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REVIEW

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Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy")

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Abstract 3,4-Methylenedioxymethamphetamine (MDMA or "Ecstasy") was first synthesised 80 years ago, but has recently received prominence as an illegally synthesised recreational drug of abuse. There is a widely held belief among misusers that it is safe. In the last 2–3 years there have been a number of reports of the drug producing severe acute toxicity and death and there are concerns that it may cause long term toxic damage to 5-hydroxytryptamine (5-HT) nerve terminals. There is a considerable literature on the acute pharmacological effects of MDMA in experimental animals, and this is reviewed. The drug produces both hyperthermia and the "serotonin syndrome", a series of behavioural changes which result from increased 5-HT function. Acute clinical toxicity problems following MDMA ingestion also include hyperthermia and the appearance of the serotonin syndrome. The hyperthermia appears to precipitate other severe clinical problems and the outcome can be fatal. In agreement with others, we suggest that the recent increase in the number of reports of MDMA toxicity probably results from the widespread use of the drug at all night dance parties or "raves". The phenomenon of amphetamine aggregation toxicity in mice was reported 40 years ago. If applicable to MDMA-induced toxicity in humans, all the conditions necessary to induce or enhance toxicity are present at raves: crowded conditions (aggregation), high ambient temperature, loud noise and dehydrated subjects. Administration of MDMA to rodents and non-human primates results in a long term neurotoxic decrease in 5-HT content in several brain regions and there is clear biochemical and histological evidence that this reflects neurodegeneration of 5-HT terminals. Unequivocal data demonstrating that similar changes occur in human brain do not exist, but limited and indirect clinical evidence gives grounds for concern. There are also data suggesting that long term psychiatric changes can occur, although there are problems of interpretation and these are reviewed. Suggestions for the rational treatment of the acute toxicity are made on the basis of both pharmacological studies in animals and current clinical practice. Cases presenting clinically are usually emergencies and unlikely to allow carefully controlled studies. Proposals include decreasing body temperature (possibly with ice), the use of dantrolene and anticonvulsant and sedative medication, particularly benzodiazepines. The use of neuroleptics requires care because of the theoretical risk of producing the neuroleptic malignant syndrome and the possibility of precipitating seizures. In rats, chlormethiazole antagonises the hyperthermia produced by MDMA and has been shown clinically to block MDMA-induced convulsive activity.

Key words 3,4-Methylenedioxymethamphetamine · MDMA · Ecstasy · 5-Hydroxytryptamine · Hyperthermia · Neurotoxicity · Neuroleptics · Chlormethiazole

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA; "Ecstasy" or "E") is a commonly used recreational drug of abuse. It has been widely described in the lay press as being "safe" and is clearly believed to be so by those who misuse it. However, there have been an increasing number of reports of severe acute toxicity and death following ingestion of the drug, particularly when taken at dance parties, and there appear to be no generally accepted guidelines for treatment. In addition, there

are concerns that the drug may cause long term neurotoxic damage in the brain.

In the last decade there has been considerable research on the pharmacology of MDMA in experimental animals, and there are clear indications that much of the information is relevant to the clinical pharmacology and toxicology of the drug. It is, of course, always difficult to extrapolate neurotoxicity data in animals to predict problems that may be encountered in man. Nevertheless, it is notable that in the case of MDMA, hyperthermia is induced in rats with a dose of 5 mg/kg (Dafters 1994), while human recreational doses of MDMA of 3–5 mg/kg and even 10 mg/kg have been reported or estimated (McCann and Ricaurte 1991; Schifano 1991; Henry et al. 1992) and marked hyperthermia can occur (Henry et al. 1992). The fact, therefore, that four doses of 5 mg/kg to rats results in long term neurotoxicity (Battaglia et al. 1988a) raises concerns about repeated MDMA use in humans. The purpose of this review is to examine the experimental studies on MDMA and consider whether they are relevant to the clinical reports on its effects in order to generate conclusions or hypotheses for possible treatment options that could be used in cases of MDMA toxicity.

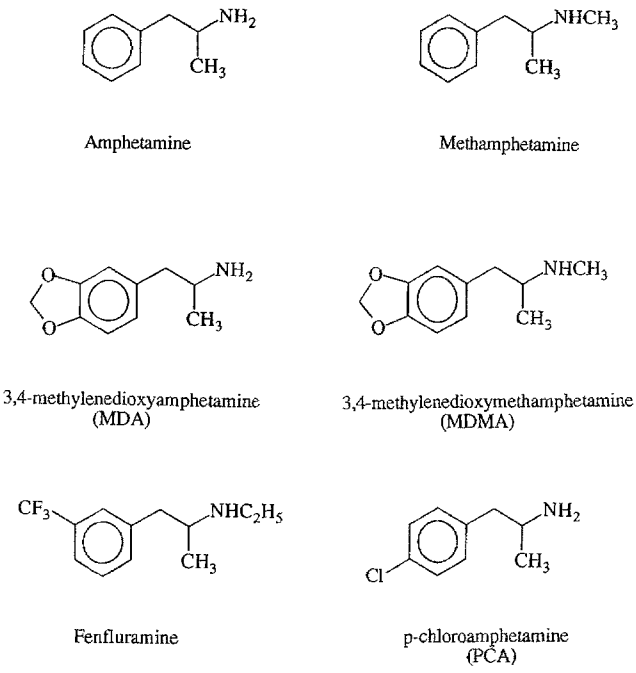

Fig. 1 Structure of MDMA and other substituted amphetamines

Historical aspects of MDMA use

MDMA (Fig. 1) was patented in 1914 as an appetite suppressant but it was never produced commercially nor did it achieve clinical use for this indication. However, there are published reports of the use of MDMA as an adjunct to psychotherapy. For example, Grinspoon and Bakalar (1986) suggested that it was a relatively mild and short acting drug that could give "heightened capacity for introspection and intimacy without perceptual changes, emotional unpredictability and adverse reactions associated with LSD". It was said to enhance the "therapeutic alliance by inviting self-disclosure and promoting trust". Downing (1986) reported that the volunteers in his investigation on the psychological and physiological effects of the drug believed it to be safe and beneficial and he stated that his study "supported the general impression among knowledgable professionals that MDMA was reasonably safe and without evidence of abuse". Nevertheless, by 1987, deaths involving MDMA use had been described and there are now a substantial number of anecdotal reports in the literature implicating MDMA with severe acute toxicity problems or death (see later). This surge of problems seems to be associated with a change in the way that the drug is used recreationally.

