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Altered states: the clinical effects of Ecstasy

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Abstract

Ecstasy is the second most widely abused illegal drug in Europe. Ecstasy is the colloquial name for 3,4-methylenedioxymethamphetamine (MDMA), but not all Ecstasy tablets contain MDMA. When taken in hot, crowded environments, Ecstasy/MDMA users have developed acute complications that have had fatal consequences. Epidemiological evidence indicates that adverse reactions to Ecstasy/MDMA intoxication are rare and idiosyncratic. Potential mechanisms of action are reviewed. In animal studies, MDMA damages serotonergic fibres and reduces the number of serotonin transporter sites within the CNS. Demonstration of neurotoxicity in human users of Ecstasy is hampered by a number of confounds that the majority of published studies have failed to address. These confounds are reviewed and their impact is discussed.

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CYP2D6, debrisoquine 4-hydroxylase; HPA, hypothalamic-pituitary-adrenal; LSD, lysergic acid diethylamide; MDA, 3,4-methylenedioxyamphetamine; MDE, 3,4-methylenedioxyethamphetamine; MDMA, 3,4-methylenedioxymethamphetamine.

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1. Introduction

Ecstasy is the colloquial name used to describe the entactogen, 3,4-methylenedioxyamphetamine (MDMA). Hallucinogens are a class of drugs that cause an altered state of consciousness characterised by illusions or hallucinations. This classification encompasses a wide range of drugs, including lysergic acid diethylamide (LSD), phencyclidine, and mescaline (Kovar, 1998). Nichols (1986) has argued that 3,4-methylenedioxyamphetamine (MDA), which is usually classified as a hallucinogen, does not produce profound sensory disruption or hallucinations. Instead, it increases emotional sensitivity and empathy; thus, MDA has colloquially been referred to as the “love drug.” As MDA does have some hallucinogenic activity, it is appropriate for it to be classified as a hallucinogen (Nichols, 1986). As the *N*-methyl derivative of MDA, MDMA does not reliably produce hallucinations or generalise to LSD in the drug discrimination paradigm (i.e., MDMA does not produce the same internal state as other hallucinogens; e.g., Nichols & Oberlender, 1990). Based on this, Nichols (1986) postulated that MDMA represents a novel class of compound, in that it possesses unique effects, which means that it cannot be classified as either a hallucinogen or a psychostimulant. Nichols (1986) proposed the neologism “Entactogen” (from Greek and Latin roots, literally “producing a touching within”) to describe the effects of MDMA and related compounds. This definition is based on the claimed ability of MDMA to allow therapists and patients to access and deal with repressed painful emotional issues (Greer & Tolbert, 1990; Grinspoon & Bakalar, 1986).

MDMA was patented in 1914 by Merck, but was never made commercially available. During the 1950s and 1960s, the United States Army tested MDMA (designation EA-1475) and related drugs at its Edgewood Arsenal and at the University of Michigan (Shulgin, 1990). In 1977, the United Kingdom Home Office listed MDMA as a class A drug and placed it into schedule 1 of the Misuse of Drugs Act (1971), indicating that it had no medicinal uses. However, MDMA only came to the attention of the public when it was added to schedule 1 of the Controlled Substances Act by the United States Food and Drug Administration in 1985. Until then, MDMA use was restricted to few areas of the United States, such as Texas, where it could be purchased in bars (Beck, 1990; Shulgin, 1990). The schedule 1 status was based on the premise that MDMA had no accepted medical use and a high abuse potential. 3,4-Methylenedioxyamphetamine (MDE or “Eve”) was not included in this process, and its use became widespread before the Analogue Substance Act came into force in 1986. This Act made any

drug illegal, which has actions or structures “substantially similar” to existing controlled substances.

In the United Kingdom during the mid-1980s, all night dance parties were becoming popular. These events, called “raves,” were typically hot, crowded venues with loud repetitive electronic music and light shows. The drug of choice for people attending raves was Ecstasy, and the popularity of this youth culture led to an explosion of recreational Ecstasy use.

Ecstasy is normally sold as “brand name” tablets, which are given identifiable features such as imprints and/or colours (e.g., Cole et al., 2002a; Forsyth, 1995; Sherlock et al., 1999). The amount of MDMA that is present in these tablets varies widely, even within identical tablets (Arimany et al., 1998; Bell et al., 2000; Cole et al., 2002a; Lenton et al., 1997; Milroy et al., 1996; Rothe et al., 1997; Saunders, 1997; Sherlock et al., 1999; Spruit, 1999; Wolff et al., 1995). In addition, a large percentage of the tablets, which are sold as Ecstasy, do not contain MDMA, but either contain other controlled drugs, such as MDE and amphetamine, or noncontrolled drugs, such as ketamine and ephedrine (Arimany et al., 1998; Baggott et al., 2000; Lenton et al., 1997; Milroy et al., 1996; Ramsey et al., 2001; Rothe et al., 1997; Saunders, 1997; Sherlock et al., 1999; Spruit, 1999; Wolff et al., 1995). In 1997, only 34% of the Ecstasy tablets tested in Holland contained MDMA, and in previous years, this figure rarely increased beyond 50%. In 1998, the amount of MDMA increased significantly to 75% of all Dutch tablets (Spruit, 1999). This has led the World Health Organization to conclude that the term Ecstasy is generic for a wide range of compounds (WHO, 1997). The content of Ecstasy tablets is the most important issue in determining whether the clinical effects of Ecstasy are due to MDMA.

2. Patterns of Ecstasy use

According to the United Nations International Narcotics Control Board, Ecstasy is the second most commonly used controlled drug in Europe (United Nations, 1997). In the United Kingdom, ~10% of young adults aged between 15 and 29 have tried Ecstasy (Bradley & Baker, 1999; Gore, 1999; Miller & Plant, 1996; Ramsey et al., 1999; Webb et al., 1997, 1998). In the United States, 8% of high school seniors admitted MDMA use in 2000 (Johnson et al., 2001). Between 1989 (4%) and 1994 (43%), there was a statistically significant increase in the knowledge and experience of Ecstasy amongst 14- to 15 year olds in the United Kingdom (Wright & Pearl, 1995). Although these figures may not represent actual usage, it does suggest that there is a

significant proportion of young people who are exposed to Ecstasy before the age of 16.

Young adults who attend raves and nightclubs are around 14 times more likely to have used Ecstasy than the general population, with ~90% of subjects reporting use (Bean et al., 1997; Forsyth, 1996; Hammersley et al., 1999; Lenton et al., 1997; Riley et al., 2001; Solowij et al., 1992; Winstock et al., 2001). This indicates that within certain youth subcultures and specific locations, there may be high densities of Ecstasy users and, therefore, an increase in Ecstasy-related problems. The most common drugs used at such events are Ecstasy and amphetamine, closely followed by the hallucinogens LSD and psilocybin (Bean et al., 1997; Forsyth, 1996). In addition, some of these drugs are used simultaneously to gain specific effects, and some depressant drugs, such as heroin and benzodiazepines, are used after the event (Boys et al., 1997; Forsyth, 1996; Hammersley et al., 1999; Schuster et al., 1998; Solowij et al., 1992; Topp et al., 1999; Williams et al., 1998; Williamson et al., 1997).

3. Preclinical pharmacology of MDMA and MDE

As an in-depth examination of the preclinical pharmacology of MDMA and MDE is beyond the scope of this review, only a brief summary will be detailed here for comparative purposes (for more in-depth reviews, see Green et al., 1995; Hegadoren et al., 1999; Ricaurte et al., 2000; Steele et al., 1994; White et al., 1996). The most characteristic acute effect of MDMA administration to animals is a rapid release of 5-hydroxytryptamine (5-HT) from presynaptic vesicles and inhibition of 5-HT reuptake, followed by a pronounced decrease in brain levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) and the activity of tryptophan hydroxylase (Crespi et al., 1997; Irvani et al., 2000; Stone et al., 1989). This decrease in 5-HT content within the brain recovers within 24 hr (Schmidt, 1987b). Within 3 days, however, there is a sustained and regionally specific depletion of 5-HT and 5-HIAA content, which has been shown to last for up to 12 months in the rat (Battaglia et al., 1988; Fischer et al., 1995; Lew et al., 1996; Sabol et al., 1996; Scanzello et al., 1993). The most severe reductions of 5-HT and 5-HIAA are found in the striatum, hippocampus, and prefrontal cortex, with smaller reductions in the brain stem and hypothalamus (Sabol et al., 1996). There is also a persistent reduction in the density of 5-HT transporter sites in the rat brain labeled by [³H]paroxetine, which suggests presynaptic terminal degeneration (Lew et al., 1996). Immunocytochemistry has been used to show that MDMA causes loss of fine axons projecting from the dorsal raphe nuclei, whilst it spares the thick beaded axons projecting from the median raphe nuclei (Axt et al., 1994). This loss of axon terminals is most pronounced in the striatum, hippocampus, and prefrontal cortex, and parallels the loss of 5-HT transporter sites (Battaglia et al., 1991). There have been no similar observations of long-term

damage to other neurotransmitter systems in either rat or primate. Therefore, MDMA is considered to be a selective serotonergic neurotoxin. The cell bodies in the dorsal raphe nuclei are not damaged by MDMA, and this suggests that there is a capacity for regeneration (Battaglia et al., 1990; McKenna & Peroutka, 1990; Sprague et al., 1998). Animal studies have shown that there is recovery of serotonergic function after neurotoxicity induced by repeated high doses of MDMA, although it may be abnormal (e.g., Fischer et al., 1995; Hatzidimitriou et al., 1999; Scanzello et al., 1993).

