

Ecstasy

MDMA and other ring-substituted amphetamines

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Executive Summary

Executive Summary

The term "ecstasy" is primarily applied to 3,4-methylenedioxymethamphetamine (MDMA) but other drugs are sold as ecstasy, and ecstasy tablets can contain a range of drugs in addition to, or in place of, MDMA.

MDMA combines stimulant and hallucinogenic properties. Its use has been associated with a global trend of dance parties and "techno" or dance music.

In the 1970s, MDMA was increasingly being used in the USA as an adjunct to psychotherapy. In 1985, the US Food and Drug Administration classified MDMA as Schedule I (no acceptable therapeutic use). Debate regarding the decision may have unintentionally increased public awareness of the drug and its psychoactive effects.

Illicit production of MDMA is relatively easy but quality control is difficult to achieve. Forensic analysis of drugs seized as "ecstasy" have revealed other amphetamine-type stimulants as well as chemically unrelated compounds with little or no psychotropic activity. Wide variations in the dose of MDMA contained in tablets have also been detected.

Epidemiological information on ecstasy use is sparse and data collection procedures are variable, complicating analysis. However, it is clear that there was significant growth in the popularity of amphetamine-type stimulants during the 1990s with use now a global phenomenon.

Data from Europe and the USA indicate that ecstasy has ever been tried by between 0.5 and three per cent of the general population and from one to five per cent of young adults. In general ecstasy is the third most used illicit drug, after cannabis and amphetamines.

In most countries ecstasy is used recreationally as part of a particular youth culture centred on dance parties and raves and a preference for specific types of music. Users tend to be young, well educated, socially well integrated, with high levels of employment and less likely to have a criminal record than other populations of illicit drug users. However, ecstasy is also part of a pattern of polydrug use.

Sociability is a major characteristic of ecstasy use. It is almost exclusively taken in a social setting with part-

ners or groups of friends. Users particularly seek the feelings of empathy and closeness with others, which result from ecstasy use, to foster a group identity and sense of belonging. Use of ecstasy by friends is a significant factor in initiation and continuation of ecstasy use.

Ecstasy is associated with a variety of specific cultural trends in particular networks where the importance of the group is emphasised, for example the gay club and party scene and the "techno" music scene.

Ecstasy is primarily used recreationally, mainly at weekends in association with social events, but studies, particularly in the UK and Australia, have identified regular and intensive use. There may also be a trend of increasing use by injection. Most users appear able to regulate their use of ecstasy but some progress to problematic use. Some researchers have suggested that problematic use might constitute dependence but this is an aspect for further debate.

MDMA has high affinity for serotonin receptors and transport sites in the brain. Serotonin-producing neurones in the brain regulate aggression, mood, sexual activity, sleep and sensitivity to pain. Serotonin is also important in memory and temperature regulation.

MDMA initially enhances extracellular brain concentrations of serotonin, but eventually this leads to depletion of the neurotransmitter and hence a decrease in serotonin levels. MDMA also increases release of dopamine, another neurotransmitter that is involved in the control of movement, cognition, motivation and reward.

Findings of surveys of users and studies using controlled administration of MDMA are consistent, namely immediate positive psychological effects of euphoria, increased energy, and a feeling of closeness to others, and negative psychological effects of paranoia, anxiety and depression. Common short-term physical effects are pupil dilation, increased jaw tension and grinding of teeth, loss of appetite, dry mouth, tachycardia, hot and cold flushes, and sweaty palms. Longer term effects reported by users include insomnia, depression, headaches and muscle stiffness.

Tolerance to the effects of MDMA appears to develop rapidly. In surveys users report a decrease in "positive" effects and an increase in "negative" effects

with successive doses. “Negative” effects are also reported to increase, and “positive” effects decrease, with increasing doses of ecstasy.

MDMA is well absorbed from the gastrointestinal tract. Following oral administration, effects become apparent in about 20 minutes and last for about four hours. Recent evidence indicates that the relationship between MDMA dose and blood concentration may not be linear. Hence small increases in dose may produce disproportionate increases in effect, possibly contributing to toxicity.

In the liver, MDMA is metabolised by a number of cytochrome P450-mediated pathways. One of the enzymes involved, CYP2D6 exhibits genetic variability such that some people have low activity of the enzyme and are denoted poor metabolisers. It has been suggested that these people, due to reduced metabolism, will be at greater risk of MDMA toxicity. However, no evidence has been found to support this hypothesis. It is likely that, in vivo, other enzyme pathways make up for the deficit. Some of the metabolic products of MDMA are bioactive and may also contribute to toxicity. MDMA is metabolised in the liver and eliminated via the urine.

Drug interactions may influence MDMA toxicity by altering the elimination of MDMA from the body, or through an additive effect if the interacting drug has a similar effect to MDMA. Reported cases of adverse reactions possibly arising from drug interaction involved fluoxetine (two cases) and ritonavir (one case).

Animal studies have shown that administration of MDMA produces damage to axons and axon terminal fibres containing serotonin. Decreases in the density of brain serotonin axons have been seen in squirrel monkeys more than seven years after MDMA administration. Some regrowth of axons occurs, but is abnormal and incomplete.

These findings in animals are the basis of concerns regarding neurotoxicity of MDMA. Although animal studies are indicative of effects in humans, there always remains a degree of uncertainty about transferability of findings. However, a series of studies using sophisticated brain imaging techniques to assess different aspects of the human brain have found persisting abnormalities in brain morphology in ex-users of ecstasy, even with moderate use. These studies tended to use small numbers of users and many are confounded by uncertain histories of MDMA use and use of other drugs. Although providing additional evidence of neurotoxicity, these imag-

ing studies do not indicate the functional significance of the changes in brain morphology.

The functional significance of the neurotoxic effects of ecstasy has been explored in a number of recent studies using psychological tests to assess cognitive function, memory and aspects of mood in current and former ecstasy users compared to non-using controls. Again, these studies are confounded to some extent by small numbers of participants, difficulties in determining histories of ecstasy use, concomitant use of other drugs such as cannabis, and the lack of baseline data from periods prior to ecstasy use (some differences between ecstasy users and non-users, such as impulsivity, may reflect existing personality differences rather than the effects of ecstasy). Despite these limitations, and despite some variability between studies, there is a consistent finding of impairment in short-term memory function in ecstasy users that cannot be attributed to concomitant use of other drugs, in particular cannabis.

Overall the combination of animal and human studies constitutes mounting evidence of ecstasy having a neurotoxic effect. However, the long-term functional consequences of ecstasy use in humans will remain uncertain pending large scale epidemiological studies. The mechanism of MDMA's neurotoxicity is also uncertain, and an area of active research.

Any analysis of case reports of adverse health effects will inevitably be biased. More serious effects, particularly cases with fatal outcomes, and more unusual cases are more likely to be published. Published reports are also likely to follow areas of debate at a particular time, such as the use of dantrolene in the treatment of ecstasy-related hyperthermia. A further limitation of case report analysis is the inability to relate the number of case reports to a population base. This makes it impossible to quantify relative risks of the various adverse effects reported. However, in the absence of structured epidemiological studies, analysis of case reports constitutes the best evidence available on the risks associated with use of ecstasy.

The first reports of deaths involving MDMA use appeared in scientific literature around 1987. A subsequent surge in case reports of significant health effects seems to be associated with a change in the setting in which the drug was most commonly used – from the clinical psychotherapy setting of the 1970s to the dance party and “rave” setting of the 1990s. MDMA can produce hyperthermia in quiet surroundings, when taken in sufficient quantity, but in the setting of “raves” or dance parties, the toxicity

appears to be enhanced. It is probably a combination of direct effects of MDMA, high ambient temperature, sustained physical activity and inadequate fluid replacement, all impairing temperature regulation, that creates the greatest toxicity.