Until the mid 1980s, illicit use was confined predominantly to people taking the drug when alone or in a small party. Users said the drug made them feel euphoric, more verbal and closer to other individuals (Peroutka et al. 1988; Randall 1992a). A study performed at that time indicated that 39% of students (total study: 369) on a major USA university campus had taken the drug at least once in the previous year (Peroutka 1987).

At the same time reports were beginning to appear that the drug and its demethylated metabolite, 3,4-methylenedioxyamphetamine (MDA; Fig. 1) had long term neurotoxic effects in laboratory animals (Ricaurte et al. 1985; Schmidt et al. 1986; Stone et al. 1986). These observations did little to dent the image of the compound as being a safe recreational drug and from the late 1980s to the present time, particularly in the UK, it has enjoyed a new impact in terms of cultural use (Henry 1992; Randall 1992a, b). It is widely claimed that MDMA is now used extensively at dance clubs or parties, often called "raves", where there is all-night dancing to loud electronically generated sound, often with computerised light and video shows, and it is this new use that has probably given rise to a substantial increase in the number of reports of toxic reactions and deaths (Henry 1992; Randall 1992a, b).

One of the problems in assessing the cause of toxicity in subjects who have taken MDMA is the purity of the ingested substance. Synthesis of MDMA is relatively simple and the illegal drug is often made in illicit laboratories, or even domestic locations such as garages, with little regard for cleanliness or purity of the product, so there may be various intermediates present (Ziporyn 1986). The product may also have been mixed or "cut" with various other psychoactive products including amphetamine or lysergic acid diethylamide (LSD). In addition, the subject may have knowingly taken other psychoactive compounds,

Table 1 Behavioural changes observed following either MDMA or L-tryptophan together with a MAO inhibitor or 5-HT uptake inhibitor in various species including human.

Behaviour	MDMA administration				Serotonin syndrome	
	Rat[a]	Dog[b]	Monkey[b]	Human[c]	Human[d]	Rat[e]
Piloerection	–	–	–		–	
Diaphoresis				–		
Tremor	–	–	–	–	–	
Restlessness	–	–	–	–	–	–
Salivation	–	–	–			–
Ataxia	–	–	–		–	–
Limb movement	–	–	–	–	–	–
Change in mental state	–	–	–	–	–	–
Myoclonus	–	–	–	–	–	–
Hyperthermia	–	not recorded		–	–	–
Diarrhea	–	–	–	–	–	–

[a]Dafters 1994, Nash et al. 1988, Schmidt et al. 1990b, Gordon et al. 1991, Colado et al. 1993, Hewitt and Green 1994, Spanos and Yamamoto 1989, Slikker et al. 1989
[b](*Macaca mulatta*) Hardman et al. 1973
[c]Henry et al. 1992, Chadwick et al. 1991, Brown and Osterloh 1987, Bedford-Russell et al. 1992, Ames and Wirshing 1993, Friedman 1993
[d]Sternbach 1991
[e]Grahame-Smith 1971a, b, Green and Grahame-Smith 1976, Green and Heal 1985, Goodwin and Green 1985, Goodwin et al. 1987, Hjörth et al. 1982, Tricklebank et al. 1984
Note that a blank does not necessarily mean that a behaviour does not occur but merely that it has not been recorded

including opiates and alcohol. Nevertheless, the similarity of the reports on MDMA toxicity and its characteristic features indicate that most of the problems can be exclusively associated with the ingestion of MDMA or its demethylated metabolite, MDA. In some cases of toxicity or premature death, screening for chemicals other than MDMA and MDA has been negative (Brown and Osterloh 1987; Chadwick et al. 1991; Henry et al. 1992).

Acute neuropharmacological effects of MDMA in experimental animals

Administration of MDMA to animals results in a biphasic response. The first phase lasts less than 24 h, followed immediately by the second phase which lasts for approximately 12 months (or possibly longer). These phases are generally referred to as the "acute" and "long term" effects (McKenna and Peroutka 1990), and while they cannot be considered in isolation, it is clear that the events observed in the acute phase are not necessarily associated with the long term toxicity.

When MDMA is given to rats, two major events rapidly follow. The first is hyperthermia (Nash et al. 1988; Schmidt et al. 1990b; Gordon et al. 1991; Colado et al. 1993; Dafters 1994), which is related to the ambient temperature. Both Gordon et al. (1991) and Dafters (1994) showed that at normal (24°C) and high (30°C) ambient temperatures, MDMA administration resulted in an increase in rectal temperature of approximately +2.0°C, whereas administering the drug to animals that had been kept at low ambient temperature (11°C) for 24 h before injection resulted in a fall in rectal temperature. Transferring the rats to a low temperature room 30 min after drug administration attenuated the temperature rise (Dafters 1994).

Rather few attempts have been made to block the body temperature rise pharmacologically. Nash et al. (1988) reported that pretreatment with the 5-HT_2 antagonist, ketanserin, was effective, while Colado et al. (1993) found that chlormethiazole administration reversed the hyperthermic effect when given 2 min after the MDMA injection. Haloperidol and the excitatory amino acid receptor antagonist, dizocilpine, also attenuate the temperature rise (Hewitt and Green 1994).

