Acute toxic effects of ‘Ecstasy’ (MDMA) and related compounds: overview of pathophysiology and clinical management

A. P. Hall1* and J. A. Henry2

1Department of Anaesthesia and Intensive Care Medicine, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester LE1 5WW, UK. 2Academic Department of Accident and Emergency Medicine, Imperial College London, 1st Floor QEQM Wing, St Mary’s Campus, Norfolk Place, Paddington, London W2 1PG, UK

*Corresponding author. E-mail: andrew.p.hall@uhl-tr.nhs.uk

Since the late 1980s ‘Ecstasy’ (3,4-methylenedioxymethamphetamine, MDMA) has become established as a popular recreational drug in western Europe. The UK National Criminal Intelligence Service estimates that 0.5–2 million tablets are consumed weekly in Britain. It has been reported that 4.5% of young adults (15–34 yr) in the UK have used MDMA in the previous 12 months. Clinically important toxic effects have been reported, including fatalities. While the phenomenon of hyperpyrexia and multi-organ failure is now relatively well known, other serious effects have become apparent more recently. Patients with acute MDMA toxicity may present to doctors working in Anaesthesia, Intensive Care and Emergency Medicine. A broad knowledge of these pathologies and their treatment is necessary for anyone working in an acute medical speciality. An overview of MDMA pharmacology and acute toxicity will be given followed by a plan for clinical management.

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Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) has been described as ‘the love drug’ and is also known under a number of other names including ‘XTC’, ‘Adam’ or simply ‘E’. It became established as a dance drug, popular at ‘rave’ parties and is taken for its mood-enhancing properties, principally the 3 Es; energy, empathy and euphoria. According to the British Crime Survey for 2000, 5% of 16–19-yr-olds use Ecstasy. In England during 1995–6 there were 18 deaths related to Ecstasy. From 1997 to 2000 there were 81 Ecstasy-related deaths in England and Wales. The risk of death for first-time users has been estimated to be between 1 in 2000 to 1 in 50 000.

The immediate effects of Ecstasy vary from almost universal minor symptoms to those that are rare but potentially life-threatening. Minor side-effects include trismus, tachycardia and bruxism. Delayed effects include midweek ‘lows’ and a prolonged ‘hangover’ that may last up to 5 days. Severe effects include sudden death, hyperpyrexia, rhabdomyolysis and multi-organ failure, the serotonin syndrome, isolated liver failure, an acute panic disorder and hyponatraemia with cerebral oedema (Table 1). An additional association and possible causation in morbidity and mortality related to trauma is hard to quantify. It has been reported that recreational drugs have become a major associated factor in fatal road traffic accidents.

Pharmacology and pharmacokinetics

Over 16 ‘Ecstasy’-related compounds have been identified. These include its ‘sister’ drug 3,4-methylenedioxyamphetamine, MDEA, ‘Eve’ and their common metabolite 3,4-methylenedioxyamphetamine, MDA, ‘Ice’ (Fig. 1). Tablets sold as Ecstasy may contain varying amounts of MDMA (typically 30–150 mg) or none at all. Other MDMA-related compounds may be sold as Ecstasy, and ‘Ecstasy’ tablets have also been found to contain a variety of other drugs including amphetamine, methamphetamine, caffeine, ketamine and acetaminophen.