Given the hundreds of thousands of ecstasy tablets that are probably consumed each weekend, the number of published cases of adverse effects (we located 160) is very small. This, combined with the findings of the surveys of users that have been undertaken, indicates that the prevalence of serious acute adverse events arising from ecstasy use is low. It is the unpredictability of those adverse events and the risk of mortality and substantial morbidity in young people that makes the health consequences of ecstasy significant.

We identified from published reports, 69 separate cases of acute reactions to "ecstasy" involving hyperthermia, 48% of which resulted in death.

Hyperthermia is typically accompanied by a number of clinical problems, induced or made worse by the hyperthermia, including seizures or convulsions, abnormalities in blood coagulation, rhabdomyolysis, and impairment of kidney and liver function. There is an apparent correlation between body temperature and mortality, with around two-thirds of cases where the body temperature exceeded 41.5°C ending in death.

This data emphasises rapid reduction of temperature as the most important response to hyperthermia related to MDMA use. It also indicates the importance of educating users on strategies to avoid hyperthermia, and to seek medical assistance promptly if hyperthermia becomes apparent.

Adequate fluid intake and rest periods in a cool room are important measures for the prevention of hyperthermia, but excessive fluid intake can also be harmful. We identified 14 cases with features of confusion, reduced consciousness and, in some cases, seizures or convulsions, apparently induced by disturbances in salt or water balance following ecstasy use. Three of the cases were fatal; consumption of copious water was reported to have occurred in five of the 14 cases.

Other reported acute adverse effects included:

- seizures without hyperthermia or hyponatraemia (possibly due to consumption of amphetamine derivatives other than MDMA);
- disturbances of cardiac function (often associated with pre-existing cardiac disease);

- cerebral ischaemia or blood vessel ruptures (possibly related to the stimulatory action of ecstasy, or to the presence of amphetamine in the "ecstasy" or taken concurrently with "ecstasy");
- respiratory difficulties;
- trauma whilst intoxicated;
- chest pain not related to cardiac factors (air in tissues, spasm of intercostal muscles from strenuous exercise);
- ophthalmic conditions (probably related to extended periods of activity with reduced blinking and tear formation); and
- aplastic anaemia (the link with ecstasy use is unclear).

Longer term physical effects include excessive tooth-wear arising from tooth-grinding and jaw clenching associated with ecstasy use. One limited study has also identified a possible increased risk of birth defects following ecstasy use during pregnancy. The study had insufficient statistical power to confirm a causal relation but, given the young age of ecstasy users, is an aspect that should be monitored.

An issue with analysis of case reports is the lack of certainty as to the nature and amount of drugs consumed, which makes it difficult to attribute adverse effects specifically to MDMA use. For 108 of the 158 cases of acute adverse effects we examined, drug use was confirmed by analysis of blood and/or urine samples. Although these analyses indicate the presence, in some cases, of a number of amphetamine derivatives, alcohol or other drugs, they also support a conclusion that MDMA alone can produce adverse effects including hyperthermia, disturbances of sodium and fluid balance, disturbances of cardiac function, cerebral haemorrhage, disturbed respiratory function, sudden collapse and trauma whilst intoxicated.

The dose of MDMA taken (as indicated by recorded serum levels of MDMA) is not predictive of the severity of outcome. Variable individual susceptibility to the effects of MDMA has been suggested as an explanation for the lack of correlation, but, as yet, plausible explanations of individual susceptibility have not been found in cases of severe reactions. In addition there appears to be a mix of first time and experienced MDMA users affected, making this explanation unlikely, or at least uncommon. The detection of MDMA in some cases of adverse effects, and reports of the affected person using from the same supply as

others who were not affected, also makes contaminants an unlikely basis for adverse reactions. It seems most likely that it is the combination of dose, setting and individual behaviour that determines the outcome of MDMA use. Whether this is also true for PMA and other amphetamine derivatives, which may be more toxic than MDMA, is unclear – to date all reported cases of adverse effects subsequent to PMA use have been fatal.

Severe liver damage can occur shortly after ingestion of ecstasy, typically in conjunction with hyperthermia. However, liver damage, apparently unrelated to hyperthermia, can also occur days or weeks after single or multiple episodes of ecstasy use. We identified 39 such cases. The majority of these cases resolved spontaneously over weeks to months, but 11 cases required some form of transplant and six cases were fatal. It also appears that those who resume ecstasy use after recovery are at risk of a recurrence of their liver damage and the development of chronic hepatitis. The mechanism of ecstasy-related liver damage is uncertain.

Our search of published literature also resulted in the identification of 44 separate cases of psychiatric sequelae attributed to ecstasy use. Nine of these cases involved alterations in mental state associated with intoxication, four were suicides, and 31 cases involved persistent or chronic sequelae.

Alterations in mental state appear atypical of MDMA intoxication – information relating to several of the reported cases is suggestive of contaminants being a factor. In most cases symptoms resolved in hours to days with minimal or no treatment.

The 31 cases of post-acute sequelae generally comprise persistent episodes of depression, panic disorders, “flashbacks” and delusions. A delay of days to weeks between last ecstasy use and presentation for assessment prevented toxicological confirmation of drug use. It appears from the reports that these more severe psychiatric sequelae are probably related to ecstasy use but generally only in individuals made vulnerable by personal or family history, or by concurrent use of other drugs such as cannabis. However, there appears to be a clear association between ecstasy use and short-term mood changes.

Prevention aims to reduce the demand for drugs by decreasing the risk factors associated with drug use and increasing protective factors. There is very little specific literature on prevention of ecstasy use. However, the principles of prevention are applicable to all drugs.

Prevention programs are of three types: primary (addressing uptake of drug use); secondary (interventions early in use to prevent progression to problematic use and to minimise the risks of adverse effects); and tertiary (treatment to minimise the extent of damage caused by drug use).

The two most common forms of primary prevention are school-based education and media information campaigns.

To be effective, school-based programs should be culturally and developmentally appropriate; promote peer influence; promote anti-drug use social norms; foster bonding to the school and the community; teach drug resistance skills through interactive teaching and learning methods; use a well-tested standardised intervention with detailed lesson plans and student materials; be ongoing with sequence progression and continuity over time; and target children at all stages of their school life.

Information only approaches and personal development approaches are generally ineffective at reducing drug use, while ‘scare’ tactics are counterproductive. Programs which are part of the school health curriculum and taught by regular teachers have more effect than those which rely on specific sessions taught by outside experts.

The major role for mass media campaigns is raising awareness and agenda setting. The effectiveness of school drug education and mass media campaigns can be enhanced if they are used as components of comprehensive, community based, multi strategy prevention programmes.

Hyperthermia and hyponatraemia are the most significant, and potentially life-threatening, acute adverse effects associated with ecstasy use. Given that both appear to arise largely as a result of the setting of use and individual behaviour, it is a good target for secondary prevention initiatives. Obvious measures include the provision of free water and temperature control at venues, together with education to increase the knowledge of users, venue operators and support staff, about the importance of controlling body temperature and fluid intake, how to recognise early signs of adverse effects, and the importance of seeking medical assistance promptly. A number of countries have developed guidelines for dance parties and night clubs that support this approach.

Testing of ecstasy tablets has some value in enabling users to avoid more toxic substances, such as PMA,

but it is important that users are aware that use of MDMA by itself can result in adverse effects. Testing of tablets should therefore always be accompanied by secondary preventive education.

Currently there are no treatment interventions designed specifically to address ecstasy use. Interventions that would be most appropriately applied to ecstasy use are those non-pharmacological approaches which have demonstrated the most efficacy in treating psychostimulant users. These are relapse prevention (particularly for heavy users), cue exposure/response prevention, and possibly multifaceted behavioural therapy. Contingency management approaches may also be of value.