The second major consequence of MDMA administration to rats is the appearance of hyperactivity and the so-called serotonin behavioural syndrome (Slikker et al. 1989; Spanos and Yamamoto 1989; Callaway et al. 1992; Colado et al. 1993). This syndrome, first described in rats by Grahame-Smith (1971a), has been the subject of considerable investigation, both into its aetiology and the effect of psychoactive drugs upon it (for reviews see Green and Grahame-Smith 1976; Green and Heal 1985). The syndrome consists of a complex series of behaviours including enhanced locomotor activity, reciprocal forepaw treading, head weaving, piloerection, hind limb abduction, proptosis, ataxia, unawareness, leading finally to convulsions and death (Table 1). Hyperthermia has also been reported to occur in these animals (Grahame-Smith 1971a). The syndrome results from procedures which increase the function of serotonin (5-hydroxytryptamine; 5-HT) in the brain. For example, increasing the synthesis and release of the amine by administration of L-tryptophan and a monoamine oxidase inhibitor (Grahame-Smith 1971a; Green and Grahame-Smith 1976; Green and Heal 1985) or administering relevant 5-HT agonists

including 5-methoxy *N,N*-dimethyltryptamine (Grahame-Smith 1971b) and 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) (Goodwin and Green 1985; Goodwin et al. 1987) results in the appearance of the syndrome.

The hyperthermia is not a simple dynamic consequence of the hyperactivity since injection of the 5-HT_{1A} receptor agonist 8-OH-DPAT simultaneously produces both the hyperactivity syndrome (Hjörth et al. 1982; Tricklebank et al. 1984; Goodwin and Green 1985; Goodwin et al. 1987), and hypothermia (Goodwin and Green 1985; Goodwin et al. 1987; Green and Goodwin 1987). Furthermore, MDMA-induced hyperthermia is blocked by the 5-HT_2 antagonist ketanserin (Nash et al. 1988), while ritanserin, another 5-HT_2 antagonist, has no effect on the behavioural syndrome (Goodwin and Green 1985). It seems likely, therefore, that the hyperthermia and behavioural syndrome associated with MDMA administration results from a marked enhancement of cerebral 5-HT function, with stimulation of both 5-HT_2 and 5-HT_1-like receptors. The recent proliferation of 5-HT receptor subtypes has, of course, overwhelmed the conventional classification of central behavioural actions of 5-HT in relation to broad classes of 5-HT_1 and 5-HT_2 receptors (Humphrey et al. 1993). In the absence of sufficiently selective agonists and antagonists, however, the older classification has provisional value for the present discussion.

The proposal that MDMA produces relatively non-selective effects on postsynaptic 5-HT receptors is supported by the major biochemical consequence of MDMA administration, namely a massive and rapid depletion in 5-HT content of the brain. There can be an 80% loss in the content of brain 5-HT and its metabolite, 5-HIAA, within 4 h of MDMA injection (Schmidt et al. 1986; Stone et al. 1986, 1987; Schmidt 1987; Gibb et al. 1990; Colado and Green 1994). This loss results from the release of neuronal 5-HT and possibly also inhibition of re-uptake of the amine by MDMA and MDA (Johnson et al. 1986; Steele et al. 1987). This proposed mechanism of action makes it different from many other psychoactive amines which interact directly with 5-HT receptors, but is supported by observations that MDMA has only moderate affinity (micromolar) for 5-HT receptors (Lyon et al. 1986; Battaglia et al. 1988b).

The proposed association of the 5-HT releasing properties of MDMA with both the behavioural syndrome and the hyperthermia is also supported by observations made in rats on *p*-chloroamphetamine (PCA; Fig. 1) which also induces a rapid release of cerebral 5-HT (Sanders-Bush et al. 1972; Fuller et al. 1975; Neckers et al. 1976; Colado and Green 1994) and produces both hyperthermia (Colado et al. 1993) and the 5-HT behavioural syndrome (Green and Kelly 1976; Trulson and Jacobs 1976; Colado et al. 1993).

The acute 5-HT depleting effects of MDMA can be blocked by simultaneous administration of the 5-HT uptake inhibitors fluoxetine or citalopram (Schmidt 1987; Schmidt and Taylor 1987; Hekmatpanah and Peroutka 1990). However, this does not seem to be because MDMA is transported by the amine uptake pump; rather, that the release is carrier-mediated and blocked by these antidepressant drugs (Schmidt and Taylor 1987; Wang et al. 1987), or alternatively, that both MDMA and 5-HT uptake inhibitors act at a similar membrane receptor recognition site (Wang and Taylor 1987).

Similar behavioural changes were observed in both monkeys and dogs (Table 1) in the first study of the acute toxicity of MDMA and MDA (Hardman et al. 1973) and the syndrome can also occur in man (Sternbach 1991; see Table 1 and later).

Few studies have been performed on approaches to antagonising the MDMA-induced behavioural syndrome. However, there is a considerable literature on the blockade of the syndrome when it has been induced by administration of tryptophan plus a monoamine oxidase inhibitor or various 5-HT agonists (Green and Heal 1985). Colado et al. (1993) found dizocilpine to be a very effective antagonist of MDMA-induced behaviour, while chlormethiazole injection produced more modest effects. When the behaviour has been induced by administration of 5-HT precursors or agonists, several non-selective 5-HT antagonists such as methysergide and methiothepin block most of the behaviours, but enhance the locomotor activity (Green et al. 1981). The β-adrenoceptor antagonists propanolol and pindolol, by virtue of their 5-HT_{1A} antagonist actions, are also effective blockers of the behaviour produced by 8-OH-DPAT (Goodwin and Green 1985) and also antagonise the behaviour when induced by MDMA administration (Callaway et al. 1992). Neuroleptics, including chlorpromazine and haloperidol, block the hyperlocomotor component of the behaviour and the other behavioural changes following both tranylcypromine/L-tryptophan (Grahame-Smith 1971b; Heal et al. 1976; Green et al. 1981) and MDMA (Green, unpublished).

Phenomenon of amphetamine aggregation toxicity

This phenomenon has not to our knowledge been reported to occur with MDMA. However, it has been demonstrated convincingly with several other sympathomimetic amines, particularly amphetamine, and should it have a parallel in man, may help to explain why the use of MDMA at "raves" has resulted in an upsurge of toxicity problems.