MDMA also induces the release of dopamine, and there is a correlation between this release and the extent of serotonergic transporter deficits (Nash & Nichols, 1991; White et al., 1996). 5-HT_{2A} receptor activation is known to increase dopamine synthesis and release, and it is possible that the 5-HT released by MDMA may activate the 5-HT_{2A} receptor (Gudelsky & Nash, 1996; Koch & Galloway, 1997; Schmidt et al., 1994). The extracellular levels of dopamine and the neurotoxicity following MDMA administration are reduced after administration of a 5-HT_{2A} receptor antagonist (Malberg et al., 1996; Nash, 1990). Reducing availability of dopamine with synthesis inhibitors or destruction of dopaminergic terminals also protects against MDMA-induced neurotoxicity (Brodkin et al., 1993; Schmidt et al., 1990). In addition, increasing the extracellular levels of dopamine potentiates MDMA neurotoxicity (Schmidt et al., 1991). Reuptake of dopamine into the 5-HT terminal has been hypothesised to cause neurotoxicity, as metabolism of dopamine by monoamine oxidase-B produces hydrogen peroxide, which could lead to lipid peroxidation and oxidative stress (Sprague et al., 1998).

MDE produces a smaller release of dopamine than MDMA, but is equipotent at releasing 5-HT in the rat (McKenna & Peroutka, 1990; Nash & Nichols, 1991; Schmidt, 1987a). After a single administration, MDE does not produce such a profound loss of 5-HT and 5-HIAA as MDMA in the rat (Nash & Nichols, 1991; Schmidt, 1987a). Multiple high doses of MDE, however, do cause a pronounced decrease in the number of fine serotonergic axons in a similar fashion to MDMA (Series & Molliver, 1994). Ricaurte and colleagues (1987) have concluded that MDMA is 4 times more potent than MDE at producing long-term serotonergic damage in the rat.

In the rat, core temperature changes induced by the administration of MDMA are dependent upon environmental variables, such as cage type and ambient temperature. Different types of cages have been shown to affect the hyperthermic properties of MDMA, with acrylic cages producing an increase of over 2°C and metal cages producing no hyperthermia (Gordon & Fogelson, 1994). At high ambient temperatures, MDMA causes hyperthermia; conversely, in low ambient temperatures, it causes hypothermia (Dafters 1994, 1995; Farfel & Seiden, 1995a; Gordon et al., 1991; Malberg et al., 1996; Malberg & Seidean, 1998; Schmidt et al., 1990). Intermediate ambient temperatures typically produce a biphasic response, initially hypothermia followed by

hyperthermia (Dafters & Lynch, 1998). High ambient temperatures increased the lethality of MDMA, which is consistent with the large number of fatal reactions reported from raves (Gordon et al., 1991; Malberg & Seiden, 1998). In addition, sustained hyperthermia enhances MDMA-induced neurotoxicity (Broening et al., 1995; Colado et al., 1998), although neurotoxicity sometimes occurs in the absence of core temperature change or even after hypothermia (Broening et al., 1995; Marston et al., 1999). Most drugs that protect against MDMA-induced neurotoxicity either cause hypothermia or prevent MDMA-induced hyperthermia (Colado et al., 1998, 1999a, 1999b). It has been found that the neuroprotective effects of pentobarbitone, haloperidol, ketanserin, and α -methyl-*p*-tyrosine are lost by increasing the core temperature of the animal (Colado et al., 1999a, 1999b; Malberg et al., 1996). This does not mean, however, that the neurotoxicity and hyperthermia are mediated by the same systems. MDL 11,939, a 5-HT₂ receptor antagonist, blocked the hyperthermia and neurotoxicity caused by low doses (10–20 mg/kg) of MDMA, but these effects were dissociated at a higher dose (30 mg/kg) when MDL 11,939 failed to alter the hyperthermic response to MDMA, and still prevented neurotoxicity (Schmidt et al., 1990). In addition, fluoxetine has no effect on MDMA-induced hyperthermia, but still protects against MDMA-induced neurotoxicity (Malberg et al., 1996). At present, the precise relationship between MDMA-induced hyperthermia and neurotoxicity is unknown.

Behavioural neurotoxicology studies have generally failed to find baseline changes in a variety of tests using similar long time periods after neurotoxic doses of MDMA (e.g., Dornan et al., 1991; Frederick & Paule, 1997; McNamara et al., 1995; Ricaurte et al., 1993; Robinson et al., 1993; Seiden et al., 1993). When MDMA is readministered after neurotoxic dosing regimens, there are changes in behavioural responding (e.g., Frederick & Paule, 1997; Li et al., 1989; Schechter, 1991; Virden & Baker, 1999). This effect is also seen with opiates and cocaine after MDMA-induced neurotoxicity (Horan et al., 2000; Fletcher et al., 2001; Kalivas et al., 1998; Morgan et al., 1997; Nencini et al., 1988). This suggests that the neurotoxic effects of MDMA are not manifested behaviourally, although there are underlying neurochemical changes.

4. Physiological effects of MDMA and MDE

In humans, serum levels of MDMA and MDE peak 2 hr after administration, although they are detectable after 15 min (Brown & Osterloh, 1987; Brunnenberg et al., 1998; De La Torre et al., 1999, 2000a, 2000b; Helmlin et al., 1996; Mas et al., 1999; Vereby et al., 1988). The elimination half-life is 8 hr, and large amounts of MDMA are excreted in the urine. By increasing the dose of MDMA by a factor of 3 (from 50 to 150 mg), the area under the plasma concentra-

tion versus time curve increases by a factor of 10 (457–5439 ng mL⁻¹ hr⁻¹) and peak plasma concentrations increase by a factor of 6 (0.051–0.465 mg/L). The nonlinear pharmacokinetics of MDMA suggest that small increases in dose could lead to large increases in plasma concentrations of MDMA and increased risk of overdose (De La Torre et al., 1999, 2000a, 2000b; Mas et al., 1999).

The stereoisomers of MDMA are metabolised and eliminated at different rates, with *S*(+)-MDMA being metabolised faster than *R*(-)-MDMA (Fallon et al., 1999; Moore et al., 1996). In the rat, *S*(+)-MDMA has been shown to be more neurotoxic than *R*(-)-MDMA (Johnson et al., 1988; Schmidt, 1987a). Intracerebroventricular injections and injections into the hippocampus and raphe nuclei of MDMA do not produce neurotoxicity, despite equivalent brain concentrations to peripheral administration (Esteban et al., 2001; Paris & Cunningham, 1991; Schmidt & Taylor, 1988). This indicates that a toxic metabolite is responsible for MDMA-induced neurotoxicity. The main metabolic pathway for MDMA is oxidation of the methylenedioxyphenyl group, which is catalysed in the liver by debrisoquine 4-hydroxylase (CYP2D6), a member of the cytochrome P450 family of enzymes (Tucker et al., 1994). The primary product of this process is 3,4-dihydroxymethamphetamine (DHMA). *N*-demethylation of MDMA results in the formation of MDA, which explains its presence in blood and urine after MDMA ingestion (Chu et al., 1996; Tucker et al., 1994).

Tucker and colleagues (1994) proposed that reduced metabolism of MDMA may increase the risk of hyperthermia, and as ~7% of Caucasians are deficient in the CYP2D6 enzyme (“poor metabolisers”), this may explain otherwise “idiosyncratic” hyperthermic reactions. Females of the Dark Agouti rat strain have been proposed as an animal model of the human poor metaboliser, and it has been found that these animals are more susceptible to the hyperthermic effects of MDMA (Colado et al., 1995). These rats are also less susceptible to the neurotoxic effects of MDMA, suggesting that metabolites may be partly responsible (Chu et al., 1996; Colado et al., 1995). Ingestion of MDMA and ritonavir, which inhibits the CYP2D6 enzyme, leads to higher than expected blood levels of MDMA (4.56 mg/L from an estimated 180 mg of MDMA) and a toxic reaction (Henry & Hill, 1998). As anecdotal reports suggest that recreational users are now using fluoxetine to reduce post-Ecstasy depression and potential neurotoxicity (McCann & Ricaurte, 1993), it is possible that there may be an increase in the number of similar cases, as fluoxetine also inhibits the CYP2D6 enzyme (Byard et al., 1998). In a sample of patients reporting adverse reactions to Ecstasy ingestion, none of them were homozygous for the mutation of the CYP2D6 gene on chromosome 22, which suggests that they were not poor metabolisers (O’Donohoe et al., 1998). It should be noted, however, that the 7 cases used did not actually present with the typical adverse reaction to Ecstasy ingestion (hyperthermia), and the routine toxicology screens used were not capable of detecting

MDMA. In 3 cases of hepatotoxicity, the patients were not homozygous for the mutation of the CYP2D6 gene. As these patients were also afebrile, fulminant hyperthermia was not the cause of the liver damage. These results suggest an idiosyncratic reaction, as the severity of the damage did not correlate with the amount or frequency of Ecstasy use (Jones & Simpson, 1999; Schwab et al., 1999). The relationship of CYP2D6 to the adverse effects of MDMA still remains to be determined.