MDMA causes the release of serotonin (5-hydroxytryptamine; 5-HT), dopamine and norepinephrine in the
of these important neurotransmitters are also shown in Figure 1. These compounds are involved in the control of mood but are also central to the mechanisms of thermoregulation and control of sleep, appetite, reward and the autonomic nervous system.\textsuperscript{20,44} Additionally, after MDMA administration, there is an increase in blood levels of cortisol, prolactin, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone and antidiuretic hormone (ADH).\textsuperscript{29,68} It has been suggested that the increase in prolactin may be responsible for the feeling of emotional closeness and may mimic the post-orgasmic state.\textsuperscript{41,50} MDMA has slight monoamine oxidase (MAO) inhibiting activity and some direct activity at several receptor types (5-HT\textsubscript{2}, M\textsubscript{1}-muscarinic, H\textsubscript{1}-histamine and \(\alpha_2\)-adrenergic), the significance of which is not known.\textsuperscript{68} MDMA has a plasma half-life of 7.6 h. Typically, after oral ingestion (75–150 mg), desired effects begin within 1 h and last 4–6 h.\textsuperscript{68} Blood levels in asymptomatic users and those with serious side-effects are often similar, suggesting that adverse reactions are likely to relate to the circumstances in which the drug is taken, and that there may also be an idiosyncratic component.\textsuperscript{28} A number of fatalities have been reported with blood levels of 0.1–2.1 mg litre\textsuperscript{-1}.\textsuperscript{31} However, a case of a deliberate overdose of MDMA in which the blood level reached 4.3 mg litre\textsuperscript{-1} with no more than mild sinus tachycardia and a degree of somnolence has been reported.\textsuperscript{54} Another analytically documented overdose resulted in a plasma MDMA of 7.72 mg litre\textsuperscript{-1}, the highest recorded in a surviving patient, with just a 'hangover', tachycardia and hypertension.\textsuperscript{31} The highest level reported in association with multi-organ failure in a subsequent survivor was 7 mg litre\textsuperscript{-1}.\textsuperscript{6}

MDMA metabolism involves two main pathways. In one, \(O\)-demethylation is followed by catechol-\(O\)-methyltransferase (COMT)-catalysed methylation and/or glucuronide or sulphate conjugation. In the other, \(N\)-dealkylation, deamination and oxidation is followed by conjugation with glycine. The cytochrome P450 isoenzyme CYP2D6 partially regulates the \(O\)-demethylation pathway. As CYP2D6 displays genetic polymorphism in human subjects, it might be suspected that slow metabolizers are at a higher risk of acute MDMA toxicity. However, the formation of an enzyme–metabolite complex results in auto-inhibition that renders all subjects, regardless of genotype, phenotypically poor metabolizers after two consecutive doses. This limits the effect of CYP2D6 pharmacogenetic variation on the acute toxicity of MDMA.\textsuperscript{58,68} COMT activity is also subject to genetic variation. This enzyme converts 3,4-dihydroxymethamphetamine (HHMA) to 4-hydroxy-3-methoxymethamphetamine (HMMA). \textit{In vitro} studies have shown that HMMA is even more potent than MDMA in releasing ADH. COMT polymorphism may thus contribute to inter-individual differences in ADH release after MDMA (see below).

There is considerable scope for interaction between Ecstasy and other drugs that affect these pathways.
HIV-1 protease inhibitors (antiretrovirals) such as ritonavir are potent inhibitors of CYP2D6 and prolonged effects of a small dose of MDMA have been reported.23,30

**Adverse effects**

A number of minor clinical symptoms and signs in Ecstasy users relate to a disturbance in the central and autonomic nervous systems. The principal features are shown in Table 2.

An increased risk of trauma, particularly from road traffic accidents, is self-evident. This is particularly likely as most recreational drug users travel to venues, often by car because of late finishing times. They may combine Ecstasy use with that of other agents that may impair judgement, principally alcohol, marijuana and cocaine.

An association between Ecstasy use and cerebral haemorrhage, cerebral venous sinus thrombosis, and aplastic anaemia has been reported.18,26,33,37,56 There have also been a number of reports of pneumothorax and pneumomediastinum in Ecstasy users.3,39,53 In one report, two cases occurred on the same evening among a group of friends.55 It is thought that the mechanism of injury here relates to sustained physical activity with a closed glottis, a form of Valsalva manoeuvre. This can lead to alveolar rupture and subsequent tracking of air along the perivascular space. However, in one case, a small oesophageal tear was found.55 All subjects reported recovered with conservative management, but most involved several days in hospital. They were investigated with chest radiographs and contrast swallow and treated with i.v. antibiotics when oesophageal injury was proven or suspected.