In 1940, Gunn and Gurd reported that when mice were grouped or aggregated, as opposed to being singly housed, both the behavioural and the toxic effects of amphetamine were markedly enhanced. This work was

confirmed and extended by Chance (1946), who demonstrated that the number of animals housed together was important, even if the total area for each mouse was unchanged, and that toxicity was further increased when animals were aggegrated at high ambient temperatures. He also found that in solitary mice toxicity was increased by elevated ambient temperature, external sound and poor hydration (Chance 1947). It is noteworthy that MDMA administration increases evaporative water loss in rats (Gordon et al. 1991).

The possible relevance of this work to the problem of MDMA when used at raves is striking, since all the "worst" conditions are present for amphetamine toxicity – aggegration, high ambient temperature, loud sound and probably dehydration. The dehydration is often promoted by the deliberate high charges made to customers requiring bottled water.

The mechanism of the lethality of amphetamine in aggregated mice had been assumed to be directly related to raised body temperature (Askew 1961; Craig and Kupferberg 1972). However, fatal toxicity can occur without a marked hyperthermia (Wolf and Bunce 1973), so vascular events may also be implicated (see later). Nevertheless, it is still reasonable to regard hyperthermia as a major factor that must be treated in human subjects.

Acute clinical pharmacology and toxicology of MDMA

While Downing (1986) found little evidence for adverse effects in normal volunteers when MDMA was given at a modest but mood changing dose, Greer and Tolbert (1986) and Peroutka et al. (1988) both reported the occurrence of undesirable physical symptoms, including loss of appetite, trismus, nausea, muscle aches, ataxia, sweating, tachycardia, fatigue and insomnia. These effects were stated by the volunteers to increase with successive doses, while the "positive" mood enhancing effects decreased (Peroukta et al. 1988).

Hyperthermia is a major feature in cases presenting with MDMA-induced toxicity, body temperatures as high as 43°C having been reported (Henry et al. 1992). There is an impression that this acute and sometimes fatal problem is generally related to the use of the drug at all night dance sessions or "raves" (Henry 1992; Randall 1992a). This was certainly true of 3/3 cases reported by Screaton et al. (1992) and 5/5 cases reported by Henry et al. (1992). Other publications on severe toxic reactions have not reported the situations in which the drug was taken (Brown and Osterloh 1987; Chadwick et al. 1991; Campkin and Davies 1992). Since amphetamine-induced hyperthermia in mice is promoted by crowded conditions, high ambient temperature, physical activity and volume depletion, it is reasonable to propose that misuse of MDMA at raves may well exacerbate the toxicity problem. Nevertheless, the report of a 13 month old boy who accidentally ingested one tablet and who became hyperthermic indicates that the drug can produce this effect when taken in sufficient quantity in quiet surroundings (Bedford-Russell et al. 1992).

It is probable that it is the hyperthermia that results in the appearance of other, often fatal toxicological problems that have been regularly reported, particularly rhabdomyolysis, disseminated intravenous coagulation and acute renal failure (Brown and Osterloh 1987; Chadwick et al. 1991; Fahal et al. 1992; Henry et al. 1992; Screaton et al. 1992). The same problems have been reported both after MDA (Simpson and Rumack 1981; Woods and Henry 1992) and amphetamine (Ginsberg et al. 1970; Kendrick et al. 1977).

Another consequence of ingestion of MDMA can be the appearance of all the features listed in Table 1. The metabolite MDA also produces these symptoms (Woods and Henry 1992). The similarity of the problems to the serotonin syndrome is striking, as noted by others (Ames and Wirshing 1993; Friedman 1993) who compared the signs and symptoms of MDMA toxicity with those reported by Sternbach (1991) in his review of the serotonin syndrome. The child cited above displayed all these clinical features (Bedford-Russell et al. 1992).

MDMA also causes vascular problems. Hypertension and arrhythmias have been reported (Bedford-Russell 1992; Henry et al. 1992; Screaton et al. 1992) and these effects, together with coagulopathy, are probably responsible for cases of cerebral haemorrhage (Harries and De Silva 1992; Gledhill et al. 1993). This suggestion is supported by a study showing that MDMA administration to rats results in forced cerebrovascular dilatation (Cursham et al. 1994). Some vascular effects may be related to the drug having reasonable affinity for α_2-adrenoceptors (Battaglia et al. 1988b).

It is possible that the adverse reactions are unrelated to the amount of MDMA taken (Henry et al. 1992). However, the veracity of the subjects (Verebey et al. 1988), problems of purity of substance and concomitant ingestion of other psychoactive compounds, both illegal and legal (Smilkstein et al. 1987), must all be taken into account. Repeated exposure to some amphetamine derivatives increases the behavioural and biochemical responses of the animals to the drug (Kazahara et al. 1989). Sensitisation also occurs after repeated low doses of MDMA, with the behaviours associated with the serotonin syndrome increasing in both duration and intensity, while locomotor activity increases only in intensity (Spanos and Yamamoto 1989). Previous MDMA use may therefore exacerbate toxicity problem in humans. A further explanation for the apparent lack of a dose-response relationship has been proposed on the basis of in vitro studies on the metabolite fate of MDMA which may be predominantly metabolised in man and rats by debrisoquine 4-hydroxylase (Kumagai et al. 1994; Tucker et al. 1994).

Since it is probable that it is the parent MDMA that induces the amine release and therefore the hyperthermic response, Tucker et al. (1994) proposed that persons who are poor metabolisers (i.e. deficient in this enzyme; 5–9% of caucasians) may be at greater risk of a severe toxic response to the drug.

