheated conditions at 'rave' events. A possible genetic vulnerability to toxicity from MDMA has been proposed [60], and adverse drug interactions between MDMA and prescribed and non-prescribed drugs can occur. Evidence from animal studies suggests that MDMA can cause chronic serotonergic neurodegeneration, at doses close to those that are used by humans. There are some indications that serotonergic function

in humans is altered by MDMA use [35], although it is not known if the postulated effect is transient or represents permanent serotonergic damage.

In view of the increasing popularity of MDMA, it is important that the causes of acute MDMA-related toxicity and the possible long-term effect of MDMA on humans are further investigated and clarified. Given its popularity and its reputation as a safe drug, any potential neuropsychiatric consequences in this young population would be of considerable concern [47].

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