**MDMA and sudden death**

Little is known about the aetiology of sudden death in individuals who had taken MDMA. It seems likely that the sympathomimetic effects of the drug may precipitate a dysrhythmic catastrophe. This may occur in an otherwise perfectly healthy individual. However, undiagnosed cardiomyopathy, hypertension or viral myocarditis may be involved. A number of other congenital cardiac conduction abnormalities may go undiagnosed in young people (such as Wolff–Parkinson–White, Romano–Ward, Brugada, and Jervell and Lange–Nielsen Syndromes). These individuals are evidently at risk of sudden death from excessive sympathetic stimulation.8,60,74 Furthermore, a long QT interval has been reported in association with MDMA toxicity.27

### Table 2 Minor clinical symptoms and signs seen with MDMA

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
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<tbody>
<tr>
<td>Tachycardia</td>
<td>Elevated mood</td>
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<tr>
<td>Hypertension</td>
<td>Confusion</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Nystagmus</td>
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<tr>
<td>Sweating</td>
<td>Bruxism (jaw clenching)</td>
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**Hyperpyrexia, rhabdomyolysis and multi-organ failure**

The syndrome of hyperpyrexia together with rhabdomyolysis and multi-organ failure is well described.31 Most cases appear to be associated with excessive exertion with inadequate fluid replacement to facilitate thermoregulation. Some of these effects may be explained by the euphoric effects of the drug, accentuated by repetitive music and a crowded environment. It is known that both 5-HT and dopamine are involved in central control of thermoregulation and that MDMA effects lead to the activation of mechanisms that both conserve and generate heat. The serotonin syndrome is probably the most extreme of these effects. The occurrence of gross hyperpyrexia and its consequences in predominantly nightclub-going UK users, led to the suggestion that the circumstances in which the drug is taken is pivotal to the occurrence of this complication.28 Users who spend the night dancing energetically in a warm environment predispose themselves to the development of exertional hyperpyrexia. There is an excess of deaths in relation to parties in the summer and at New Year.29 Interestingly, laboratory studies with rats have shown that MDMA-induced hyperthermia in males is increased significantly in a warm environment, with overcrowding (‘aggregation toxicity’)22 and by social interaction with a female.3 A switching effect has been demonstrated whereby rats fail to show a hyperthermic response to MDMA if housed below 20°C.22

Patients present with hyperpyrexia, muscle rigidity, hyper-reflexia and are often subsequently found to have rhabdomyolysis. Impaired consciousness, disseminated intravascular coagulation (DIC) and multi-organ failure rapidly follow. Five organ-system failure is not unusual; some of these cases have survived after prompt treatment in an intensive care environment.24 The height and duration of hyperpyrexia are indicators of the risk of mortality. There are few survivors if the peak core temperature exceeds 42°C, though the highest recorded value in a survivor reached 42.9°C.36 Rhabdomyolysis can be pronounced, with peak creatine phosphokinase (CPK) levels in the region of 30 000–100 000 u litre⁻¹. The highest recorded peak CPK in a survivor is 555 000 u litre⁻¹.25

Denborough and Hopkinson12 suggested that there might be a direct effect of Ecstasy on muscle. They showed some augmentation of the halothane and caffeine induced muscle contraction produced in vitro while testing muscle biopsy specimens in the investigation of possible malignant hyperthermia (MH). However, this work has been criticized for using concentrations of MDMA up to 2000 times greater than that found in the plasma of Ecstasy-related fatalities.23 More recent work, in a rat model, suggests that MDMA uncouples skeletal muscle mitochondria in vivo, but that this is the result of an indirect mechanism.57

The overlap in clinical features between MDMA-induced hyperthermia and severe heat stroke, neuroleptic malignant
syndrome, serotonergic syndrome and MH cannot be ignored. It may be that these pathological entities ultimately share a final common pathway associated with the consequences of extreme hyperthermia. All would agree, that rapid cooling measures are essential along with the support of failing organ systems. Dantrolene has been used in the treatment of Ecstasy-related hyperpyrexia. While of established benefit in MH, its use in these other conditions remains controversial. It has been suggested that dantrolene treats the effects and not the cause of hyperpyrexia and that it may be better to direct treatment at central mechanisms of thermoregulation.\textsuperscript{48} It is, of course, difficult to perform a proper controlled trial when cases present \textit{in extremis} and require urgent management. This is particularly so when they occur sporadically, across a variety of centres. However, this is not always the case with heatstroke. The use of dantrolene in the treatment of heatstroke has been investigated by the Heatstroke Centre in Makkah, Saudi Arabia. An experienced unit, they were able to study 52 patients over a 4 day period in a randomized double blind controlled trial.\textsuperscript{5} Dantrolene made no difference to the rate of cooling. This group is, however, well-practised and has equipment for patient cooling not usually available in other countries, where severe heatstrokes occur less commonly.