Inactivation of tryptophan hydroxylase in rat brain by MDMA

MDMA produces a rapid inhibition of tryptophan hydroxylase, the rate limiting enzyme in the pathway of 5-HT synthesis. This effect lasts for 2 weeks or longer following a single dose of MDMA to rats (Schmidt and Taylor 1987). The drug produces an irreversible inhibition of the enzyme, with restoration of activity requiring synthesis of new enzyme. However, it is probably not the MDMA molecule that causes the inhibition, since it has no effect on hydroxylase activity in vitro (Schmidt and Taylor 1987). Rattray (1991) pointed out that MDMA can be metabolised to a quinone (Hiramatsu et al. 1990), which could combine with sulphydryl groups within the enzyme molecule. Alternatively, MDMA metabolites may generate free radicals that inactivate tryptophan hydroxylase and cause neuronal damage. Support for the first proposal comes from the finding that in the early period (3 h) following MDMA administration, activity of the enzyme can be restored by reduction with sulphydryl reagents under anaerobic conditions (Stone et al. 1989).

Sustained inhibition of tryptophan hydroxylase would be expected to decrease 5-HT synthesis and function which could have psychiatric or other physiological consequences.

Long-term neurotoxicity following MDMA administration to animals

It has been known for many years that administration to rats of several large doses of methamphetamine (Fig. 1) results in long term damage to both 5-HT and dopamine neurones in the brain (Koda and Gibb 1973; Hotchkiss and Gibb 1980; Gibb et al. 1990; Green et al. 1992). Ricaurte and colleagues (1985) first reported that MDA administration damaged 5-HT nerve terminals in rat brain, and this group, and others, subsequently provided substantial evidence for MDMA also having this effect in the brain of rats (Stone et al. 1986; Battaglia et al. 1987, 1988a; Commins et al. 1987; Mokler et al. 1987; Schmidt 1987; O'Hearn et al. 1988; Slikker et al. 1989; Schmidt and Kehne 1990; Colado et al. 1993), guinea pigs (Commins et al. 1987) and several species of non-human primates, namely cynomolgus monkeys (Ricaurte et al. 1988a, b; Wilson et al. 1989), squirrel monkeys (Ricaurte et al. 1988a, b) and rhesus monkeys (Ricaurte et al. 1988a, b; Insel et al. 1989; Kleven et al. 1989; Slikker et al. 1989; Wilson et al. 1989). Unlike methamphetamine, MDMA is a fairly selective neurotoxin for 5-HT pathways in rats, leaving dopamine pathways spared (Schmidt and Kehne 1990). In mice, however, it induces neurotoxic damage to dopamine terminals in the striatum, with little effect on 5-HT in major brain regions (Logan et al. 1988; Laverty and Logan 1990; Miller and O'Callaghan 1994).

Studies on rat brain have shown that after the initial release of 5-HT, which results in massive indole amine depletion, amine levels start to return towards normal. However, after approximately 24 h, brain 5-HT content (particularly in cortex, hippocampus and striatum) starts to fall again. This decrease becomes unequivocal by 2–3 days (Gibb et al. 1990) and concentrations are decreased over many months. This second phase is also marked by loss of tryptophan hydroxylase activity (Schmidt and Taylor 1987). Immunocytochemical and visualisation studies have demonstrated that neurodegenerative changes are seen in the second phase and include increased 5-HT axon calibre, huge swollen varicosities, fragmentation and dilated proximal axon stumps, with forebrain 5-HT terminals being lost (O'Hearn et al. 1988; Molliver et al. 1990).

Other evidence for degeneration of 5-HT nerve terminals includes decreased binding of [^{3}H]-paroxetine to the 5-HT uptake site (Battaglia et al. 1987; Nash et al. 1991; Sharkey et al. 1991; Hewitt and Green 1994) and reduced high affinity uptake of 5-HT (Ricaurte et al. 1985; Commins et al. 1987b; Hewitt and Green 1994). Decreased [^{3}H]-paroxetine binding has been shown to correlate closely with degenerative changes following the 5-HT neurotoxin, 5,7-dihydroxytryptamine (Habert et al. 1985). The hypertrophy of astrocytes in the mouse striatum following MDMA administration (Miller and O'Callaghan 1993) is further evidence for neurodegeneration of dopamine in this species. In rodents most of these changes return to near normal after 12–15 months, but may persist in primates (Ricaurte et al. 1992; Scanzello et al. 1993).

Both acute and long term effects of the drug on monoamine function are influenced by the dose and number of doses administered. Acute release of 5-HT can be induced in rats by a single low dose of MDMA of 5–10 mg/kg (Schmidt and Kehne 1987), while the longer term effects require either a large single dose (20 mg/kg or more) or several lower doses (Battaglia et al. 1988; Ricaurte et al. 1988c; Colado et al. 1993). It seems probable that the long term effects are not related to the acute release of 5-HT, since *S*(+)-MDMA produces the long term toxicity more effectively than R(-)-MDMA but both isomers produce the acute release (Schmidt 1987; Schmidt et al. 1987). It is also likely that it is a MDMA metabolite that produces the long term toxicity, since intracerebral injection of MDMA does not produce neurodegenerative changes (Molliver et al. 1986; Paris and Cunningham 1992).

Furthermore, administration of a 5-HT uptake inhibitor several hours after MDMA results in at least some protection (Schmidt 1987), suggesting that uptake of a toxic MDMA product has been prevented. There is little evidence to support the proposal (Commins et al. 1987; Schmidt 1987) that the released 5-HT has been converted to a neurotoxic derivative such as 5,6- or 5,7-dihydroxytryptamine (Commins et al. 1987; Wrona and Dryhurst 1991), since compounds that protect against MDMA-induced toxicity, including chlormethiazole or dizocilpine, do not prevent either the release of 5-HT (Colado and Green 1994) or the degeneration induced by intracerebral administration of 5,7-dihydroxytryptamine (Snape et al. 1994). A more plausible proposal is that metabolites formed from demethylenation of MDMA might be neurotoxic (Lim and Folz 1991).