In general, however, ecstasy users do not present for treatment, except in instances of adverse effects serious enough to require medical assessment, or in instances of significant concomitant use of alcohol or other drugs. An approach that is well suited to this situation is that of brief intervention. Brief interventions aim to investigate a potential problem and motivate an individual to begin to do something about their substance use. Brief interventions can be delivered opportunistically when ecstasy users are identified, such as at emergency departments of hospitals, support services at major events such as dance parties, primary health care, law enforcement settings, and through computer based applications. While brief interventions are of potential value, much of the evidence of their effectiveness relates to alcohol abuse. It is desirable for there to be development, and evaluation through structured research, of brief interventions appropriate to ecstasy users and the contexts for delivery of the interventions.

Treatment of adverse effects related to ecstasy is largely a case of selecting medical procedures suitable to the symptoms exhibited. Particular attention should be given to monitoring and control of hyperthermia and hyponatraemia, both of which can quickly become life threatening.

Medical personnel need to be informed of the nature of adverse effects that may arise subsequent to ecstasy use. This would support the opportunistic identification of ecstasy use, as well as indicating the pattern of monitoring of health status that is appropriate for ecstasy users.

There remain many gaps and inadequacies in our knowledge of the health effects of ecstasy. Systems of monitoring emergency room attendances should be considered as means of monitoring the prevalence of adverse effects. Such systems can also help

to identify emerging problems. Controlled epidemiological studies to establish the prevalence of harms, to quantify the risks of ecstasy use, and assess the long-term functional consequences of ecstasy use are also desirable. The question of whether ecstasy does produce dependence remains unanswered. If the answer is yes, it is then of interest to determine whether the assessment of ecstasy dependence is of diagnostic value. A final, important research direction is that of the pharmacology and toxicology of MDMA and other amphetamine derivatives in animals, in vitro cellular systems, and humans. Increased understanding of the mechanisms and toxicity of these compounds is critical if we are to respond to changes in illicit drug markets and predict the likely adverse effects in a given situation.

Introduction

1.1 Background

"Ecstasy" is the popular street name for 3,4-methylenedioxymethamphetamine (MDMA). MDMA is one of a family of drugs variously known as "amphetamine analogues", "ring-substituted amphetamines", or "designer drugs". While the name "ecstasy" was initially applied to MDMA, and continues to be primarily applied to MDMA, other drugs are also sold as ecstasy, and ecstasy tablets can contain a range of drugs (amphetamine, various ring-substituted amphetamines, caffeine, aspirin) in addition to, or in place of, MDMA.

MDMA is a derivative of amphetamine that combines stimulant and hallucinogenic properties – because of these properties it is sometimes described as a "psychedelic amphetamine". It is sometimes also referred to as an "empathic entactogen" – this reflects the primary positive effects of MDMA reported by users, namely an elevated mood state encompassing feelings of euphoria, intimacy and closeness to other people (Solowij 1993). It is this property of MDMA that underlies the history of its use as an adjunct to psychotherapy (Greer & Tolbert 1990).

The combination of stimulant and euphoric properties helps to explain the association between ecstasy and nightclub or dance party settings. A global trend of increasing use of ecstasy has coincided with a global trend, commencing in the 1980s, towards dance parties and dance music – also referred to as "raves" and "techno".

The association of ecstasy with aspects of youth entertainment and fashion and its rapid global spread made it an issue of interest to the media. The first reports of deaths associated with ecstasy use in the late 1980s conflicted with common perceptions of ecstasy as a "safe" drug. Further reports of deaths, particularly those involving teenagers without a history of drug use, led to a sustained period of media interest in the adverse effects of ecstasy.

Animal models have for some years pointed towards MDMA having a neurotoxic effect; human studies are now indicated functional impairment possibly related to the neurotoxic effects. These findings have renewed concern about the health effects of ecstasy.

The World Health Organization has previously undertaken a review of amphetamine-type stimulants

(World Health Organization 1997). This review included some general discussion of the use and effects of ecstasy, but, given the sustained high level of interest in ecstasy and recent findings relating to neurotoxicity, it was considered timely to undertake a specific review of the health effects of ecstasy.

1.2 Scope of the report

The primary focus of this review is MDMA. However, some consideration is given to structurally related ring-substituted amphetamines, particularly those that are used or sold as ecstasy, either intentionally or through manufacturing errors (eg. methylenedioxy-amphetamine, or MDA, methylenedioxyethylamphetamine or MDEA, and para-methoxyamphetamine or PMA).

1.3 Chemistry

The group of drugs identified as "amphetamine-type stimulants" is large. It includes 3,4-methylenedioxymethamphetamine (MDMA, "Adam", "ecstasy", "XTC", "E"), methylenedioxyethylamphetamine (MDEA, "Eve"), amphetamine ("speed", "whizz"), methamphetamine ("speed", "ICE"), para-methoxyamphetamine (PMA), N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB, "methyl-J", "Eden") and methylenedioxyamphetamine (MDA). Their actions range from being stimulants with little or no hallucinogenic properties in the case of amphetamine, to those with structures and actions similar to the hallucinogen mescaline.

The key structural determinants of the activity of amphetamine-type stimulants are their (1) unsubstituted phenyl ring, (2) alpha methyl group, (3) primary amino group and (4) two-carbon side-chain connecting the phenyl ring and the primary amino group. Any structural modifications will accentuate some of the actions, abolish or attenuate others, or uncover latent actions (Biel 1970).

The psychomotor stimulant activity of the amphetamine molecule is reduced by (1) N-alkylation (as in N-ethylamphetamine and N-propylamphetamine), (2) addition of a hydroxyl group to the alpha carbon (as in ephedrine and pseudoephedrine), (3) removal of the alpha methyl group (as in 4-bromo-2,5-dimethoxyamphetamine), (4) deamination, or (5)