When given acutely in recreational doses to human volunteers (0.25–1.9 mg/kg p.o.), MDMA increased cardiovascular activity, which peaked between 1 and 2 hr post administration (De La Torre et al., 2000a, 2000b; Downing, 1986; Grob et al., 1996; Lester et al., 2000; Liechti & Vollenweider, 2000a, 2000b; Mas et al., 1999; Vollenweider et al., 1998, 1999a, 1999b). At a dose of 1.5 mg/kg, mean heart rate was increased by 28 bpm, systolic blood pressure by 25 mm Hg, diastolic blood pressure by 7 mm Hg, and cardiac output by 2 L/min (Lester et al., 2000). These changes were greater in males than in females (Liechti et al., 2001a). Increased heart rate and blood pressure were also observed for 4 hr post MDE (140 mg p.o.) administration (Gouzoulis et al., 1993a; Gouzoulis-Mayfrank et al., 1999). Several researchers report that their subjects had no awareness of these cardiovascular changes, and they were not associated with any reported discomfort (Downing, 1986; Gouzoulis et al., 1993a; Gouzoulis-Mayfrank et al., 1999; Grob et al., 1996). However, Vollenweider and colleagues (1998) found that one-third of their subjects reported palpitations, but no other signs of hypertension or discomfort. Gouzoulis-Mayfrank and colleagues (1999) found that when subjects did report somatic changes, they were not perturbed by those changes. As the subjects are either unaware of the physiological changes or pay no attention to them, there is a possibility that toxic reactions may be exacerbated by Ecstasy users' behaviour.

In the laboratory, MDMA administration (0.25–1.9 mg/kg p.o.) to human volunteers does not reliably increase body temperature, and any observed increases do not exceed 0.4°C (De La Torre et al., 2000a, 2000b; Grob et al., 1996; Liechti et al., 2001a; Liechti & Vollenweider, 2000a, 2000b; Mas et al., 1999; Vollenweider et al., 1998). These changes in temperature were not found in females when compared with males (Liechti et al., 2001a). Administration of MDE causes a statistically significant increase in body temperature, which did not exceed 0.6°C (Gouzoulis-Mayfrank et al., 1999). As preclinical studies indicate that there is an interaction between the environmental variables and the effects of MDMA on body temperature, the fulminant (i.e., sudden onset) hyperthermia observed in adverse reactions to MDMA ingestion is probably caused by its use at raves and in nightclubs.

Low-dose MDMA administration (0.25–1.0 mg/kg p.o.) increased plasma levels of adrenocorticotrophic hormone (ACTH) (+0–5 g/mL), cortisol (+15 µg/dL), prolactin (+17.5 ng/mL), and arginine vasopressin (AVP) (+2.5

pM), with a decrease in plasma Na⁺ concentrations (De La Torre et al., 2000a, 2000b; Forsling et al., 2001; Grob et al., 1996; Henry et al., 1998; Pacifici et al., 1999, 2001). MDE administration produces significant long-lasting increases in serum cortisol and prolactin levels, but no change in growth hormone levels (Gouzoulis et al., 1993a; Gouzoulis-Mayfrank et al., 1999). The neuroendocrine changes induced by MDMA and MDE are compatible with the effects of serotonergic drugs on the hypothalamic-pituitary-adrenal (HPA) axis (Abel & Cleare, 1999; Fuller, 1996). The rave environment itself may also produce similar effects, as normal volunteers listening to “techno music” have increases in heart rate, systolic blood pressure, stress, and plasma levels of noradrenaline, adrenaline, prolactin, cortisol, growth hormone, ACTH, and β-endorphin compared with listening to “classical music.” Listening to fast music alters the glucocorticoid response to exercise and increases endurance, which may explain the preference for loud, fast music at all night raves (Gerra et al., 1998a). It is possible that the rave music may be contributing to the toxic profile of the entactogens through one of these mechanisms, but ethical constraints do not permit a direct examination of this hypothesis.

Retrospective reports from large numbers of recreational Ecstasy users have supported the laboratory findings on MDMA and MDE. Users report sweating, tachycardia, hypertension, increased body temperature, and palpitations (Cohen, 1995; Cregg & Tracey, 1993; Davison & Parrott, 1997; Greer & Tolbert, 1986; Hayner & McKinney, 1986; Peroutka, 1990; Peroutka et al., 1988; Siegel, 1986; Solowij et al., 1992). In addition, most retrospective studies report nausea and vomiting as prominent features of Ecstasy intoxication, although this has only occurred in few laboratory studies of MDMA (e.g., Downing, 1986; Vollenweider et al., 1998). Muscle tension and muscular phenomenon, such as motor tics and bruxism (grinding of the teeth), are also extensively reported (Cohen, 1995; Cregg & Tracey, 1993; Davison & Parrott, 1997; Greer & Tolbert, 1986; Hayner & McKinney, 1986; Liester et al., 1992; Peroutka, 1990; Peroutka et al., 1988; Siegel, 1986; Solowij et al., 1992). Bruxism in the acidic environment caused by co use of fizzy drinks is believed to cause increased wear of the teeth in Ecstasy users (Redfeam et al., 1998; Milosevic et al., 1999).

Subjects also report sleep disturbances and insomnia (Liechti et al., 2001a; Vollenweider et al., 1998). MDE, when given to volunteers immediately prior to going to bed, caused the subjects to wake up after 30–90 min and to stay awake for about 125 min. After the subjects had fallen asleep again, rapid eye movement sleep was suppressed and a cyclic alternation of slow wave sleep with periods of light sleep emerged in the latter part of the night, which is similar to the effects of amphetamine intoxication (Gouzoulis et al., 1992). A retrospective laboratory study found reduced total sleep time and nonrapid eye movement sleep in abstinent Ecstasy users when compared with matched controls (Allen

et al., 1993). The mechanisms by which the entactogens affect sleep in both short-term and long-term have not been investigated.

5. Fatalities caused by MDMA and MDE intoxication

Prior to the use of Ecstasy at raves, there were very few reports in the United States of fatal reactions to MDMA and MDE ingestion alone, despite widespread use. In most cases, MDMA and MDE are believed to have contributed to death by either (1) exacerbating an existing condition, such as asthma, coronary atherosclerosis, and idiopathic cardiomyopathy, or (2) altering/impairing behaviour, such as driving (Bost, 1988; Dowling, 1990; Dowling et al., 1987; Suarez & Riemersma, 1988). In the rat, MDMA causes dysrhythmias in heart rate and vasoconstriction, which may exacerbate an existing cardiovascular condition (Fitzgerald & Reid, 1994). Dowling (1990) also cites post-mortem data when MDMA was not related to the cause of death, but was simply found in the toxicology screen.

In England and Wales between 1993 and 1999, there were 113 deaths in which Ecstasy/MDMA was mentioned on the death certificate (Office for National Statistics, 2000, 2001). Of these deaths, 50% involved another substance, and the mortality rate was highest amongst the 15–19 age group. In contrast, there were 263 deaths involving amphetamine and 263 deaths involving cocaine during this period. In these statistics, death due to the indirect effects of intoxication, such as road traffic accidents, was not included. This suggests that Ecstasy is no more dangerous than comparable recreational drugs of abuse, such as amphetamine and cocaine. In addition, the figures also indicate that the number of deaths per annum was falling over this period. This may reflect an increase in the effectiveness of harm reduction education and/or an increase in the effectiveness of treatments for the adverse reactions to Ecstasy intoxication. In the United Kingdom between 1995 and 1996, 29 deaths in the 15–24 age group were recorded with Ecstasy/MDMA written on the death certificate, although other drugs may also have been present (Gore, 1999). Of this number, 50% were under 20 years old. The death rate per 10,000 Ecstasy users in England was estimated to be 5 times lower than the death rate from traffic accidents in the same age group as a whole, although it was comparable in Scotland. Using estimates of the pattern of use within this group, Gore (1999) argues that the death rate varies according to how users are classified, but as this was not done on the death certificates themselves, these post hoc estimates are unreliable.

There are, at present, no statistics in the United Kingdom for hospital admissions with successful outcomes. Hospital-based surveys indicate that most cases present with symptoms characteristic of Ecstasy intoxication (see Section 6 below; Rella et al., 2000; Williams et al., 1998). The most common time of presentation is between 22:00 Saturday

night and 09:00 Sunday morning after the use of Ecstasy at a rave or nightclub. Most patients reported using more than one drug, with the psychostimulants amphetamine and cocaine being the most common. These were exclusively the patients who suffered severe complications, such as delirium, seizures, and coma, and they were more likely to be admitted to the hospital (Williams et al., 1998). A community-based survey found that a large proportion of adverse effects experienced by stimulant users, including Ecstasy users, went untreated by hospitals and other health care agencies. This survey also found that 20% of Ecstasy users had an adverse reaction to intoxication and that 77% of these reactions occurred in a rave or nightclub (Williamson et al., 1997). The overall level of adverse reactions to Ecstasy use is unknown, and those cases reported in the literature may only be the tip of the iceberg.

6. Adverse physiological reactions to MDMA and MDE intoxication

The most prominent adverse reaction to MDMA and MDE intoxication is fulminant hyperthermia, with core temperatures as high as 44°C, which usually precedes disseminated intravascular coagulation, rhabdomyolysis, and (multiple) organ failure, usually acute renal failure. Although there are few cases with a patient surviving a core temperature of 42°C (Logan et al., 1993), the majority of adverse reactions with core temperatures of 42°C and above are fatal. This reaction has been compared with those of severe heat stroke, the serotonin syndrome, malignant hyperthermia, and neuroleptic malignant syndrome (Ames & Wirshing, 1993; Demirkiran et al., 1996; Gillman, 1999; Lane & Baldwin, 1997; Watson et al., 1993). This toxic profile is similar to that produced by amphetamine, methamphetamine, and MDA (Ginsberg et al., 1970; Kendrick et al., 1977; Simpson & Rumack, 1981). There is evidence that some people may have a genetic predisposition to heat stroke when doing strenuous exercise, as hyperthermia and rhabdomyolysis can occur after exertion per se, in the absence of drug ingestion (Box et al., 1997; Watson et al., 1993). The serotonin syndrome and neuroleptic malignant syndrome are both the result of exposure to pharmacotherapy: serotonergic drugs alone or in combination with monoamine oxidase inhibitors for the former and dopaminergic neuroleptics for the latter. The serotonin syndrome is characterised by a rapid onset, agitation, confusion, hyperactivity, clonus, myoclonus, ocular oscillations (nystagmus), shivering, tremor, and hyperreflexia. The neuroleptic malignant syndrome is characterised by a slow onset, bradykinesia/stupor, rigidity, and autonomic instability. In addition, there are symptoms that are common to both syndromes: hyperthermia/hyperpyrexia, diaphoresis, tachypnoea, tachycardia, hypertension, confusion, and raised creatinine phosphokinase (Gillman, 1999). The majority of these overlapping symptoms have been observed in cases of MDMA and MDE intoxication. Due to the number of

overlapping symptoms between the two syndromes, it is necessary to determine which adverse reaction a patient is experiencing by the precipitating agent. However, with MDMA, this is problematic, as it is a potent releaser of both DA and 5-HT (Demirkiran et al., 1996; Gillman, 1999; Lane & Baldwin, 1997).