While dopamine pathways in rat brain are spared from the degenerative damage, there are indications that MDMA administration acutely alters dopamine release and the levels of dopamine metabolites (Schmidt et al. 1986; Schmidt 1987; Johnson et al. 1991; Colado and Green 1994) and it has been proposed that this effect may be related to the initial release of 5-HT (Gazzara et al. 1989). Nevertheless, it is probable that dopamine is involved in the degenerative process, since prior lesioning of the neostriatum with the selective dopamine toxin 6-hydroxydopamine (6-OHDA) or inhibition of dopamine synthesis with α-methyl p-tyrosine results in MDMA producing much less long term damage to 5-HT neurones (Stone et al. 1988; Schmidt et al. 1990c). Blockade of dopamine receptors with haloperidol also prevents the long term neurotoxicity (Schmidt et al. 1990c; Hewitt and Green 1994). In contrast, damage can be enhanced by administration of the dopamine precursor L-dopa with the MDMA (Schmidt et al. 1991a).

There is now a reasonable body of evidence as to which drugs can prevent the long term neurotoxic damage to 5-HT pathways induced by MDMA administration (Table 2). While most of these have only been shown to prevent the loss of tissue 5-HT content, this loss can be shown to relate directly to neurodegenerative changes that have occurred (Molliver et al. 1990; Hewitt and Green 1994). In addition, chlormethiazole, dizocilpine and haloperidol have been reported to prevent loss of [^{3}H]-paroxetine binding, a more direct neurochemical index of neurodegeration (Hewitt and Green 1994). Despite the apparent heterogeneity of the actions of the drugs, a possible common thread may link the actions of many of them as protective agents, ,since inhibition of dopamine function appears to provide protection against MDMA-induced toxic loss of 5-HT. This would therefore explain the actions of haloperidol (Schmidt et al. 1990c; Hewitt and Green 1994): γ-butyrolactone, which inhibits dopamine release (Colado and Green 1994): α-methyl *p*-tyrosine, which inhibits dopamine synthesis (Stone et al. 1988):

Table 2 Compounds which prevent the long term neurotoxic loss of brain 5-HT following MDMA administration to rats

Compound	Reference
5-HT uptake inhibitors	
Fluoxetine	Schmidt 1987
Citalopram	Schmidt and Taylor 1987
5-HT antagonists	
MDL 11939 (5-HT_2)	Schmidt et al. 1990c
Ritanserin (5-HT_2)	Schmidt et al. 1990a, c
Methiothepin (non-selective)	Schmidt and Taylor 1987
Dopamine antagonists	
Haloperidol	Schmidt et al. 1990c, Hewitt and Green 1994
Antagonism of dopamine release	
γ-butyrolactone	Colado and Green 1994
α-methyl *p*-tyrosine	Stone et al. 1988
Dopamine neurotoxic lesion	
6-hydroxydopamine	Stone et al. 1988
Drugs enhancing GABA function	
Chlormethiazole	Colado et al. 1993, Colado and Green 1994
Pentobarbitone	Colado and Green 1994
Excitatory amino acid antagonists	
Dizocilpine	Colado et al. 1993, Colado and Green 1994, Laverty and Logan 1990
Dextromethorphan	Finnegan et al. 1990

and 6-hydroxydopamine which produces a selective lesion of dopamine pathways (Stone et al. 1988). Both chlormethiazole (Colado et al. 1993; Hewitt and Green 1994), and pentobarbitone (Colado and Green 1994), by enhancing GABA function, would also be expected to inhibit dopaminergic neurotransmission in the striatum (Dray 1979). Similarly, 5-HT antagonists (Schmidt et al. 1990a, b) have been shown to prevent toxicity by blocking the stimulating effects of MDMA on dopamine synthesis (Schmidt et al. 1991b). The 5-HT uptake inhibitors may act to block MDMA inducing 5-HT release (Schmidt and Taylor 1987; Wang et al. 1987) and thereby again prevent the changes in dopamine turnover associated with this release (Gazzara et al. 1989). Why changes in dopamine function are necessary for the action of a postulated neurotoxic MDMA metabolite (Molliver et al. 1986; Paris and Cunningham 1992) is unclear. Finally, it is reasonable to propose that excitatory amino acids (particularly glutamate acting through the *N*-methyl-D-aspartate or NMDA receptor) are involved in the neurodegenerative process. The non-competitive NMDA receptor antagonist dizocilpine (MK 801) protects against neurotoxic loss of amine induced by methamphetamine (Johnson et al. 1989; Sonsalla et al. 1989; Green et al. 1992), MDMA (Johnson et al. 1989; Laverty and Logan 1990; Colado et al. 1993; Hewitt and Green 1994) and amphetamine (Henderson et al. 1992). The NMDA antagonist dextromethorphan is also efficacious against MDMA toxicity (Finnegan et al. 1990).

Administration to rats of *p*-chloroamphetamine (PCA) or fenfluramine (Fig. 1) also induces both the acute and massive 5-HT release and the long term neurotoxic loss of this neurotransmitter (Sanders-Bush et al. 1972; Fuller et al. 1975; Harvey and McMaster 1975; Neckers et al. 1976; Sabol et al. 1992; Colado et al. 1993; Colado and Green 1994). While both these compounds are also reasonably specific in terms of damaging 5-HT neurones while sparing dopamine, the mechanisms involved in their long term neurotoxicity may not be identical to those following MDMA, since long term neurotoxicity cannot be prevented by either dizocilpine (Henderson et al. 1992; Sabol et al. 1992; Colado et al. 1993) or chlormethiazole (Colado et al. 1993).

Long-term clinical neurotoxic effects of MDMA

A major consideration in predicting whether long-term neurotoxic damage occurs in humans has to be the doses and metabolism of MDMA in man vis a vis rodents and primates. The doses used to produce damage in rats are certainly comparable to those that are often used by human subjects (3 mg/kg or considerably more). A dose of 5 mg/kg produced long-term toxic damage to serotonergic neurones in the brains of squirrel monkeys whether given subcutaneously or, more importantly, orally (Ricaurte et al. 1988c).