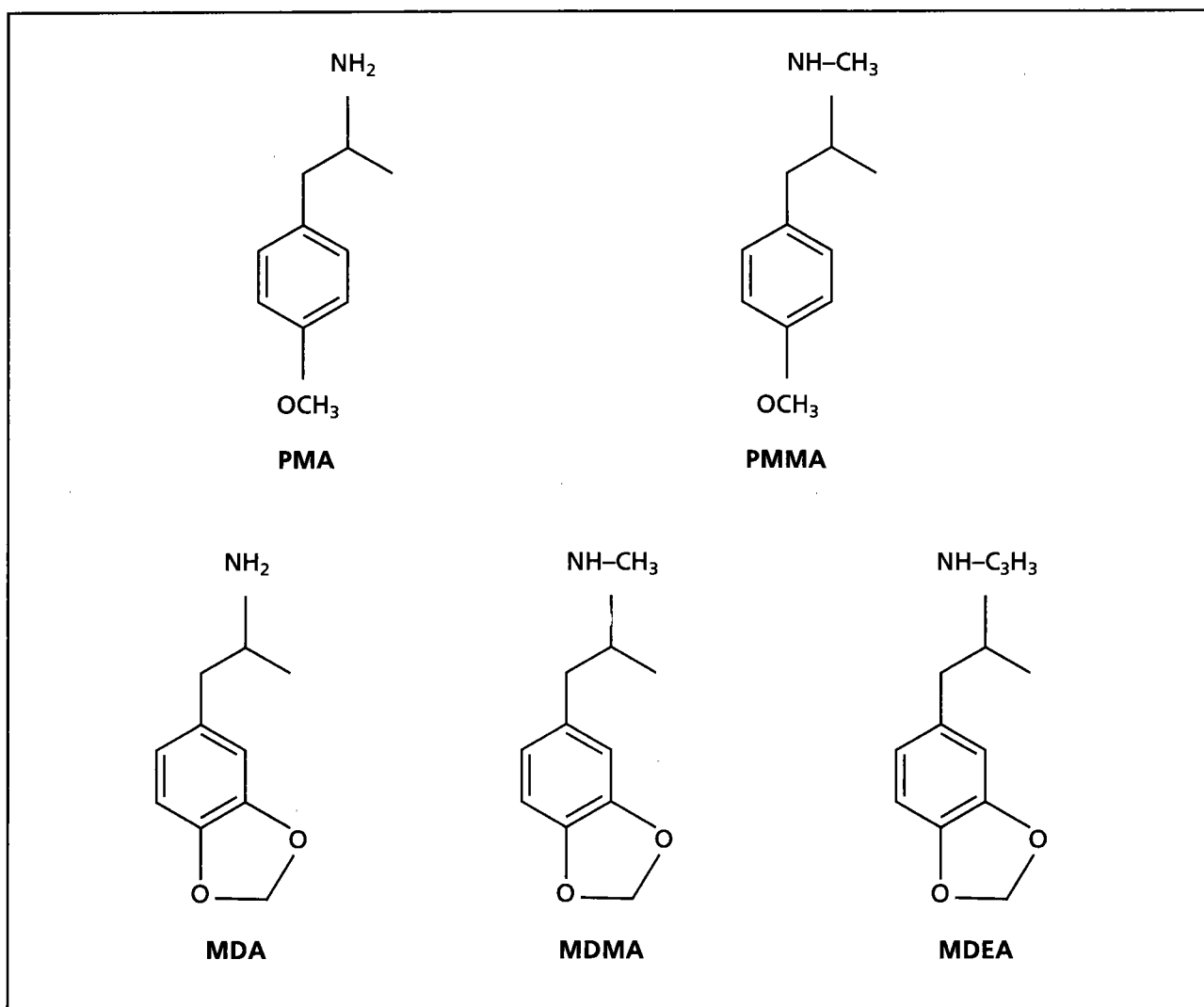


Figure 1: Molecular structure of MDMA and related amphetamine derivatives.

(Refer to Glossary of terms and abbreviations for full chemical names.)

multiple ring substitutions (as in fenfluramine, dexfenfluramine) (World Health Organization 1997).

Multiple substitutions on the phenyl ring of amphetamine tend to confer hallucinogenic activity. Thus, 2,5-dimethoxy-4-methylamphetamine (DOM) and 4-bromo-2,5-dimethoxyamphetamine (DOB) are potent hallucinogenic agents (World Health Organization 1997). Substitution of a methoxy group in the para position of the amphetamine molecule is important for hallucinogenic properties. Thus, para-methoxyamphetamine (PMA) has a hallucinogenic potency five times that of mescaline and three times that of MDA (Cimbura 1974).

Placement of a methylenedioxy moiety on the 3 and 4 positions of the phenyl ring of amphetamine and methamphetamine yields 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymetham-

phetamine (MDMA), respectively (see Figure 1). An important structural feature of MDMA is that it is a secondary amine – ie. the basic nitrogen is substituted with an N-methyl. This distinguishes it from hallucinogenic amphetamines that are most potent as primary amines (Nichols & Oberlender 1990).

Other amphetamine analogues with MDMA-like properties include 3,4-methylene-dioxyethylamphetamine (MDEA), N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), para-methoxymethamphetamine (PMMA) and N-hydroxy-3,4-methylenedioxyamphetamine (N-OH-MDA). Of these, MDA and MDMA appear to be the most potent in terms of empathic effects (World Health Organization 1997).

MDMA exists as two enantiomers, ie. molecular configurations that are mirror images of each other. In the laboratory enantiomers are identical in all

respects, except the direction in which they rotate the plane of polarised light passing through them. However, biological systems are sensitive to molecular configuration. MDMA is typically manufactured as a mixture of the two enantiomers, denoted S and R. The S enantiomer of MDMA is more potent than the R enantiomer (Sparago *et al* 1996). In this aspect MDMA differs from the potent hallucinogenic amphetamines, such as 2,5-dimethoxy-4-methylamphetamine (DOM) which invariably are more active in the levorotatory (R) form (Nichols & Oberlender 1990; Steele *et al* 1994).

1.4 History

MDMA was first synthesised by Merck Pharmaceuticals in 1912, and patented in 1914. It has been widely reported that MDMA was manufactured as an appetite suppressant but this has been disputed – it has also been claimed that it was merely an accidental intermediate chemical (Milroy 1999). Whatever its origins, it was never commercially successful.

MDMA resurfaced in the 1950s, when it was studied by the US Army as a potential agent in psychological warfare (Milroy 1999). In the late 1960s the drug was synthesised and used experimentally by Alexander Shulgin in California, USA. In the 1970s it was increasingly being used in the USA as an adjunct to psychotherapy to help lower inhibitions in patients undergoing psychoanalysis (Grob 1998; Rochester & Kirchner 1999). In 1977 the drug was prohibited in the UK, and in 1985 perceptions of increasing recreational use of MDMA and reports that MDA had neurotoxic effects in animals, resulted in the USA Food and Drug Administration, in 1985, classifying MDMA as Schedule I (no acceptable therapeutic use). Nonetheless, a degree of interest in therapeutic application of MDA and MDMA has been maintained.

In psychotherapy the usefulness of MDMA is seen as its capacity to (1) reduce the client's "fear response" that may inhibit ability to deal with traumatic material, (2) facilitate the client's interpersonal communications with the therapist, spouse or significant others; and (3) accelerate formation of a therapeutic alliance between client and therapist (Riedlinger & Riedlinger 1994). To date there have been no controlled studies of the effectiveness of MDMA as an adjunct to psychotherapy. Claims of effectiveness rely largely on testimonies from therapists and their clients (Grob & Poland 1997) although the Multidisciplinary

Association for Psychedelic Drugs (MAPS) has been supporting research (see <http://www.maps.org>).

1.5 Manufacture

Synthesis of MDMA is from materials containing the methylenedioxyphenyl ring. The main starting materials are piperonal, isosafrole, safrole and piperonylacetone. At least six methods of making MDMA are described in the scientific literature. Several recipes are easily located on the Internet. Some specialised equipment is required as well as some expertise in organic chemical synthesis (Rochester & Kirchner 1999). Nonetheless, illicit production of MDMA and similar drugs can be undertaken relatively easily in makeshift laboratories.

Quality control is difficult to achieve and restrictions on the availability of appropriate starting chemicals can lead to the final product containing chemicals other than MDMA. This can be an intentional act or due to error on the part of the chemist.

Forensic analysis of drugs seized as 'ecstasy' (MDMA) have revealed other amphetamine-type stimulants such as amphetamine, methamphetamine, MDA, MDEA, PMA, MBDB (Carter *et al* 2000), and PMMA among others. Often the tablets or capsules contain chemically unrelated compounds, such as aspirin, paracetamol, or caffeine, with little or no psychotropic activity. Ketamine, an anaesthetic agent with hallucinogenic properties, has also been found in 'ecstasy' tablets (Wolff *et al* 1995).

MDMA is usually sold as a tablet or capsule. The tablets vary widely in their appearance and typically are identified by a symbol impressed on the surface of the tablet. This leads to users referring to them as "white doves", "love hearts", etc. The quantity of active ingredient in one tablet or capsule is usually in the range of 75-150mg.

Large scale testing of ecstasy tablets at parties and agencies of the Drugs Information and Monitoring System has been undertaken in the Netherlands since 1992. Between 1992 and 1998 over 25,000 tablets were analysed in the laboratory using gas chromatography and mass spectrometry. These analyses identified a range of substances being sold as ecstasy at various times including LSD, amphetamine, 4-methylthioamphetamine (4-MTA), DOB, 4-bromo-2,5-dimethoxyphenethylamine (2CB), and atropine. In addition wide variations in the dose of MDMA contained in tablets have been detected (Niesink *et al* 1999).