Smilkstein et al. (1987) reported a case of an interaction between phenelzine, a monoamine oxidase inhibitor, and MDMA. The most profound serotonin syndrome reactions have been reported after the use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors (Lane & Baldwin, 1997). This indicates that polydrug abuse may be a contributory factor in some adverse reactions to Ecstasy ingestion (see Sections 2 and 5). After rats have been exposed to MDMA every other day for 12 days, the dose-dependent effects of MDMA on locomotor activity and serotonin syndrome behaviours are increased, indicating sensitisation (Spanos & Yamamoto, 1989). Regular users of Ecstasy, therefore, may be at increased risk of developing the serotonin syndrome. As the majority of clinical presentations rely upon patient self-report for the frequency and duration of drug use, there may be an underestimation of this phenomenon.

The sudden hypertensive effect of MDMA can cause cerebral haemorrhage or infarction in some cases (Gledhill et al., 1993; Henry et al., 1992; Manchanda & Connolly, 1993). A similar mechanism has been suggested for a retinal haemorrhage, which occurred shortly after Ecstasy ingestion (Jacks & Hykin, 1998). The absence of other aspects of the adverse reaction to MDMA and possible contributory factors, such as vigorous dancing, suggests that haemorrhages may be an idiosyncratic reaction to intoxication. MDMA has been shown to cause vasoconstriction (Fitzgerald & Reid, 1994; Pedersen & Blessing, 2001). Therefore, cerebrovascular and cardiovascular complications may be a direct effect of MDMA ingestion.

Ecstasy ingestion can cause hepatotoxicity, and there are different patterns of hepatotoxicity, which suggest that there may be different mechanisms of pathogenesis (Andreu et al., 1998; Brauer et al., 1997; Coore, 1996; Dykhuizen et al., 1995; Ellis et al., 1996; Gorard et al., 1992; Hellinger et al., 1997; Henry et al., 1992; Jones & Simpson, 1999; Milroy et al., 1996; Schwab et al., 1999; Shearman et al., 1992). In one Spanish intensive care unit between 1994 and 1996, Ecstasy was the second most common cause of acute liver failure for the under 25s (Andreu et al., 1998). Hyperthermia caused by Ecstasy ingestion can cause liver damage in a similar fashion to heat stroke. MDMA may impair the liver's tolerance to thermal stress, and this induces lipid peroxidation, but does not affect other organs (Jones & Simpson, 1999). Hyperthermia may also potentiate MDMA depletion of glutathione, increasing the risk of hepatic exposure to pro-oxidant toxicants (Carvalho et al., 2001). In addition, immunological mechanisms are important in Ecstasy-induced liver damage, as repeated use produces greater liver damage that can even occur in the absence of

hyperthermia (Jones & Simpson, 1999). This would suggest a positive correlation between the number of exposures and liver damage, but the lack of cases reported in the literature would argue against this. Subclinical cases and/or nonreporting of Ecstasy use would, however, probably escape detection; thus, clinical cases alone would be an underestimate of all cases (Hamilton et al., 1999; Jones & Simpson, 1999; Williamson et al., 1997). It is important to note that detection of MDMA in the body was not always made in cases of liver damage; thus, it is possible that other aetiological factors will be implicated. In particular, impurities or other drugs in the tablets ingested may have contributed to the hepatotoxicity.

MDMA intoxication is also associated with the syndrome of inappropriate antidiuretic hormone secretion and hyponatraemia, in the absence of hyperthermia (Holden & Jackson, 1996; Holmes et al., 1999; Kessel, 1994; Lehmann et al., 1995; Matthai et al., 1996; Maxwell et al., 1993; Milroy et al., 1996; Satchell & Connaughton, 1994). MDMA administered to volunteers induces AVP secretion (Fallon et al., 1999; Henry et al., 1998). This rise in AVP is accompanied by a drop in plasma Na^+ , and if excessive fluid intake occurred, this would cause hyponatraemia. It has also been found that high doses of Ecstasy can cause urinary retention, which may exacerbate this condition (Bryden et al., 1995). One case of hyponatraemia and rhabdomyolysis occurred 12 hr after admission to hospital, which suggests that there may also be a delayed reaction to MDMA ingestion (Lehmann et al., 1995). To combat dehydration due to Ecstasy ingestion and dancing in hot environments, drug outreach workers have been advised to recommend drinking limited amounts of water to users and to state that water is not an antidote (Finch et al., 1996). It is highly probable that this message has been misinterpreted, particularly by intoxicated users (Matthai et al., 1996). This has led to the practice of unrestricted water intake when adverse reactions occur. Cerebral oedema is believed to be caused by rapid water ingestion, which causes a sudden lowering of plasma osmolality with intracellular water shift (Box et al., 1997; Wilkins, 1996). Therefore, in the cases of cerebral oedema, inappropriate behaviour may have exacerbated the direct effect of MDMA. The advice given to users has now changed, and they are recommended to consume isotonic sports drinks and/or "salty" foods with small amounts of water during intoxication.

Other severe complications of Ecstasy intoxication include pneumomediastinum secondary to severe vomiting (Levine et al., 1993), pulmonary oedema (Bost, 1988; Dar & McBrien, 1996; Dowling et al., 1987; Holmes et al., 1999; Moore et al., 1996; Walubo & Seger, 1999; Weinmann & Bohnert, 1998), petechial haemorrhages (Lora-Tamayo et al., 1997; Weinmann & Bohnert, 1998), severe chest pains due to intercostal muscle spasms (Rittoo & Rittoo, 1992), aplastic anaemia (Clark & Butt, 1997; Marsh et al., 1994), and a case of malignant hyperpyrexia whilst undergoing an operation (McCoy et al., 1994).

Although it is tempting to attribute the adverse reactions of Ecstasy ingestion to environmental variables, such as elevated temperatures and vigorous dancing, there are few unique cases that would caution against such a simplistic explanation. A 13-month-old child accidentally ingested MDMA and presented with convulsions, tachyarrhythmia, and hypertension. In this case, there were no haematological or biochemical abnormalities or the marked hyperthermia associated with the majority of adverse reactions, although these may have been prevented by prompt treatment (Bedford et al., 1992). In addition, a paraplegic presented with all the symptoms of an adverse reaction to Ecstasy ingestion, but as he was confined to a wheelchair and had taken the drug in a pub, this could not have been due to vigorous exercise at a rave (Hall et al., 1996). Thus, adverse reactions to Ecstasy ingestion may be a direct effect of the drug in some cases.

7. Psychological effects of MDMA and MDE

There have been numerous studies that have looked at the psychological effects of MDMA and MDE in both the laboratory and retrospectively in recreational users. The effects reported for MDMA or Ecstasy from large-scale surveys and clinical studies are detailed in Table 1 as either positive/pleasant effects or negative/adverse effects, as defined by the study authors. It is possible that some of the adverse effects will be considered desirable by recreational users, such as the ability to stay awake, loss of appetite with subsequent weight loss, or “flashbacks.”

Acutely, MDMA and MDE produce euphoria, changes in perception, relaxation, and a reduction in negative affect and defensiveness. These effects are similar, but not identical, to those produced by hallucinogens such as psilocybin and psychostimulants such as methamphetamine (Gouzoulis-Mayfrank et al., 1999; Hermle et al., 1993; Parrott & Stuart, 1997). Isomeric study of MDE has indicated that the *S*-enantiomer may be responsible for entactogenic and psychostimulant effects and the *R*-enantiomer for hallucinogenic effects (Spitzer et al., 2001). Compared with amphetamine but not with placebo, MDMA increased self-reported feelings of sedation, whilst having no effect upon “intellectual efficiency and energy” (Cami et al., 2000). Despite some reports of “mental slowing,” psychomotor performance was only mildly disturbed in subjects receiving MDMA, and no change in performance was reported on the Stroop test, a test of higher executive cognitive function (Cami et al., 2000; Vollenweider et al., 1998). The subjective effects of MDMA are much more intense in women, and they report more hallucinogenic effects than men at equivalent doses (Liechti et al., 2001a). Citalopram or ketanserin pretreatment abolished most of the psychological and “hallucinogen-like” effects of MDMA, including intensification of sensory perception, meaning of percepts, and subjectively facilitated imagina-

Table 1

Self-reported positive and negative psychological effects reported after ingestion of MDMA or Ecstasy tablets

Positive psychological effect	Negative psychological effect
Altered time perception	Agitation/restlessness
Compassion	Amnesia/vagueness
Confidence	Anxiety/fear
Cognitive changes	Blurred vision/visual distortions
Decreased aggression	Cognitive deficits
Decreased alienation	Confusion
Decreased defensiveness	Decreased libido
Decreased fear	Depersonalisation
Decreased impulsivity	Depression
Decreased obsessive/compulsive behaviour	Excessive mood swings
Distorted vision	Fatigue/exhaustion
Empathy	“Flashbacks”
Escape from worries	Increased aggression
Euphoria	Increased defensiveness
Exhilaration/excitement	Increased obsessiveness/compulsiveness
Friendly	Insomnia/sleep disturbance
Hallucinations	Irritability
Heightened perception	Motivational deficits
Humour	Panic attacks
In touch with body	Paranoia
Increased energy	Passing out
Increased perception of colour	Vertigo/dizziness/ataxia
Increased perception of sound	Weight loss/decreased appetite
Increased perception of touch	
Openness	
Relaxation	
Sexual arousal	
Talkative	
Wisdom	

Data taken from studies where MDMA has been administered to volunteers or large community-based samples. The study authors determined whether the reported effects were positive or negative.

tion, whilst haloperidol only attenuated the euphorant, “amphetamine-like” aspects and potentiated anxious derealisation (Gamma et al., 2000a; Liechti & Vollenweider, 2000a, 2000b). This suggests that dopaminergic and serotonergic mechanisms underlie subjective effects. The psychological response to MDMA is largely dependent upon enhancement of serotonergic transmission.