A review of case reports over the initial 10 yr of widespread use of MDMA lends some support to the use of dantrolene. While an entirely arbitrary period, it allows for a reasonable number of cases to be considered. Cases described beyond this time have been excluded because dantrolene had become well established on the basis of anecdotal evidence and withholding the drug might suggest inadequate care on a number of levels. Cases reported over this period have been broken down into those with peak temperatures in the ranges 41–41.9°C and 40–40.9°C. Patients with a peak temperature of 42°C or more are considerably less likely to survive irrespective of treatment, while those with a peak of less than 40°C might not be expected to develop rhabdomyolysis and multi-organ failure. Peak temperatures in the range 41–41.9°C have been associated with 4/4 survivors in the dantrolene treated group and 2/5 in the non-dantrolene treated group.\textsuperscript{6,25,31,45,62,72,77}

In the lower range 40–40.9°C, there were 6/6 survivors with dantrolene and 4/5 without it.\textsuperscript{5,15,31,46,62,64,66,72,73} Overall, considering cases in the range 40–41.9°C, there were 10/10 survivors with dantrolene treatment and 6/10 without. It has been noted that more rapid control of temperature was achieved in cases where dantrolene was used.\textsuperscript{35,64} In most centres, where a patient is \textit{in extremis}, requiring intubation, ventilation, transfer to intensive care facilities and the establishment of invasive monitoring and support, any aid to cooling at this critical time may be of benefit. Once hyperthermia occurs, the calcium requirement for excitation–contraction coupling is reduced, so that hyperthermia alone can cause a degree of muscle contraction with a consequent increase in heat production and metabolic demand. This added complication can be counteracted by the administration of dantrolene, which raises the calcium requirement for excitation–contraction coupling in skeletal muscle. This may be the reason why dantrolene appears to make a difference in survival for patients presenting with very high body temperatures. Possible reasons for hyperthermia associated with MDMA are summarized in Table 3.

### Serotonin syndrome

MDMA is one of the many pharmacological triggers of the serotonin syndrome. This syndrome is characterized by a rapid onset, with confusion, diaphoresis, diarrhoea and cardiovascular instability. Increased muscle tone and rigidity are accompanied by shivering, tremor, heightened deep tendon reflexes and myoclonus.\textsuperscript{17} The excessive muscle contraction may lead to hyperthermia and death, and this condition has a mortality rate of 10–15%. Serotonin syndrome clearly shows great similarity to the acute hyperthermia and multi-organ failure seen with MDMA toxicity, and also MH and neuroleptic malignant syndrome.\textsuperscript{71} An overlap of these conditions seems likely with both being part of the same clinical spectrum. Other drugs known to cause the serotonin syndrome include amphetamines, cocaines and various anti-depressant agents. There is particularly a risk with the combination of MAO inhibitor (MAOI) and any serotonin reuptake inhibitor (SRI). A number of agents commonly used in anaesthesia and critical care also display these characteristics. The phenylpiperidine series opioids, pethidine (meperidine), tramadol, methadone, dextromethorphan and propoxyphene all have a weak SRI effect and linezolid and isoniazid have MAOI properties.\textsuperscript{17,47}

The serotonin syndrome may cause severe hyperthermia in MDMA users that have not engaged in significant physical exertion. Mild cases may resolve spontaneously, but should be monitored closely. In severe cases, deep sedation, paralysis and ventilation should be undertaken. As the production of heat is secondary to muscle contraction, and hyperthermia arises because heat production exceeds the body’s capacity to lose heat, paralysis immediately cuts heat production and body temperature should decrease rapidly without any further active cooling measures.