Epidemiology

Reviewing the epidemiology of ecstasy use is a difficult task because of the paucity of reliable information. The illicit nature of ecstasy use gives rise to significant under-reporting in general population studies and makes it difficult to access populations of users. In addition, many countries do not have adequate mechanisms for epidemiological monitoring of substance use and much of the available information is anecdotal. Historically heroin and cocaine have been perceived as the main drugs associated with 'the drug problem' and, as a result, amphetamine-type stimulants, including ecstasy, have been of lesser priority in the information gathering activities of many countries.

Currently, most available epidemiological information on ecstasy comes from Europe, North America and Australia. This makes it very difficult to generalise about the prevalence and patterns of use of ecstasy at a global level.

Systematic comparison of the available data is generally not possible because of variations in methodology and difficulties in interpretation of a number of indicators. These relate to the substances involved, age ranges used, how use is measured, and the interpretation of law enforcement, treatment and mortality and morbidity data.

Identification of exactly which substances are involved when ecstasy use is reported is problematic because of the wide range of substances which are marketed as ecstasy and the fact that tablets may contain mixtures of different substances. In addition, classification of drugs varies from country to country and between studies. Ecstasy may be classified as an amphetamine-type stimulant, synthetic drug, designer drug, dance drug, or be listed by name in different data sets (Anonymous 1999f; Commission on Narcotic Drugs 1999; World Health Organization 1997). Even when one classification is used comparisons can be misleading. For example, amphetamine-type stimulant (ATS) use is widespread in most regions of the world but amphetamine and methamphetamine predominate in some regions while ecstasy prevails in others.

Estimates of prevalence among different age cohorts are complicated by the variety of age ranges used in different studies. This is especially true for studies of young people. The report of the UN Economic and

Social Council, Youth and drugs: a global overview, (Commission on Narcotic Drugs 1999) mainly referred to young people aged 15-24 but found considerable diversity in the age ranges used in individual studies. Information from several countries was based on samples of only a one year birth cohort (usually 15 to 16 year olds). There is very little data on use at ages younger than 15 although it is known that drug use (which may include ecstasy) often occurs at younger ages.

Much of the available data reports rates of lifetime use, which includes all those who have ever used ecstasy even if it was only once. In many cases, lifetime use and recent use are not distinguished. Where rates of recent use are reported these are much lower than lifetime use rates, indicating that only a very small proportion of those who have ever used ecstasy use it regularly. Reliance on data on lifetime use may lead to significant over-estimation of the size of the problem.

Ecstasy users rarely present to drug and alcohol services for treatment of their drug use and are less likely to appear in law enforcement data sets than other drug users. This precludes use of treatment and law enforcement data as indicators of ecstasy use. Similarly, morbidity and mortality statistics are limited in their usefulness as indicators.

The information in this chapter is synthesised from a variety of sources including: annual reports of the United Nations International Drug Control Programme (UNDCP) and the European Monitoring Centre for Drugs and Drug Dependence (EMCDDA); country reports presented at WHO and UN meetings on amphetamine-type stimulants; national household surveys and school children's surveys from the USA, Australia and Europe; and published reports of studies of specific populations and samples of users.

2.1 Global spread

There has been significant growth in the popularity of amphetamine-type stimulants including ecstasy, during the 1990s and in recent years the most pronounced increase in drug use world wide has been reported for these synthetic drugs (United Nations International Drug Control Programme 1997). In 1997, increases in the prevalence of amphetamine-type stimulants were reported by larger numbers of

countries than previously in all regions except Africa. Most of the increase in the Far East and South East Asia region is reported to be related to amphetamines but ecstasy use is rising in several countries (UNDCP 1999).

Ecstasy first emerged as a recreational drug in the USA in the 1980s, from whence it spread to Europe and the UK (Milroy 1999). Ecstasy is most popular in the industrialised world, but use is spreading to other regions. Consumption of ecstasy by young people increased rapidly during the 1990s especially in Western Europe where highest rates of use are found in Belgium, Germany, Ireland, Italy, the Netherlands, Spain and UK. It appears that extensive media coverage may have contributed to the rapid increase in the numbers of people experimenting with ecstasy (Gamella 1999; Topp *et al* 1997c). Use is also spreading to Central and Eastern Europe (Croatia, Slovenia, Hungary, and Poland) and there is some evidence of ecstasy use in Southern Africa (South Africa and Swaziland) and South East Asia (Indonesia, Singapore and Thailand) although the nature and extent of use varies from region to region and country to country. Recent reports from EMCDDA and the Commission on Narcotic Drugs suggest that consumption has stabilised in those countries with longer history and higher prevalence of ecstasy use but is still rising in countries with lower rates (Commission on Narcotic Drugs 1999; European Monitoring Centre for Drugs and Drug Addiction 1998; European Monitoring Centre for Drugs and Drug Addiction 1999).

2.2 Population prevalence of use

For many countries there are no data available on the prevalence of ecstasy use, while for others, such as Australia, the UK, and the USA, data are available from national surveys and from studies of specific populations.

Estimates of population prevalence vary widely within and between countries and regions and use is generally higher among young adults and student samples than among the general population. Data from Europe and the USA indicate that ecstasy has ever been tried by between 0.5 and three per cent of the general population and from one to five per cent of young adults (Anonymous 1999c; European Monitoring Centre for Drugs and Drug Addiction 1999). The highest reported lifetime prevalence among the general population comes from Australia where 4.7% reported ever having used ecstasy (Australian Institute of Health & Welfare 1999).

Smart and Ogborne (Smart & Ogborne 2000) compared drug use among students in 36 countries and reported ecstasy use among high school students ranging from zero (Czech Republic, Ukraine, Estonia, Finland, Hungary, Lithuania, Latvia and the Slovak Republic) to 12% in Scotland. This review was based on published research reports only and some studies used limited samples.

The United Nations Economic and Social Council (Commission on Narcotic Drugs 1999) drew on studies conducted between 1990 and 1997 to report lifetime prevalence rates of ecstasy use among youth in 27 countries. Rates ranged from 0.2% in Finland to nine per cent in Ireland, with an average over all countries of 2.6%. These data came from studies with varying age ranges and differing methodologies and were therefore not directly comparable.

2.2.1 Africa and Middle Eastern Countries

Very few data have been identified for Africa and Middle Eastern Countries, however there is evidence that ecstasy use occurs in Southern Africa. Ecstasy use appeared in South Africa in 1989-91 but has only been seen as a problem in recent years. Anecdotal evidence suggests that use is growing alarmingly (Commission on Narcotic Drugs 1999).

2.2.1.1 South Africa

There are few data available on prevalence of ecstasy use in South Africa. The South African Community Epidemiology Network on Drug Use (SACENDU) reported that six per cent of students surveyed in a study of five high schools in 2000 had ever used ecstasy. Rates were highest among grade 12 students, 12% of whom had ever tried ecstasy (Parry *et al* 2001). The Commission on Narcotic Drugs reported that a study of black youth found lifetime prevalence of 0.1% (Commission on Narcotic Drugs 1999).

2.2.2 North America

2.2.2.1 Canada

No national study of ecstasy use has been undertaken in Canada. Available data come from the Ontario student survey and studies of street youth populations. Past year use among Ontario students has increased from less than one per cent in 1991 to

4.8% in 1999. Use was higher among street youth populations with 13% reporting lifetime use and 10% reporting use in the past year. A study of Ontario youth found that 13% of the sample had attended raves and were heavy users of drugs (Smart 1999).