The ability of entactogens to reduce the defensiveness of users and to increase empathy led to their use in psychotherapy before legal controls were implemented (Bakalar & Grinspoon, 1990; Greer & Tolbert, 1986, 1990). However, the effectiveness of such drug-assisted psychotherapy is difficult to assess when compared with double-blind placebo-controlled studies of pharmacotherapies (Bakalar & Grinspoon, 1990). Recently, clinical studies investigating the efficacy of MDMA-assisted psychotherapy in patients with a diagnosis of posttraumatic stress disorder have been approved in Spain and the United States. A further protocol is under review in Israel. It remains to be determined whether MDMA has any clinical applications.

The prepulse inhibition paradigm is an operational measure of sensorimotor gating, which is reduced in schizo-

phrenic patients. A recreational dose of MDMA (1.7 mg/kg p.o.) increased prepulse inhibition in human volunteers, whereas in rodents, MDMA produced dose-dependent reductions (Braff et al., 2001; Dulawa & Geyer, 2000; Liechti et al., 2001b; Vollenweider et al., 1999a, 1999b). This effect was also seen with psilocybin and to lesser extent with MDE and methamphetamine (Gouzoulis-Mayfrank et al., 1998a). In addition, MDE administration did not affect indirect semantic priming, which is linked to formal thought disorder and schizophrenia (Gouzoulis-Mayfrank et al., 1998b). The prepulse inhibition paradigm is believed to have a high degree of cross-species homology (Geyer & Markou, 1995); thus, the opposite effects may be due to procedural variations and/or species differences in the response to MDMA, MDE, and psilocybin.

8. Adverse psychopathological reactions to Ecstasy intoxication

The two most common adverse psychopathological reactions to the ingestion of Ecstasy are panic attacks and toxic psychoses (Benazzi & Mazzoli, 1991; Cohen, 1996; Cohen & Cocores, 1997; Creighton et al., 1991; Gouzoulis et al., 1993b; Hammersley et al., 1999; Hayner & McKinney, 1986; McCann & Ricaurte, 1991, 1992; McGuire et al., 1994; McGuire & Fahy, 1991, 1992; O'Donohoe et al., 1998; Pallanti & Mazzi, 1992; Schifano, 1991; Series et al., 1994; Winstock, 1991; Whitaker-Azmitia & Aronson, 1989). It should be noted, however, that the aetiological agent is rarely confirmed by toxicology measures; therefore, the entactogens are implicated by patient self-report alone.

Both MDMA and MDE have been shown to reduce anxiety when administered to humans in the laboratory (Hermle et al., 1993; Liechti & Vollenweider, 2000a). Although there is a dose-dependent and transient increase in anxious symptomatology in women who have been administered MDMA, this resolves within the first hour of administration (Liechti et al., 2001a). Panic disorder is believed to develop from a "spontaneous" panic attack that appears to have no precipitating event, and these reoccur until the patient presents to the clinic. There is also a high degree of familial aggregation that suggests a genetic component (Nutt & Lawson, 1992). In case reports, panic attacks tend to occur within the first hour after ingestion of Ecstasy (McGuire et al., 1994; Whitaker-Azmitia & Aronson, 1989; Williamson et al., 1997). Serotonergic drugs, such as *m*CPP, have been shown to cause panic attacks in patients with panic disorder (Charney et al., 1987; Murphy et al., 1989; Nutt & Lawson, 1992). Therefore, the acute panicogenic effects of the entactogens are consistent with their pharmacological profile. In addition, other hallucinogenic drugs, such as LSD, are known to cause panic attacks that can normally be resolved by verbal reassurance to the patient rather than medication (Strassman, 1984, 1995). Ecstasy

ingestion, therefore, may cause panic attacks, particularly in predisposed individuals, and thus lead to the development of panic disorder (McCann & Ricaurte, 1992; Pallanti & Mazzi, 1992). Ecstasy users have been found to have reduced heart rate variability; an index of parasympathetic nervous system activity; and valsalva ratio, an index of overall autonomic responsiveness (Brody et al., 1998). Some Ecstasy users had autonomic dysfunction comparable with that found in diabetics. This may represent a physiological change, which predisposes some individuals to develop the cardiovascular symptoms that precede panic disorder.

When MDE was administered to healthy volunteers, one subject developed a toxic psychosis for 2.5 hr, although this is the only incident in laboratory studies using entactogens (Gouzoulis et al., 1993b). This severe reaction was attributed to the setting in which the drug was administered (immediately prior to going to bed). Increased prepulse inhibition and unaltered indirect semantic priming in healthy volunteers after MDMA and MDE administration, respectively, suggests that entactogens are not psychotomimetic (Gouzoulis-Mayfrank et al., 1998b; Vollenweider et al., 1999a, 1999b).

In some cases of psychotic reactions reported in the literature, there was a previous psychiatric diagnosis and/or a family history of psychiatric problems, which suggests that drug exposure was possibly exacerbating an existing condition and/or a genetic predisposition. As both experimental substance misuse and adult psychopathology emerge during adolescence, it is more than likely that the developmental sequence will never be accurately ascertained by patient self-report alone (McGuire, 2000). In addition, as the majority of Ecstasy users are polydrug users, there is the possibility that there may have been other aetiological factors, such as cannabis use, which is supported by urine screens (McGuire et al., 1994). Some of the patients reported similar symptoms after exposure to other drugs of abuse, such as cocaine and LSD (McGuire et al., 1994; Series et al., 1994).

In the only large-scale study of patients in a clinical setting, the majority of the sample (83%) were single male polydrug abusers who had been using Ecstasy in nightclubs (Schifano et al., 1998). Just over half of the entire sample was diagnosed with a psychiatric disorder, and the patients denied that these were premorbid conditions. The most common were depression, psychotic disorders, and bulimic episodes with specific food cravings.

Cognitive impairment was also seen in this group, with a subgroup showing impairment on tests of memory and planning ability when compared with controls. These impairments, however, could have been a result of their psychiatric conditions. Users who had taken a larger number of Ecstasy tablets in their lifetime were more likely to develop psychopathology. In addition, users who had used alcohol at the same time as Ecstasy were more likely to develop psychopathology than those who abstained. In

contrast, opiate users were less likely to develop psychopathology. The opiate users tended to have used less Ecstasy in their lifetime and to have not used it with alcohol. Most of these patients spontaneously self-referred to this drug dependency clinic, and they believed that their psychopathology was caused by their Ecstasy use. Therefore, this may have been an unrepresentative sample, and there was no appropriate control group used. In addition, there was a large number of opiate users in the sample, which is unusual (see Section 2), and this may have influenced the findings (Schifano, 2000). In a nonclinical sample of Ecstasy users in the United States, only 2% of the sample reported any long-term psychological effects, and these were not psychopathological (Peroutka et al., 1988). The majority of adverse reactions to Ecstasy reported in a community-based survey in the United Kingdom were also rated as “mild” (Williamson et al., 1997). In an Australian survey, the respondents were more likely to ascribe their physical and psychological side effects to Ecstasy use in combination with polydrug use, lack of sleep, and sustained exertion than Ecstasy use per se (Topp et al., 1999).

Studies that have been conducted in recreational users of Ecstasy have routinely failed to find any quantifiable long-term changes in psychopathology. Several studies have found a transitory increase in depressive symptomatology in the weeks following Ecstasy ingestion (Curran & Travill, 1997; Gerra et al., 1998b; MacInnes et al., 2001; Verkes et al., 2001). However, other studies using the same or similar measures have failed to find long-term changes in depressive symptomatology (Dafters et al., 1999; Hammersley et al., 1999; Klugman et al., 1999; Krystal et al., 1992; Obergreißer et al., 2001; Parrott et al., 2000, 2001). Reported increases in depressive symptomatology in Ecstasy users are not clinically relevant and do not remain significant when confounding covariables such as education level and youth hyperactivity (DSM-IV diagnosis of ADHD) are controlled (Cole & Sumnall, 2002; Verkes et al., 2001).