### Table 3 Aetiology of hyperthermia associated with MDMA

- **Prolonged exertion**
- **Warm environment**
- **Amphetamine-like effects**
- **Promotion of repetitive activity (dancing)**
- **Disregard for body signals (thirst, exhaustion)**
- **Mood-enhancing effects**
- **Euphoria**
- **Energy**
- **Serotonin effects**
- **Increased muscle tone**
- **Heat production**
- **Secondary effects of hyperthermia**
- **Increased muscle tone**
- **Further heat production**
Hyponatraemia and cerebral oedema

Awareness of the danger of hyperthermia among users of MDMA led to the practice of drinking large volumes of water to prevent the compounding effect of dehydration. Clubs have been encouraged to provide ‘chill-out’ areas with free/cheap drinking water available. However, a number of deaths in Ecstasy users have been reported resulting from dilutional hyponatraemia and consequent cerebral oedema. Patients generally present with confusion, and convulsions, delirium, or both, and can rapidly progress to coma and death as a result of ‘coning’ (cerebral oedema, hypoxia and uncal herniation). The practice of drinking large amounts of water, sugared/carbonated drinks, or both, appears to be a major contributory factor. In one case associated with recreational use of MDMA, an elevated level of ADH was reported. In order to examine this phenomenon, Henry and colleagues administered a modest dose of MDMA, 40 mg, to eight healthy volunteers. They showed a marked increase in plasma levels of ADH that would not have been expected at that time of day and were not matched by increases in ACTH (as might be expected if part of a stress response). MDMA thus promotes ADH release in humans. Additionally, as is described above, some genetic polymorphism in relation to COMT may result in a greater release of ADH in some individuals. However, it is clear once again that the circumstances in which the drug is taken affects the incidence of a significant complication, in this case, fluid consumption which exceeds the body’s requirements. It is likely that many users who hydrate themselves vigorously would have some degree of hyponatraemia, but only those who consume excessive quantities of fluids achieve clinically significant levels (generally Na \(<125 \text{ mmol litre}^{-1}\)). There may be some benefit if users of MDMA rehydrate with electrolyte-containing fluids.

Conventional management of dilutional hyponatraemia is with fluid restriction, and this is adequate in the great majority of cases of MDMA-associated hyponatraemia. Distinction should be made between the treatment of chronic hyponatraemia and the management of MDMA-associated hyponatraemia, where an acute derangement has occurred. In chronic hyponatraemia, correction should be no faster than 6–8 mmol litre\(^{-1}\) per day in order to avoid the osmotic demyelination syndrome. This would be unlikely in the case of an acute hyponatraemia. However, the patient with mild to moderate MDMA-associated hyponatraemia will usually correct automatically by producing a diuresis within hours. The more severely ill patient may not be sufficiently stable to allow such a conservative approach and the use of hypertonic saline solution may be required. There is little evidence concerning the effectiveness of diuretics or mannitol in this situation. In cases of MDMA-related hyponatraemia, other complications may coexist including cardiovascular instability. A more rapid volume correction may be required. Isotonic saline may be most appropriate in this circumstance. Possible reasons for hyponatraemia associated with MDMA are summarized in Table 4.

Liver failure

Hepatic failure has been reported as part of a picture of multi-organ failure attributable to hyperpyrexia. Isolated liver damage of varying severity has also been reported. In the former, liver histology generally shows a picture of centrilobular necrosis and microvascular steatosis, a picture consistent with heatstroke. In isolated liver failure, the histology has been reported to be characteristic of an acute cholestatic hepatitis. The presence of eosinophils and histiocytes constitute strong evidence for a hypersensitivity reaction. Patients commonly present with jaundice, abdominal pain, raised serum transaminases, hypoglycaemia and elevated prothrombin time. Encephalopathy may occur and presentation can be fulminant. Andreu and colleagues reported that 31% of drug-related hepatopathy may occur and presentation can be fulminant. Patients with end-stage liver failure after MDMA use have undergone successful liver transplantation.

Acute severe anxiety/panic disorder

Though anxiety is often seen as a minor side-effect of MDMA use, there have been a number of reports of more severe reaction with an acute panic disorder. This has been reported in subjects without prior personal or family history of an anxiety disorder and where a modest dose of Ecstasy was taken. In one report, another user from the same source reacted similarly though this has not been seen elsewhere. Prior and subsequent Ecstasy use has been reported without similar effect. Though most anxiety and panic reactions settle within hours, there have been reports of a persisting condition lasting several months. Benzodiazepines have been found to be acutely effective. Longer-term therapy has been recorded with a
It is important to replace fluid losses and thus enable thermoregulation. Paralysis may be required in order to break the cycle of heat generation. Any patient with a significantly impaired level of consciousness, seizures or hyperpyrexia requiring aggressive cooling and dantrolene, should be sedated, the trachea intubated and lungs ventilated. It should be remembered that dantrolene takes some time to dissolve and prepare. Each vial of dantrolene contains 20 mg along with 3 g of mannitol and sodium hydroxide to give a final pH of 9.5 after the addition of 60 ml sterile water. Alkalinization of urine along with an adequate diuresis may protect the kidneys from failure because of myoglobinuria. The mannitol contained with dantrolene may help to promote the desired diuresis of 1–2 ml kg\(^{-1}\) h\(^{-1}\), though this may require supplementation.