2.2.2.2 United States of America

The results of a national household survey conducted in 1998 indicated that 1.5% of Americans aged 12 or older had ever tried ecstasy (Anonymous 1999c). The rates are much higher among young people and student populations. The Monitoring the Future surveys of school children show that ecstasy use has been increasing especially among older students (10th and 12th graders) (Stocker 2000). In 1996, five per cent of 10th and 12th graders and two per cent of 8th graders had used ecstasy in the past year (Anonymous 1997). In 1999 lifetime use among 12th graders had increased to eight per cent, past year use had increased to 5.6% and past month use to 2.5% (Anonymous 1999c).

Use among specific student populations has been investigated in a number of studies, with widely varying rates of lifetime use reported. Peroutka found that 39% of a sample of 369 undergraduates at one campus had ever used ecstasy (Peroutka 1987). Another study conducted in 1986 at a different campus found that only 15% reported lifetime use (Cuomo *et al* 1994). A more recent study at the same campus found that lifetime prevalence had increased to 24% by 1994 (Cuomo *et al* 1994). Johnson *et al* (Johnston *et al* 1996) reported that overall five per cent of 16 year olds had used ecstasy while a study in Texas found that eight per cent of high school seniors (and one per cent of seventh graders) had ever used (Maxwell & Liu 1999).

Consistent with survey data indicating increased prevalence of ecstasy use, data from the Drug Abuse Warning Network (DAWN) in the USA is indicating a dramatic increase in emergency department episodes relating to MDMA and GHB (also considered a "dance party" drug) from 1997 to 1999. However, methamphetamine continues to be more frequently associated with emergency department episodes – 10,447 in 1999 compared to 2850 for MDMA. Similarly, for drug-related deaths reported by medical examiners between 1994 and 1998, 2601 were attributed to methamphetamine compared to 27 attributed to MDMA (Anonymous 2000).

2.2.3 Latin America

Very little information is available from Latin America regarding ecstasy use. Reports from Brazil to the WHO indicate that ecstasy has recently appeared in big cities as a rave drug used at weekends (de Lima 1999). In Suriname, lifetime prevalence of 0.4% among university students has been reported (Commission on Narcotic Drugs 1999). No data are available from other Latin American countries.

2.2.4 East Asia and Western Pacific

The use of amphetamine-type stimulants is increasing in the region, however, with the exception of Australia, most of the rise is due to amphetamines rather than ecstasy and very little ecstasy use has been identified (Commission on Narcotic Drugs 1999; UNDCP Regional Centre for East Asia and the Pacific 2000). There is some evidence that manufacture of ecstasy occurs in the region (UNDCP Regional Centre for East Asia and the Pacific 2000).

2.2.4.1 Australia

Data from the National Drug Strategy Household Survey indicates that use of ecstasy by Australians aged 14 and over doubled between 1995 and 1998. Lifetime use increased from 2.4% to 4.7% while use in the last year increased from 0.9% to 2.4%. Ecstasy was the drug of first choice for one per cent of the population (Australian Institute of Health & Welfare 1999). The national survey on the use of over the counter and illicit substances by secondary students (aged 12-17) found that four per cent of students had ever used ecstasy and that around two per cent of students aged 15 and over had used ecstasy in the last month (Letcher & White 1999). The Illicit Drug Reporting System (IDRS) has found a trend to increasing use of ecstasy since 1997. In 1997, ecstasy had been used by five to 16 per cent of injecting drug users (IDU) interviewed (Hando *et al* 1998). In 1999 in South Australia, 64% of IDU had ever used ecstasy, and 22% reported past year use. Key informants in this study also reported that ecstasy use was increasing. Ecstasy is readily available and price and purity have remained stable (Humeniuk 2000).

2.2.4.2 China

Seizures of ecstasy and ecstasy-related crime have been increasing steadily in China since 1994 (UNDCP Regional Centre for East Asia and the Pacific 2000).

Ecstasy first entered Hong Kong from Taiwan but is now found in all provinces (Liu 1999). No specific data on prevalence are available.

2.2.4.3 Indonesia

Ecstasy use was identified in Indonesia in 1996 but has been replaced by increasing use of amphetamines (UNDCP Regional Centre for East Asia and the Pacific 2000).

2.2.4.4 Japan

The major drug of concern in Japan is methamphetamine. Reports to the WHO on amphetamine-type stimulants make no mention of ecstasy or other amphetamine-type stimulants (Anonymous 1999b).

2.2.4.5 Philippines

Ecstasy first appeared in the Philippines in 1994. It is relatively expensive and use appears to be confined to a small group of wealthy young people and entertainers (Sunga 1999).

2.2.4.6 Singapore

Singapore has a very low level of drug use generally and there appears to have been a reduction in ecstasy use in 1997. However, this was accompanied by an increase in arrests related to methamphetamine in the same year (UNDCP Regional Centre for East Asia and the Pacific 2000).

2.2.4.7 Thailand

Thailand has experienced considerable problems with amphetamine-type stimulant use which now exceeds heroin use. Methamphetamine and ecstasy are the most prevalent ATS and, while the problem is spread across the country, it is most prevalent in the north (UNDCP Regional Centre for East Asia and the Pacific 2000). There are few specific data on ecstasy use, but the data available suggest that ecstasy is much less prevalent than methamphetamine. Ecstasy-related arrests increased from seven in 1995 to 24 in 1998, compared to 151,000 arrests for ATS overall. It is also reported that "a few tablets are occasionally found in raids on entertainment venues" (Poshyachinda *et al* 1999). Initially, ecstasy use was mainly confined to visitors to Thailand, however 90% of those arrested for ecstasy-related offences in 1998 were Thai (Poshyachinda *et al* 1999). Although there has been a significant increase

in the manufacture of amphetamines in Thailand, there is no evidence of ecstasy manufacture (UNDCP Regional Centre for East Asia and the Pacific 2000).

2.2.4.8 Vietnam

No use of amphetamine-type stimulants, including ecstasy, has been reported in Vietnam (UNDCP Regional Centre for East Asia and the Pacific 2000).

2.2.5 Central and Eastern Europe

The use of ecstasy and other amphetamine-type stimulants spread to Central and Eastern Europe during the 1990s, although prevalence remains lower than in Western Europe, Australia and the USA. In some former Soviet Union countries ATS have replaced or supplemented traditional locally produced ephedrine based stimulants (Anonymous 1999a; Anonymous 1999g). Amphetamine and ecstasy use increased in most countries in the region in the later part of the 1990s except in Turkey, Latvia and Greece where reported use declined (UNDCP 1999). There is little population level data available for this region. Most of the data available come from studies of 15 to 16 year old school children as part of the European School Survey Project on Alcohol and other Drugs which was carried out in 25 countries (Commission on Narcotic Drugs 1999).

2.2.5.1 Croatia

Very few data are available for Croatia, however, the European School Survey Project found lifetime use of ecstasy by 2.5% of 15 to 16 year old school children in 1995 (Commission on Narcotic Drugs 1999).

2.2.5.2 Hungary

Lifetime use of ecstasy by 1.5% of 15 to 16 year old school students was reported in 1995 (Commission on Narcotic Drugs 1999).

2.2.5.3 Poland

Ecstasy has only recently appeared in Poland as a drug used on Saturday nights in association with raves and parties (Moskalewicz *et al* 1999). However, the European Monitoring Centre for Drugs and Drug Abuse reports that ecstasy is manufactured in Poland (European Monitoring Centre for Drugs and Drug Addiction 1999).

2.2.5.4 Russian Federation

Ecstasy is the fourth most widely used drug among school children in the Russian Federation. Lifetime use was reported by 2.4% of 15 to 16 year olds, while 0.4% reported using more than three times. A survey of 14-15 year olds in Moscow in 1998 found 4.3% lifetime use, while a 1999 survey of 15 to 16 year old school students found that use was highest among students of professional schools (4.3%), followed by technical college students (3.4%) and general school students (2.2%). Ecstasy was the first drug used for 0.5% of the sample (Anonymous 1999g).