Other types of psychopathology, such as anxiety, psychoticism, and paranoid ideation, have been reported for polydrug users who have also used Ecstasy (Parrott et al., 2000, 2001). As these subjects were polydrug users, it is impossible to determine from the data that Ecstasy was the causal agent. In addition, as no attempt was made to assess previous diagnoses of psychiatric disorders, it is impossible to identify whether these differences were premorbid. The time since last use of any drugs was not recorded, and as the scale used records symptoms over the previous 4 weeks, drug use was probably confounding the results (Cole et al., 2002c).

Ecstasy users report higher state levels of psychopathology, but these subjects also report higher levels of trait psychopathology, suggesting that these effects are probably premorbid (Gamma et al., 2000a, 2000b). Ecstasy users also do not differ from non-Ecstasy-exposed polydrug users on psychopathological scales, suggesting that these increases

may be due to drug abuse per se (Gamma et al., 2000b; Morgan, 1998). Transitory mood changes would fit with the self-reports of “depression” found in surveys of recreational users (see Table 1). It is possible, however, that this effect is due to (reversible) neurotransmitter depletion and/or fatigue following Ecstasy ingestion. Three days after clinical administration of MDMA, negative affect was only reported in few volunteers (25% of volunteers) (Liechti & Vollenweider, 2000a, 2000b). In this context, it is important to note that Ecstasy users with reduced 5-HT transporter binding, reduced cerebrospinal fluid (CSF) 5-HT/5-HIAA, and reduced neuroendocrine response to fenfluramine/*m*CPP challenge do not have a diagnosis of clinical depression (exclusion criteria for the studies), suggesting that Ecstasy use does not cause depression in every user (Bolla et al., 1998a, 1998b; Gerra et al., 1998b, 2000; McCann et al., 1994a, 1994b, 1998, 1999a, 1999b; Reneman et al., 2000a, 2000b, 2001a, 2001b; Semple et al., 1999; Verkes et al., 2001).

9. The effects of Ecstasy exposure on the human CNS

Studies of recreational Ecstasy users have found changes in several parameters indicative of serotonergic neurotoxicity (see Table 2). Independent laboratories have reported a drop in the number of 5-HT transporter sites in the brain using in vivo brain imaging techniques (McCann et al., 1998; Reneman et al., 2001a, 2001b; Semple et al., 1999). McCann and colleagues (1998) found that there were global reductions in 5-HT transporter binding, whereas Semple and colleagues (1999) found regionally specific changes. Semple and colleagues (1999) also reported unaltered numbers of dopamine transporter sites and that there was no correlation between the estimated lifetime dose of Ecstasy and the 5-HT transporter binding. There was a correlation between time since last use of Ecstasy and 5-HT transporter binding, indicating a fast recovery of function. McCann and colleagues (1998) found that there was a significant positive correlation between the number of times Ecstasy was used and the decrease in 5-HT transporter binding (but see Section 1). In both studies, there was no correlation between length of abstinence from Ecstasy and decreases in the 5-HT transporter.

Reneman and colleagues (2001a) recently reported that there was no difference in binding between groups of heavy, medium, and abstaining Ecstasy users and control subjects. However, heavy female users with a mean of 530 exposures showed decreased [¹²³I]β-CIT-binding ratios compared with male users and control subjects. Furthermore, female ex-Ecstasy users (mean abstinence period > 1 year) showed increased 5-HT transporter binding compared with current female users. In a concurrent study from the same laboratory, 5-HT transporter density was significantly lower in recent users compared with controls, but not with ex-users (Reneman et al., 2001b). Taken together, these results

Table 2
Summary of neurochemical laboratory studies of recreational Ecstasy users

MDMA use of subjects	Polydrug use history	Polydrug user control	Psychopathology	Results	Reference
2–5 mg/kg 18 times	Not assessed	No	Not assessed	CSF 5-HIAA: 0, CSF HVA: 0, CSF MHPG: 0	Peroutka et al., 1987
125 mg once a month for 3.5 years	Yes, but drug free at test	No	No	CSF 5-HIAA: ↓, CSF HVA: 0, CSF MHPG: 0	Ricaurte et al., 1990
1.8 mg/kg 2 times a month for 5 years	Yes	No	Yes, but none at time of testing	Prolactin response	Price et al., 1989
170 mg 4 times a month for 5 years	Yes	No	No (SCID)	To intravenous L-tryptophan: 0 CSF 5-HIAA: ↓, CSF HVA: ↓, CSF MHPG: 0, prolactin response to intravenous L-tryptophan: 0	McCann et al., 1994b
106 mg 5 times a month for 14 months	No (urine screen)	No	Axis I: no, Axis II: yes (PD)	Prolactin response to intravenous D-fenfluramine: ↓, cortisol response to intravenous D-fenfluramine: ↓	Gerra et al., 1998b
386 mg 6 times a month for 4.6 years	Yes, but drug free at test	No	No (SCID)	PET 5-HT transporter binding: ↓	McCann et al., 1998
158 mg 2 times a month for 5 years	Yes, but drug free at test	No	No (SCID)	CSF 5-HIAA: ↓	Bolla et al., 1998b
672 tablets	Yes (some positive at test)	No	No	SPET 5-HT transporter binding: ↓, DA transporter binding: 0	Semple et al., 1999
12–840 tablets over 1–39 months	Yes, but drug free at test	No	No (SCID)	PET cerebral glucose metabolism: ↓ in some areas and ↑ in some areas	Obrocki et al., 1999
272 mg 6 times a month for 4.5 years	Yes, but drug free at test	Yes	No (SCID)	CSF 5-HIAA: ↓, CSF HVA: 0, CSF MHPG: 0, prolactin response to i.v. <i>m</i> CPP-↓, cortisol response to i.v. <i>m</i> CPP-↓	McCann et al., 1999a, 1999b
218 tablets	Yes, but drug free at test	No	No	SPET 5-HT _{2A} receptor binding:	Reneman et al., 2000a
> 50 tablets	Yes, but drug free at test	Unmatched polydrug control	No (CIDI)	SPET 5-HT _{2A} receptor binding: ↓ in recent users and 0 in ex-users	Reneman et al., 2000b
(1) 28.6 tablets over 4.1 years (light users)	Yes, but drug free at test	Unmatched polydrug control	No (CIDI)	SPET 5-HT transporter binding: ↓ in female heavy users and 0 in all other groups	Reneman et al., 2001a
(2) 530 tablets over 4.6 years (heavy users)					
(3) 268 tablets over 4.6 years (ex-users)					
(1) 485 tablets over 5.5 years (recent users)	Yes, but drug free at test	Yes	No (CIDI)	SPET 5-HT transporter binding: ↓ in recent users and 0 in ex-users	Reneman et al., 2001b
(2) 268 tablets over 4.6 years (ex-users)					

MDMA doses estimated by the authors are based on the average tablet containing 100-mg MDMA (but see Section 1). 0, no difference with controls; ↑, increase; ↓, decrease. CIDI, Composite International Diagnostic Interview; SCID, Scheduled Interview for DSM-III-R/IV; CSF, cerebrospinal fluid; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; SPET, Single Photon Emission Tomography; PET, Positron Emission Tomography; *m* CPP, meta-chlorophenyl piperazine.

suggest that changes in 5-HT transporter binding density are exposure- and sex-dependent, but are not permanent.

All of these imaging studies have been criticised on methodological grounds, which indicates that caution is warranted when interpreting these data as evidence of neurotoxicity (Heinz & Jones, 2000; Kish, 2002; Kuikka & Ahonen, 1999; McCann & Ricaurte, 2001b; Reed et al.,

1999). Heinz and Jones (2000) questioned the binding specificity of the ligands used in imaging studies to the 5-HT transporter, noting that in nonhuman primates, [¹²³I]β-CIT uptake is unaffected by pretreatment with the SSRI citalopram. 5-HT transporter density is only present in sufficient density to be reliably measured in the thalamus and brainstem with [¹²³I]β-CIT. It is notable that Semple

and colleagues (1999) found no significant effects of Ecstasy use upon uptake in the thalamus and did not take measurements from the brainstem. Subacute decrements in cerebral blood flow produced by MDMA (Chang et al., 2000) may also affect radioligand distribution, leading to an underestimation of binding density in users.

Reductions in 5-HT transporter binding and altered neuronal function may represent preexisting personality traits associated with substance abuse (Zuckerman et al., 1988). Studies of variations in the 5-HT transporter promoter gene have shown that homozygous short allele carriers have reduced 5-HT transporter activity (Lesch et al., 1993). Furthermore, homozygous carriers of the long allele variant may be more susceptible to the neurotoxic effects of some drugs of abuse such as alcohol (Heinz et al., 2000). Whether study populations of Ecstasy users have included volunteers with these polymorphisms is unknown (Kish, 2002; Lesch et al., 1993).

Changes have been found in 5-HT_{2A} receptor binding in current Ecstasy users, which were associated with changes in cerebral blood vessel volumes, with vasoconstriction in recent users and vasodilation in abstinent users (Reneman et al., 2000b). Both of these may have been due to the use of cocaine, which was higher than the control group (Bolla et al., 1998a). In addition, exposure to Ecstasy has not been found to produce long-term changes in cerebral blood flow as these data would suggest, although administration of MDMA to volunteers did produce a transient change over a 3-month period (Chang et al., 2000; Gamma et al., 2000a).

The concentration of *N*-acetylaspartate, a neuronal marker measured with Proton Magnetic Resonance Spectroscopy, in the mid-frontal, mid-occipital, and parietal brain regions is normal in recreational Ecstasy users, indicating that Ecstasy does not cause significant neuronal injury. However, elevated levels of the glial marker *myo*-inositol in the parietal white matter may indicate increased glial proliferation in response to insults to the brain and ongoing repair processes (Chang et al., 1999). Magnetic resonance spectroscopy on other small samples of Ecstasy users has shown a decreased *N*-acetylaspartate/creatinine ratio (indicative of neuronal loss or dysfunction) in the prefrontal cortex, but not in the hippocampus or mid-frontal occipital, mid-frontal, and parietal regions (Obergrößer et al., 2001; Reneman et al., 2001c).