Patients with hyponatraemia often have a normal or low temperature and should not be given i.v. fluids, as fluid restriction is usually sufficient. In most cases, treatment is essentially supportive. However, temperature control is important and immediate volume replacement followed by dantrolene and aggressive cooling is likely to be useful with severe hyperthermia. It is important to remember that temperature on arrival may not represent the peak and continued monitoring is required. Conversely, the temperature may have already peaked and significant tissue damage occurred before arrival at hospital.

Paralysis and ventilation is the best management for acute serotonin syndrome.

Consideration should be given to the early establishment of invasive monitoring access and a haemodialysis catheter if multi-organ failure and DIC is expected.

### Management of acute MDMA toxicity

A scheme for the management of patients with acute MDMA-related complications (Table 5) has been adapted from the UK National Poisons Information Service guidelines. The use of activated charcoal is recommended up to 1 h post-ingestion. However, it is unlikely that patients would present with serious adverse effects so soon. Urgent fluid replacement is essential in the patient with marked hypotension and tachycardia attributable to intravascular volume depletion.

Labetalol is preferred for the treatment of tachycardia and hypertension secondary to the sympathomimetic effects of MDMA. It has both \(\beta\)- and \(\alpha\)-adrenoceptor blocking effects and is available in an i.v. formulation. Beta-blockers used in isolation may be associated with increased hypertension because of the loss of \(\beta\)-mediated vasodilatation. However, i.v. esmolol may be useful as a short half-life makes it rapidly reversible.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>The management of acute MDMA toxicity</th>
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<tbody>
<tr>
<td>• Activated charcoal 50 g po ng (^{-1}) if (&lt;1) h post-ingestion</td>
<td></td>
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<tr>
<td>• Observe for at least 4 h</td>
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<tr>
<td>• Pulse, blood pressure, ECG, core temperature</td>
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<tr>
<td>• Blood for urea, electrolytes, creatinine, liver function, CPK; consider clotting profile and arterial blood gases</td>
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<tr>
<td>• 12-lead ECG</td>
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<tr>
<td>• Urine drug screen (a positive result for methamphetamine helps to confirm MDMA consumption; specific tests are also available)</td>
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<tr>
<td><strong>Treat</strong></td>
<td></td>
</tr>
<tr>
<td>• Anxiety or agitation—diazepam (0.1–0.3 mg kg(^{-1})) po or i.v.</td>
<td></td>
</tr>
<tr>
<td>• Seizures—diazepam (0.1–0.3 mg kg(^{-1})) i.v. or per rectum (pr)</td>
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</tr>
<tr>
<td>• Hypotension—intravascular volume expansion, consider need for central venous access, cardiac output monitoring, etc.</td>
<td></td>
</tr>
<tr>
<td>• Hyperthermia—simple cooling methods. If temperature &gt;39°C after initial measures, give dantrolene; intubation and ventilation are likely to be required</td>
<td></td>
</tr>
<tr>
<td>• Severe hypertension—consider labetalol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organ-system failure—conventional support; promote diuresis of 1–2 ml kg(^{-1}) h(^{-1}) with mannitol or furosemide</td>
</tr>
</tbody>
</table>

There is good evidence, in a rat model, for a MDMA-induced depletion in central 5-HT levels associated with anxiety and depression, and that this may be in part attenuated by chronic fluoxetine treatment. Depression and anxiety have also been reported in human MDMA users. Though there is some diminution after a period of abstinence, the incidence of problems is related to the number of occasions in which MDMA has been used. It has been suggested that some users may either be more vulnerable to the effects of MDMA or have pre-existing mental health problems for which they self medicate by using Ecstasy. The possibility of permanent neuronal damage in human users cannot be excluded.

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