2.2.5.5 Slovakia

Lifetime use of ecstasy of 0.3% among 15 to 16 year old school children was found by the European School Survey Project in 1995 (Hibell *et al* 1997).

2.2.5.6 Slovenia

In 1995, 1.5% of schoolchildren aged 15 to 16 years were reported to have ever used ecstasy (Hibell *et al* 1997).

2.2.5.7 Ukraine

Ecstasy is a relatively new drug in the Ukraine where it is available in the discos. Its use appears to be increasing among young people. A 1995 study of 15 to 16 year old students found 0.15% lifetime use. By 1998 this had increased to 7.1%. A study of youth in Kiev, also in 1998, found that one per cent of boys and 0.45% of girls have ever used (Anonymous 1999a). Prevalence tends to fluctuate according to the economic situation as users tend to switch to cheaper locally made ephedrine products when there are economic difficulties (Anonymous 1999a).

2.2.6 Western Europe

Europe is the area most affected by ecstasy use and until recently prevalence in a number of countries was high and increasing. Recent reports suggest a stabilisation or decline in ecstasy use, accompanied by an increase in the use of amphetamines, cocaine and hallucinogens (European Monitoring Centre for Drugs and Drug Addiction 1999). Ecstasy has been tried by 0.5 to three per cent of the general population and one to five per cent of young adults. Highest rates of use tend to be found among 18 to 25 year olds. Rates are significantly higher in the UK

than other European countries and lowest rates are found in Scandinavian countries (European Monitoring Centre for Drugs and Drug Addiction 1999).

School surveys have been carried out in many countries in the region and the proportion of school children who have ever tried ecstasy ranges from 0.2% in Finland, to eight or nine per cent in the UK and Ireland. Recent use is generally much less than lifetime use and is mostly in the range of one to two per cent (Commission on Narcotic Drugs 1999; European Monitoring Centre for Drugs and Drug Addiction 1999).

Ecstasy is manufactured in Europe mainly in the Netherlands, Spain and the UK. Organised crime is involved in manufacture and distribution in a number of countries. The purity and contents of pills vary widely. Seizures of ecstasy increased steadily from 1987 to 1996 but then decreased or stabilised in most countries in 1997-98 (European Monitoring Centre for Drugs and Drug Addiction 1999).

2.2.6.1 Austria

A study of 12 to 20 year olds in 1996 found lifetime prevalence of ecstasy use of 3.2% (Commission on Narcotic Drugs 1999).

2.2.6.2 Belgium

Lifetime use among 15 to 16 year old school children in 1996 was six per cent (Hibell *et al* 1997).

2.2.6.3 Denmark

A 1995 study of 15 to 16 year old school children found that 0.5% reported lifetime use of ecstasy (Hibell *et al* 1997).

2.2.6.4 Finland

Reported ecstasy use among school children in Finland is the lowest in Europe. In 1995 0.2% of 15 to 16 year olds reported ever having used ecstasy (Hibell *et al* 1997). The 1999 annual report of the EMCDDA estimated that lifetime use among school children was one per cent (European Monitoring Centre for Drugs and Drug Addiction 1999).

2.2.6.5 France

Ecstasy appeared in France in the 1980s and prevalence strongly increased in the mid-1990s. Adequate

statistics on prevalence are not available however a number of studies have been conducted and law enforcement data indicates a massive increase in ecstasy-related arrests and seizures between 1990 and 1996 (Anonymous 1998).

A 1995 survey of 18 to 75 year olds found that 0.7% reported lifetime use while 0.3% reported use in the past year. In 1996 young men in military selection centres were surveyed about their drug use: 3.9% reported ever having tried ecstasy and 1.2% used ecstasy regularly. Among school children, a study of 11 to 19 year old students found lifetime prevalence of 2.8% for boys and 1.3% for girls (Anonymous 1998).

2.2.6.6 Germany

Between 1991 and 1997, annual use of ecstasy more than doubled among 18 to 39 year olds to 1.7% which was higher than the rates for heroin and cocaine combined (Commission on Narcotic Drugs 1999). A telephone survey of 18 to 59 year olds found lifetime use of ecstasy of 0.2%. Rates were higher among 15 to 25 year olds. A study of 14 to 25 year olds conducted in the Munich area in 1995 found lifetime prevalence of 3.1% (Schuster *et al* 1998). Rates were higher for males (4%) than females (2.3%) and increased with age with 22 to 24 year olds reporting lifetime prevalence of 7.6%, compared with 0.4% of 14 to 15 year olds. 45% of those reporting lifetime use were classified as regular users (Schuster *et al* 1998).

2.2.6.7 Ireland

In 1995 the European Schools Survey Project found that nine per cent of 15 to 16 year olds in Ireland reported lifetime use of ecstasy (Hibell *et al* 1997).

2.2.6.8 Italy

Italy falls in the middle range for lifetime prevalence of ecstasy use among youth. In 1995 four per cent of 15 to 16 year olds reported ever having used ecstasy (Hibell *et al* 1997).

2.2.6.9 Luxembourg

Available data on ecstasy use in Luxembourg dates from 1992 when 0.9% of 15 to 16 year old school children reported ever having used ecstasy (Commission on Narcotic Drugs 1999).

2.2.6.10 Netherlands

A number of reports state that ecstasy use is high in the Netherlands (Anonymous 1999d; Commission on Narcotic Drugs 1999; UNDCP 1999), however, available data indicates that prevalence rates are generally lower than in the UK.

Ecstasy is the most widely used synthetic drug in the Netherlands. It first appeared in 1985 and prevalence increased rapidly in the late 1980s and early 1990s (Anonymous 1999d). Use in the past month among 12 to 18 year olds more than doubled from one per cent in 1992 to 2.2% in 1996 (UNDCP 1999). Of the general population aged 12 and over, 1.9% have ever tried ecstasy and 0.3% report use in the last month (Anonymous 1999d). A 1996 study of 12 to 19 year olds found that 5.6% reported lifetime use of ecstasy. Use is considerably higher among young people who attend raves (64%) or regular discos and parties (28%) (Anonymous 1999d).

Recent data indicates a decline in drug use among school children. The 2000 survey of Dutch school-children aged 10 to 18 years (carried out every four years) found a 40% reduction in past month use of ecstasy, from 2.2% in 1996 to 1.4% in 2000 (Sheldon 2000).

Ecstasy and other ATS are manufactured in the Netherlands for both the local and foreign markets. In 1998, 35 production sites were identified and there were 357 seizures of ecstasy. The large quantities seized indicate that organised criminal networks are involved in the manufacture and distribution of ecstasy (Anonymous 1999d).

2.2.6.11 Norway

In 1996, lifetime prevalence of ecstasy use was reported by 1.7% of Norwegian youth aged between 15 and 20 years (Commission on Narcotic Drugs 1999). However, Pedersen and Skrondal (Pedersen & Skrondal 1999) found that 3% of 14-17 year old school children in Oslo had used ecstasy in the year prior to survey. Ecstasy use was found to be significantly associated with conduct disorders and use of other drugs and to a preference for House/Techno music and attendance at house parties (Pedersen & Skrondal 1999).

2.2.6.12 Portugal

Use of ecstasy in Portugal appears to be low with 0.5% of 15 to 16 year old school children reporting lifetime use in 1995 (Hibell *et al* 1997).

2.2.6.13 Spain

The use of ecstasy has grown in Spain since 1987 with a major increase occurring since 1992. Ecstasy is seen as the most successful recreational drug of the 1990s with increases in use greater than for any other drug. In 1996 a survey of 14 to 18 year old school children found that 5.1% reported lifetime use of ecstasy, 3.9% had used in the past year and 2.2% had used in the past month. Prevalence among 15 to 65 year olds was measured in a household survey in 1997 which found that 2.5% had ever used ecstasy, one per cent had used in the last year and 0.2% had used in the last month (Gamella 1999).