More indirect measures of serotonergic function in recreational Ecstasy users have found that the levels of 5-HIAA in the CSF are lower than those in controls. There were no observed changes in other monoaminergic metabolites in the majority of studies, although McCann et al. (1994b) did report a drop in homovanillic acid (HVA). The majority of these studies, however, have come from the same laboratory and possibly the same subjects (Bolla et al., 1998b; Grob, 2000; McCann et al., 1994b, 1999a; Ricaurte et al., 1990), and the only report to come from a different laboratory found no effect (Peroutka et al., 1987). Despite this, the

lower 5-HIAA levels in the CSF of recreational users would appear to be a consistent phenomenon.

The raphe nuclei provide a substantial ascending projection to the hypothalamus and limbic area. Stimulation of these neurons causes release of anterior pituitary hormones, such as growth hormone, prolactin, and ACTH. Measuring peripheral levels of these hormones after the administration of serotonergic drugs provides a method of assessing in vivo serotonergic function (Abel & Cleare, 1999). Early studies in the United States found no difference between Ecstasy users and controls when they were administered *L*-tryptophan (Price et al., 1989; McCann et al., 1994b). Later studies, however, found that Ecstasy users failed to show the predicted increase of prolactin and cortisol when administered serotonergic drugs, such as fenfluramine and *m*CPP, suggesting serotonergic dysfunction (Gerra et al., 1998b; McCann et al., 1999b; Verkes et al., 2001). As fenfluramine is pharmacologically similar to MDMA (both drugs increase 5-HT release through activity at the 5-HT transporter and have similar neurotoxic effects), there is the possibility of cross-tolerance that would lead to decreased sensitivity compared with drug naïve controls. Similar neuroendocrine evidence of serotonergic dysfunction has been found in alcohol-dependent patients, cocaine users, cannabis users, marathon runners, depressed patients, and victims of child abuse (e.g., Becker et al., 2001; Broocks et al., 1999, 2001; Buydens-Branchey et al., 1997, 1999; Haney et al., 2001; Rinne et al., 2000; Yatham & Steiner, 1993). This suggests additional causal factors, such as regular aerobic exercise and polydrug use, which should be considered in this context.

Ecstasy use has been found to correlate positively with absolute power in the α (8–12 Hz) and β (12–20 Hz) bands of the EEG of recreational drug users. This change in EEG activity was thought to indicate reduced cortical activity caused by MDMA-induced neurotoxicity (Dafters et al., 1999). Apart from one test, these changes did not correlate with any cognitive or psychopathological measure. Dafters and colleagues (1999) have argued that this could indicate that there is very specific frontal dysfunction as a consequence of a specific reduction in the number of serotonergic terminals due to MDMA exposure. Other in vivo imaging techniques in humans do not support this hypothesis (Chang et al., 2000; McCann et al., 1998; Obrocki et al., 1999; Reneman et al., 2000b; Semple et al., 1999). Increased α and β activity has been demonstrated in regular Ecstasy users versus non-Ecstasy-exposed controls. As the regular Ecstasy users had increased ratings of trait psychopathology, particularly depression, the observed differences may be due to premorbid conditions or secondary symptomatology (Gamma et al., 2000b). The intensity dependence of the tangential auditory evoked N1/P2 source activity (measured by EEG) has been associated with a reduction in serotonergic function (Juckel et al., 1997), and Ecstasy users have an increased amplitude of the tangential auditory evoked N1/P2 source activity, indicating reduced serotoner-

gic function (Croft et al., 2001a; Tuchtenhagen et al., 2000). As acute tryptophan depletion has no effect on auditory evoked potentials, this effect may not be due to serotonergic neurotoxicity (Dierks et al., 1999).

10. Cognitive abilities of recreational Ecstasy users

Despite the lack of long-term psychopathological changes in recreational users of Ecstasy, there are numerous reports of cognitive changes. Aggression and impulsivity were found to be different in Ecstasy users when compared with controls (Gerra et al., 1998b, 2000, 2001; McCann et al., 1994b; Morgan 1998, 1999; Parrott et al., 1998, 2000; Tuchtenhagen et al., 2000). The human data are conflicting, however, with both increases and decreases found in both traits. This is complicated by the fact that individuals with both elevated impulsivity and aggression are more likely to use drugs per se (e.g., Bardo et al., 1996; Newcomb et al., 1986), and these differences would thus be premorbid. As both aggression and impulsivity are associated with serotonergic function, it is difficult to ascertain from the existing studies whether these changes are a cause or an effect of Ecstasy use (Bardo et al., 1996; Reed et al., 1999; Zuckerman et al., 1988).

The most consistent findings in recreational Ecstasy users are learning and memory deficits on a variety of neuropsychological tests (Bhattachary & Powell, 2001; Bolla et al., 1998b; Curran & Travill, 1997; Fox et al., 2001; Gouzoulis-Mayfrank et al., 2000; Klugman et al., 1999; Krystal et al., 1992; McCann et al., 1999a; Morgan, 1999; Parrott et al., 1998; Parrott & Lasky, 1998; Reneman et al., 2000a, 2001b, 2001c; Rodgers, 2000; Schifano et al., 1998; Semple et al., 1999; Verkes et al., 2001; Wareing et al., 2000; Zakzanis & Young, 2001a, 2001b). In only few of these studies was the polydrug use of the subjects controlled for, and some of the authors have recognised this as a possible experimental confound (see Section 11.3). Cannabis use in particular has been shown to covary more closely with cognitive impairments than Ecstasy use (Croft et al., 2001b; Morgan, 1999).

Only one longitudinal study has investigated the effects of continued Ecstasy use, and by implication, increased neurotoxic damage, upon memory performance (Zakzanis & Young, 2001a). Such study designs may represent the most effective means of identifying the detrimental effects of drug use. Subtle behavioural or cognitive impairments may become more obvious in longitudinal studies that aim to detect changes on an individual basis. Fifteen volunteers showed progressive memory deficits over a 12-month period in which Ecstasy was used a mean of 2.4 times a month (lifetime exposure range at $t=0$: 1–55, $t=12$ months: 3–225). Monthly consumption of Ecstasy increased dramatically in some volunteers. A maximum of 20 tablets per month was reported at the beginning of the study, but this had reached 45 per month at the end. During the same period,

use of other illicit drugs (e.g., amphetamines, cocaine, opiates, and hallucinogens) also increased, and in some instances, use was initiated. In view of intervening drug use and possible psychopathological manifestation (not assessed in the intervening time period), relating the observed changes solely to the effects of Ecstasy is problematic. Other studies attempting to identify the effects of abstinence from Ecstasy upon recovery (or otherwise) of cognitive function are difficult to interpret, as these have invariably compared independent groups and have not analysed the same population over time (Bhattachary & Powell, 2001; Morgan, 1998; Wareing et al., 2000). Furthermore, no attempt has been made to control for total Ecstasy exposure prior to cessation of use or to determine the reasons why the drug was stopped (e.g., psychological disorder independent of drug effects).

Verbal memory deficits are strongly associated with lower *N*-acetylaspartate/creatine ratios (a marker of neuronal viability) and number of exposures in Ecstasy users (Reneman et al., 2001b, 2001c). However, memory performance is not associated with binding to cortical 5-HT transporters or duration of Ecstasy abstinence, which suggests that the effects of Ecstasy on memory function are independent of serotonergic neurotoxicity. Although Bolla and colleagues (1998b) were able to find a significant correlation between the level of 5-HIAA in the CSF and memory impairment, this was not replicated in a later study from the same laboratory (McCann et al., 1999a). Thus, the relationship between measures of possible neurotoxicity and cognitive impairment has not been conclusively demonstrated in these studies.

11. Experimental confounds in research on Ecstasy users

11.1. Subject recruitment

Most studies of recreational Ecstasy users employ similar recruitment methods, with the most widely used being the “snowball technique.” This involves getting subjects to advertise the study to their peers, particularly their Ecstasy-using peers. With the large media profile of Ecstasy, subjects may be coming forward to confirm their fears about any adverse reactions that they may have suffered (Cole et al., 2002b; Turner & Parrott, 2000). In addition, this normally results in a largely student-based population, as recruitment tends to occur in and around universities as part of undergraduate projects or doctoral theses. These samples do not represent the population as a whole, as they are both self-selected and exclusive, as they largely consist of people who have attained a certain academic level (Hammersley et al., 1999).

In some studies, there are even differences in the backgrounds between the Ecstasy users and their control group. For instance, the control group displays a higher level of education (Bolla et al., 1998b; McCann et al., 1999b; Reneman et al., 2000a; Verkes et al., 2001). A more extreme

example is the use of Ecstasy users from the United Kingdom in studies conducted in the United States. As it is not reported in the relevant study where the subjects actually came from, there is the possibility of cross-cultural contamination of the results (McCann et al., 1998, 1999c). In addition, subjects who had recently made a transmeridian flight would be impaired because of circadian disruption (Grob, 2000; Wright et al., 1983). These inherent differences may have influenced the results obtained; for instance, subjects with higher educational attainment are bound to obtain better scores on cognitive tests.