There is evidence that humans can be more sensitive to some neurotoxic substances than rats or primates. One example is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is mildly toxic in rats, but extremely toxic in primates (Burns et al. 1983; Boyce et al. 1984; Chieuh et al. 1984; Langston et al. 1984) and a further 5- to 10-fold more toxic in humans leading to a severe form of Parkinsonism (Langston et al. 1983). This is perhaps the prime example of a "designer drug" synthesised illegally for recreational use producing a severe neurotoxic lesion. In this case, however, the active compound producing the lesion has been identified and there is unequivocal evidence of clinical problems. In contrast, following MDMA administration, the chemical resulting in 5-HT terminal neurodegeneration has not been identified. There are, however, some clues. Since MDMA injected directly into the brain is not neurotoxic (Molliver et al. 1986; Paris and Cunningham 1992), the assumption has been that an active metabolite must be responsible. Lim and Foltz (1991) have identified in vitro and in vivo several metabolic products of MDMA including 2,4,5-trihydroxymethamphetamine and 2,4,5-trihydroxyamphetamine. Compounds of this type are potent neurotoxins but the spectrum of damage is not identical to MDMA (Johnson et al. 1992), indicating that these metabolites are not necessarily the cause of the degeneration. There is also the problem that dopamine antagonists (Schmidt et al. 1990c; Hewitt and Green 1994) and 5-HT_2 antagonists (Schmidt et al. 1990a, b) prevent neurodegeneration. This is hard to explain within the framework of action of a neurotoxic metabolite.

The fact that fenfluramine (Fig. 1) also releases 5-HT and produces neurotoxicity in rodents and yet has been used clinically and apparently safely for many years (Grob et al. 1990; Seiden 1990) has been used as an argument against MDMA producing long-term damage in human brain. Fenfluramine, however, is not commonly misused and is taken in controlled doses of approximately 1 mg/kg per day. There are, nevertheless, those who have expressed concern about the safety of fenfluramine (Barnes 1989).

The doses of MDMA that are ingested recreationally gives rise to concern that it is producing long term neurotoxicity and there are also some worrying, albeit indirect, indications in the literature that MDMA may be neurotoxic in humans. In the first place the drug produces long term loss of 5-HT neurones in non-human primates (Ricaurte et al. 1988a, b, c, 1992; Insel et al. 1989; Kleven et al. 1989; Slikker et al. 1989; Wilson et al. 1989; Ali et al. 1993). Furthermore, this loss may not be reversible as it is in rodents, recovery not being noted in the primates after a year (Ricaurte et al. 1992).

More directly, in a group of human subjects who ingested MDMA regularly, there was a significant decrease (25%) in the concentration of 5-HIAA in the cerebrospinal fluid compared to a control group, while the levels of the dopamine metabolites homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) were the same in both groups (Ricaurte et al. 1990). MDMA-induced damage to serotonin pathways in non-human primates also resulted in lowered CSF 5-HIAA concentrations (Ricaurte et al. 1988b). Of the 33 persons who had taken MDMA in the study on CSF 5-HIAA, 30 denied any signs or symptoms of depression, sleep disturbance, altered pain perception or changes of sexual function, all known markers of changed 5-HT function in animals. However, three did report some psychiatric problems. More recently, it has been reported by the same laboratory (Allen et al. 1993) that a group of MDMA users had less non-REM and less total sleep time than controls (primarily due to an average of 37 min less stage 2 sleep). Finally, Price and colleagues (1989) noted an apparent blunting of the prolactin response to L-tryptophan administration in heavy MDMA users compared to a control group. This blunting just failed to reach statistical significance, but subject numbers were low.

All these studies can be criticised because the subjects were often poly-drug users and unreliable sources of information as to when they had ceased drug use. Therefore, it cannot be stated that any of the changes outlined above are the result of MDMA use and unequivocally indicate altered serotonergic function. All three studies nevertheless point to the possibility of decreased 5-HT function having occurred in the human brain.

Longer term psychiatric complications following MDMA ingestion

The acute psychiatric complications of MDMA use are, of course, mood alteration and visual hallucination, but these are presumably the desired effect of taking the drug in the first place. In this regard, there is one report that fluoxetine taken before MDMA failed to block the mood altering effects of the drug (McCann and Ricaurte 1993). Since fluoxetine blocks the rapid release of 5-HT which occurs after MDMA (Schmidt 1987), this suggests that the drug must interact directly with 5-HT receptors despite its modest affinity for these sites (Lyon et al. 1986; Battaglia et al. 1988). An alternative explanation is that, at the dose used, only a partial block of release was achieved.

Longer term psychiatric problems have also been reported following MDMA use, none of which are pleasant or desired. McCann and Ricaurte (1991) reported two cases: in one, symptoms included panic attacks, insomnia and depression, which continued for approximately 5 months after the last ingestion; while in the other case, anxiety, insomnia, hallucinations and paranoia persisted 2 years later despite cessation of drug ingestion. The problem of chronic paranoid psychosis after MDMA misuse has been reported by others (Creighton et al. 1991; McGuire and Fahy 1991; Schifano 1991; Winstock 1991). Symptoms have included paranoid delusions involving change in body shape, jealousy and depression. There were also periods of greater normality followed by "flashbacks", despite abstinence from further drug abuse. There have also been reports of cases of panic attack and depression following MDMA (Whitaker-Azmitia et al. 1989; Benazzi and Mazzoli 1991; McGuire et al. 1994). The diversity of the psychiatric problems in MDMA users was recently highlighted by McGuire et al. (1994).

Since these associations are with relatively common psychiatric disorders, it would be premature to claim that they offer conclusive proof of a causal link. They nevertheless offer no grounds for reassurance. However, the relationship between drug misuse of any sort and psychosis is often more confused than it deserves to be because of the lumping together of different sorts of abnormal mental state and extravagant extrapolations from single cases. It will be useful to sketch out a framework without pretending that we have sufficient evidence yet to understand the place of MDMA within it. Most acute toxic psychoses are confusional. While patients may be floridly deluded, hallucinated and fearful, there will be subsequent amnesia for the details of the episode, and usually a clear cut recovery. Some accounts of MDMA psychosis suggest it can produce a confusional state of this sort; indeed, this would be expected in the setting of significant systemic toxicity. By contrast and perhaps exceptionally, some drugs, most notoriously amphetamine and its derivatives, are described as inducing, acutely, a truly schizophrenia-like psychosis which resolves rapidly on withdrawal of the offending drug. This classical version of the "drug-induced psychosis" portrays a time limited toxic side effect of acute drug action which masquerades as a well known mental illness. The kinship between MDMA and amphetamine means that this sort of effect may be observed, although acute effects of this sort are likely to be very rare.