Studies of the long-term effects of Ecstasy typically compare a group of users to a group of nonusers at a single time point and usually within 3 weeks of using Ecstasy. As detailed above, Ecstasy users form a distinct subculture of individuals who attend raves and use drugs to aid their experience. Within this subculture, it is very difficult to identify individuals who have not used Ecstasy, as surveys estimate that over 90% of this group have used it (e.g., Bean et al., 1997; Schuster et al., 1998). The lifestyle of this subculture is one of repeated circadian disruption and extended aerobic exercise due to staying awake and dancing all through the weekend with the aid of stimulant drugs. Repeated circadian disruption over extended periods of time produces cognitive deficits in aircrew, which are very similar to those found in recreational Ecstasy users (Cho et al., 2000). Regular extended aerobic exercise (marathon running) produces identical responses to *m*CPP challenge to those seen in recreational Ecstasy users (Broocks et al., 1999, 2001; McCann et al., 1999b). This means that there are lifestyle factors that may explain the results.

11.2. Premorbid differences

Retrospective studies cannot determine if the differences they identify between users and controls existed prior to the ingestion of Ecstasy. People who use large amounts of Ecstasy may be doing so because of a preexisting condition, which people who are not inclined to try it do not have. Most studies do not probe the history of their subjects and rely upon self-report for that history, if it is taken. Certain childhood problems and personality traits, such as antisocial behaviour and sensation seeking/impulsivity, are associated with an increased risk of experimenting with controlled drugs and developing substance abuse problems (Bardo et al., 1996; Hawkins et al., 1992; Zuckerman, 1994). These childhood problems and personality traits are also associated with poorer cognitive performance and increased risk of developing adult psychopathology (Rubia et al., 1998; Tapert & Brown, 2000). These premorbid conditions may be more common in the substance-misusing population and, thus, give a misleading impression that cognitive deficits and increased psychopathology are caused by substance misuse. Some of the psychopathological effects of Ecstasy are known to be heritable, such as depression, and in some cases, there is a family history of psychiatric problems

(McCann & Ricaurte, 1991; McGuire et al., 1994; McGuire & Fahy, 1991; Series et al., 1994). Some studies rely upon the Scheduled Interview for the DSM-III-R/IV to remove subjects with a current Axis I disorder (such as anxiety, depression, and schizophrenia), but do not attempt a retrospective analysis and/or test for an Axis II disorder (such as personality disorders). As drug abuse is associated with both history of adolescent behavioural problems, such as attention deficit hyperactivity disorder and conduct disorder, and personality disorders, such as antisocial personality disorder, it is important that subjects with either of these be excluded from the study.

11.3. Polydrug use

The use of the term “Ecstasy user” implies that there exists a population of recreational drug users who only use Ecstasy on a regular basis in a similar fashion to the implication that a heroin-dependent population only uses heroin. Epidemiological studies have so far failed to identify such a group, and only a couple of studies have found a large enough sample to test, which means that these groups are not representative of the population (Gerra et al., 1998b, 2000). Ecstasy users (un)intentionally expose themselves to a cocktail of drugs, such as amphetamine, cannabis, alcohol, cocaine, LSD, benzodiazepines, and ketamine (Arimany et al., 1998; Boys et al., 1997; Forsyth, 1996; Hammersley et al., 1999; Lenton et al., 1997; McDermott, 1993; Milroy et al., 1996; Rothe et al., 1997; Saunders, 1997; Schuster et al., 1998; Sherlock et al., 1999; Solowij et al., 1997; Topp et al., 1999; Williams et al., 1998; Williamson et al., 1997; Wolff et al., 1995). There is preclinical evidence that the coadministration of Ecstasy with other drugs will affect the neurotoxicity of MDMA. When amphetamine is coadministered with MDMA, there is enhanced neurotoxicity (O’Loinsigh et al., 2000). In contrast, alcohol has been shown to protect against MDMA-induced neurotoxicity (Miller & O’Callaghan, 1994). Most drugs of abuse have been associated with similar changes in cognition and increased psychopathology to those reported following Ecstasy exposure (e.g., Ashton, 2001; Bolla et al., 1998a; Curran & Morgan, 2000; Grant et al., 2000; Halpern & Pope, 1999; Heishman et al., 1990, 1997; Lyvers, 2000; Ornstein et al., 2000; Rosselli & Ardila, 1996; Strassman, 1984, 1995). In the majority of studies, the use of other drugs of abuse exceeds the reported use of Ecstasy, and it is only the inclusion criteria that defines them as Ecstasy users. The statistical control of polydrug use will never remove this confound, as the inclusion criteria for the studies emphasise Ecstasy use and try to minimise other drug use. In addition, the amount of reported information on other drug use is never as detailed as that for Ecstasy.

Subjects are rarely urine screened at the time of testing to ensure that they are drug free, and this represents a major confound. It is possible that the subjects have been using

controlled drugs immediately prior to the study (within 24 hr). For example, cannabis has been shown to affect cognitive performance up to 48 hr after administration (Ashton, 2001; Heishman et al., 1990). Habitual cannabis users remain cognitively impaired, even when they are not actually intoxicated, and these impairments can last for many weeks or months after cessation of cannabis use (Solowij, 1998).

11.4. Self-reported use of Ecstasy tablets

Every study published to date has relied upon the self-reported drug-use histories of the subjects to ascertain their level of drug use. Given the unknown purity of street drugs, it is impossible to accurately quantify the amount of any drug used by the subjects. In addition, if the primary finding is one of memory deficits, then this calls into question the accuracy of the self-reporting. In some calculations of a dose-dependent effect of Ecstasy exposure, it is assumed that each Ecstasy tablet that the subjects used contained 100 mg of MDMA (e.g., Bolla et al., 1998b). Although this figure may be based on historical data, there is evidence that the quality of Ecstasy tablets is declining. The average MDMA content of tablets seized by police in the United Kingdom dropped from 102 mg in 1991 to 73 mg in 2001 (Cole et al., 2002a). The MDMA content of Ecstasy tablets seized in the northwest of England during 2001 ranged from 20 to 109 mg, and the mean was in the range of 60–69 mg (Cole et al., submitted for publication). However, such analyses do not take into account the number of tablets that do not contain MDMA. This may explain why there is a poor correlation between self-reported Ecstasy use and presence of MDMA in hair samples (Ditton et al., 2000). Any statistics used to demonstrate a dose-dependent effect of MDMA based upon self-reported use of Ecstasy, therefore, is fundamentally flawed. Parrott (2000) has even argued that the decreasing quality of Ecstasy tablets is neuroprotective, and this explains why several experiments have failed to demonstrate cognitive impairments in Ecstasy users. This assertion is questionable given that the subjects reporting a drop in quality must have been exposed to enough “good quality” tablets in order to detect such a change.

12. Interspecies dose scaling

The neurotoxic effects of MDMA and MDE in animals are dependent upon the number and size of doses given, the route of administration, the species receiving it, and the ambient temperature in which it is received (Green et al., 1995; Hegadoren et al., 1999; Malberg & Seiden, 1998; O’Shea et al., 1998; Ricaurte et al., 2000; Steele et al., 1994; White et al., 1996). Using allometric interspecies scaling of neurotoxic doses, it has been argued that as a single oral administration of 5 mg/kg of MDMA produces long-term damage to the nonhuman primate brain and a single dose of 1.7 mg/kg given to healthy human volun-

teers (or self-administered by Ecstasy users) will also be neurotoxic (Gijsman et al., 1999; McCann & Ricaurte, 2001a). The reliability of interspecies scaling of neurotoxic doses is contentious as (1) males of the Dark Agouti strain quoted in one such calculation are known to be extremely sensitive to MDMA-induced neurotoxicity, (2) MDMA has nonlinear pharmacokinetics, (3) it does not take account of toxic metabolites, and (4) the effects of a single oral administration of 5 mg/kg in the primate are minimal (Aghajanian & Lieberman, 2001; Lieberman & Aghajanian, 1999; O’Shea et al., 1998; Vollenweider et al., 1999a, 2001). There is also no evidence from studies that have used such doses that there are any long-term effects (Chang et al., 2000; Vollenweider et al., 2001). It remains to be determined what the threshold neurotoxic dose of MDMA is for the human user.

13. Conclusions

Ecstasy has come to symbolise one of the largest youth subcultures of the late 20th century and has established itself as one of the most popular recreational drugs of abuse. United Kingdom Government figures indicate that 4% of the population has used Ecstasy, which would equate with at least 2 million people (Ramsey et al., 1999). If Ecstasy exposure were having long-term adverse effects on psychological health and well being, there would be a sizeable increase in the number of cases presenting for treatment. This would represent a major public health problem for any country where Ecstasy is being used by large numbers of young people. In the United Kingdom, harm reduction has had a major effect on reducing the number and impact of acute adverse reactions to Ecstasy, as indicated by the falling death rate despite increasing use (Office for National Statistics, 2000, 2001; Ramsey et al., 1999). The success of harm reduction relies upon credible information being transmitted to drug users by trusted sources. It is, therefore, essential that the long-term effects of Ecstasy exposure are characterised and that this information is transmitted to users in order to reduce the harm from their drug use.

At the moment, the research available for this purpose is heavily confounded. Epidemiological studies are demonstrating that the overwhelming majority of Ecstasy users are polydrug users. The other drugs are likewise neurotoxic and have been demonstrated to cause similar long-term effects to Ecstasy. Studies examining the constituents of Ecstasy tablets have shown that identifying simple dose-response effects in retrospective human studies of Ecstasy users is impossible. Cross-sectional designs are unable to determine if any of these effects are a cause or an effect of “dance drug” use. The extrapolation of designs appropriate for animal experiments to human experiments is the cause of this problem. Without knowing the genetic and/or experiential background of the human subjects, it is impossible to determine if premorbid conditions are experimental con-

finds. In this context, the long-term effects of Ecstasy have yet to be accurately determined.

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