Much more commonly, misuse of drugs has been suggested to be associated, with a range of psychotic illnesses. It is too early to assess whether MDMA carries a special risk in this regard. The central question is whether the misuse of any drug produces new cases of chronic illness. There are three important and rather different interpretations of the existing data for other drugs.

1. If high risk individuals are more likely to misuse drugs in the first place, the apparent association may be largely statistical and drug misuse will not increase the total number of cases of mental illness in the community, although it may compound other problems.
2. If drug misuse actually increases the risk of chronic psychosis, this is most likely to occur in a vulnerable pool of individuals with a high predisposition to develop the illness anyway (McGuire et al. 1993) and the effect of the drug will be relatively unimportant for producing new cases.
3. Finally, if drug misuse can appreciably increase the morbid risk of subjects at only modest risk of illness, what should we expect to find when drug use becomes rife within a youth culture? First, there should be an increase in first admissions with psychosis (Rolfe et al. 1993). Second, we should expect a rate of psychosis in non-drug using parents that is greater than the normal population, but the same as that in case controls who have not misused drugs. Third, we should expect a disproportionate increase in the incidence of psychosis among siblings who are likely to share both the genetic and the drug related risk (see Kay 1992; Sugarman and Cranford 1994).

Other toxicological problems associated with MDMA use

This review has focussed on the acute and often life-threatening effects of MDMA primarily mediated by the hyperthermia, and on the possibility of, long term neurotoxic degeneration of brain 5-HT terminals also occurring. However, it should not be forgotten that other clinical problems have also been associated with the drug. Henry et al. (1992) reported seven cases of hepatotoxicity probably associated with the MDMA abuse, rather than with hyperthermia. Others have made similar, although anecdotal, observations (Gorard et al. 1992; Shearman et al. 1992). Sawyer and

Stephens (1992) suggested that MDMA users may well present with fits and other more clinical minor problems, which should be borne in mind in assessing young patients. Finally, Dowling et al. (1992) suggested that the deaths in three of the five cases he reviewed may have resulted from exacerbation of an underlying disease, particularly the problems of arrhythmias.

Towards a rational treatment for MDMA toxicity

There is at present no "antidote" for the patient presenting with acute MDMA-induced toxicity. However, it is clear that certain steps are mandatory and have already been used successfully in several of the clinical reports outlined earlier; Henry (1992) has also summarised his accumulated experience. The first priority is to decrease body temperature. "Chill out" rooms are sometimes present at "raves", so users appear to be aware of the problem. Clinically, it may be necessary to surround the body with ice. Dantrolene has also been used in several reports and is recommended by Henry (1992). Others support his proposal (Singarajah and Lavies 1992; Tehan 1993), while Barrett (1992) questioned its use on the basis that it is a peripherally acting muscle relaxant with no central effects and is therefore not acting at the site of the primary "problem". This is not to say, of course, that it is not efficacious. A further important point here is that in mice preventing the hyperthermia also lessens the long term neurotoxicity (Miller and O'Callaghan 1994).

On the basis of animal studies (and suggesting only drugs in current therapeutic use), chlormethiazole (Colado et al. 1993; Hewitt and Green 1994), haloperidol (Hewitt and Green 1994), a 5-HT_2 antagonist such as ritanserin (Nash et al. 1988; Schmidt et al. 1990a) or a non-selective antagonist such as methysergide can be suggested to be of possible value in decreasing body temperature. However, the use of neuroleptics requires comment because of the evidence that reduced dopaminergic function can promote hyperthermia. Indeed, the association between neuroleptic use and hyperthermia is confirmed in the "neuroleptic malignant syndrome" (Kaufmann and Wyatt 1987). Since release and depletion of 5-HT or dopamine, or both, probably contribute to the hyperthermia induced by MDMA and other amphetamines, the addition of a dopamine antagonist which will interfere with thermoregulatory pathways may be unwise. Caution is therefore warranted in the management of MDMA related toxic states with neuroleptics.

With regard to the other aspects of toxicity, both clinical and animal evidence indicates the need for rapid hydration. Henry (1992) also pointed out the need to control the excitation and convulsions. This has usually been achieved with benzodiazepines, and in one report this was done successfully with intravenous chlormethiazole following unsuccessful use of diazepam and haloperidol (Bedford-Russell et al. 1992). Indeed, chlormethiazole appears to meet many of the requirements for a drug for use in the treatment of acute toxicity; for example, sedative action, availability in parenteral form and pharmacologically relevant central actions, including antagonism of the serotonin syndrome and anticonvulsant activity. Further observations on its use will no doubt accumulate.

Selective 5-HT uptake inhibitors such as fluoxetine or citalopram are probably contraindicated. While they may block the effects of MDMA if given before the drug, if given afterwards they may result in a potentiation of the effects of the released 5-HT. There are also at least theoretical reasons for proposing that they could induce long term damage to dopamine neurones (see discussion to Ricaurte et al. 1990).

Concerns about treatment which will prevent the long term neurotoxicity cannot feature strongly in any approach in the absence of definite evidence either that this occurs, or is likely to occur, in patients presenting with an acute overdose. However, both chlormethiazole and haloperidol may be of value in the acute treatment and animal experiments suggest that they might prevent the long term toxicity (Schmidt et al. 1990c; Colado et al. 1993; Hewitt and Green 1994).

It is beyond the scope of this review to examine public health measures which might reduce the toxicity problems, given that it is unlikely that illicit MDMA use will diminish. However, obvious measures do include the provision of free water and temperature control at venues, together with a greater knowledge in users of the problems of MDMA use, the particular dangers of large doses, and recognition of the early signs of toxicity.

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