2.2.6.14 Sweden

Ecstasy use among 15 to 16 year olds in Sweden was measured in 1997 with 0.8% reporting lifetime use (Commission on Narcotic Drugs 1999).

2.2.6.15 United Kingdom

Ecstasy is the third most used illicit drug after cannabis and amphetamines (Klee 1999). The British Crime Survey found that four per cent of 16 to 29 year olds reported use in the past year (UNDCP 1999) while nine per cent of school leavers have ever used ecstasy (Klee 1999).

Recent data identified a trend of declining use of dance drugs (LSD and ecstasy) in some areas of England (Anonymous 1999f). In the London area, use among 16 to 29 year olds decreased from 13% in 1994 to 10% in 1999. In the North of England, use among 16 to 19 year olds decreased from 22% in 1996 to 12% in 1998. In the South East, ecstasy use decreased from 20% in 1994 to 13% in 1998 among 16 to 19 year olds (Anonymous 1999f).

A significant decrease in ecstasy use throughout the UK was also identified in the 1999 survey of 15 to 16 year old school children. Lifetime use among girls declined from 7.3% in 1995 to 3.2% in 1999, while use among boys decreased from 9.2% in 1995 to 3.4% in 1999 (Plant & Miller 2000).

In Northern Ireland, lifetime use among 14 to 17 year olds was 10%. Among 14 to 15 year olds life-

time use was considerably lower (3.5%), indicating that older teenagers are more likely to have ever used ecstasy (Anonymous 1999f).

Use is considerably higher among young people who attend dances and clubs: 96% of young people surveyed at a dance or nightclub had ever used ecstasy and 73% were planning to do so that night (Anonymous 1999f). Similar results were found in surveys of members of the dance scene in Scotland (Forsyth 1996) and attenders at clubs and raves in South Wales (Handy *et al* 1998).

Studies of use among university students have found wide variation in prevalence among different groups. A 1993 study in a northern city reported lifetime use of 68% among males and 42% among females with 10% using ecstasy at least once per fortnight (Tober 1994). Webb *et al* (Webb *et al* 1996) found that 13% of university students reported lifetime use, five per cent had used once or twice, 5.2% had used more than once or twice and 2.7% were regular users. Use of ecstasy was lower among medical students with 4.9% of males and 3.2% of females ever having used ecstasy. Among this sample fewer than one per cent were regular users of illicit drugs (Webb *et al* 1998).

2.3 Context of use

In most countries ecstasy is used recreationally as part of a particular youth culture centred on dance parties and raves and a preference for specific types of music. Users tend to be young, well educated, socially well integrated, with high levels of employment and less likely to have a criminal record than other populations of illicit drug users (Anonymous 1998; Commission on Narcotic Drugs 1999; Gamella 1999; Topp *et al* 1997b). However, ecstasy use is part of a pattern of poly drug use and is often used in combination with other illicit substances and among groups more usually associated with illicit drug use. There is evidence from a number of countries that ecstasy has spread beyond the rave culture and is also used in a variety of other situations (Anonymous 1999f; Anonymous 1999d; European Monitoring Centre for Drugs and Drug Addiction 1999; Forsyth 1996; Gamella 1999; Handy *et al* 1998; Klee 1999; Liu 1999; Luna 1999; Moskalewicz *et al* 1999; Smart 1999; Sunga 1999; Topp *et al* 1997c).

2.3.1 Characteristics of users

While there are some exceptions, descriptions of ecstasy users in the literature are remarkably similar between countries and regions.

2.3.1.1 Age

Use is concentrated among young adults with the average age of users ranging from 18 to 27 years (Anonymous 1998; Forsyth 1996; Handy *et al* 1998; Lenton *et al* 1997; Sherlock & Conner 1999; Sunga 1999; Topp *et al* 1997b). Teenagers are reported as being in the highest using groups in the USA (Luna 1999), Netherlands (Anonymous 1999d), and the Ukraine (Anonymous 1999a).

2.3.1.2 Gender

Males generally make up the majority (approximately two-thirds) of the population of ecstasy users (Anonymous 1998; Anonymous 1999d; Adhikari & Summerill 2000; Forsyth 1996; Gamella 1999; Handy *et al* 1998). A trend towards increased use by women has been found in Australia and the USA (Luna 1999; Topp *et al* 1997b).

2.3.1.3 Social Background

Ecstasy users tend to be middle class, socially well integrated, well educated, are more likely to be employed than other drug users and less likely to have a criminal record. In Australia, the Netherlands, the USA, and Canada, ecstasy users are predominantly white, although use is increasing among other ethnic groups in the USA (Anonymous 1998; Anonymous 1999d; Forsyth 1996; Gamella 1999; Luna 1999; Smart 1999; Topp *et al* 1997b). In the Philippines, users predominantly come from wealthy families or are professional entertainers (Sunga 1999). Associations between ecstasy use and sex workers are reported in a number of countries including China (UNDCP Regional Centre for East Asia and the Pacific 2000), Spain (Gamella 1999) and the USA (Luna 1999). In spite of these trends, ecstasy use is found across the whole range of socioeconomic backgrounds and unemployed youth are considered to be at high risk (Henry-Edwards & Ali 1999; Liu 1999; Luna 1999).

2.3.2 Social context of use

Ecstasy originally became popular as a party drug in association with so-called 'raves' at which large groups of young people gathered to listen to specific types of music and dance all night (Milroy 1999). This association has continued and rave attenders have the highest reported prevalence of ecstasy use. Ecstasy has also spread into regular nightclubs, discos and parties although prevalence of use in these settings tends to be lower (Anonymous 1999f; Anonymous 1999d; European Monitoring Centre for Drugs and Drug Addiction 1999; Forsyth 1996; Gamella 1999; Handy *et al* 1998; Klee 1999; Liu 1999; Luna 1999; Moskalewicz *et al* 1999; Smart 1999; Sunga 1999; Topp *et al* 1997b). Some users also use at home and in other venues but use seldom occurs alone (Handy *et al* 1998; Topp *et al* 1997b).

Sociability is a major characteristic of ecstasy use. It is almost exclusively taken in a social setting with partners or groups of friends. Users particularly seek the feelings of empathy and closeness with others, which result from ecstasy use, to foster a group identity and sense of belonging (Anonymous 1998; Gamella 1999; Klee 1999). Friends have a major influence on ecstasy use with the majority of users reporting that they were introduced to ecstasy by friends, and decided to try it because friends were using. A significant proportion report that they continue to use because their friends are using (Gamella 1999; Sherlock & Conner 1999; Topp *et al* 1997b).

There is a strong influence of youth culture, lifestyle and fashion trends on these social networks and groups of friends. Ecstasy is associated with a variety of specific cultural trends in particular networks where the importance of the group is emphasised. These groups have been likened to tribes which go out together, share the same taste in music or dance and develop the same norms (Anonymous 1998; Luna 1999). There is fairly universal acceptance of drugs as a component of the music and dance scene among these groups (Gamella 1999; Klee 1999). The gay club and party scene and the 'techno' music scene are two examples of particular subcultures in which ecstasy use is popular (Gamella 1999; Luna 1999) (Anonymous 1998). In the UK, there are large differences in drug use at nightclubs and parties depending on the type of music played, with 'rave' and 'techno' music most associated with ecstasy use (Anonymous 1999f; Forsyth *et al* 1997; Klee 1999). In spite of the significance of drug use within the club and party scene, users in the UK rate drug use

as only the fifth most pleasant experience after music, socialising, atmosphere and dancing (Klee 1999).

Researchers in Spain have identified a series of phases of ecstasy use in that country which illustrate the importance of fashion in ecstasy trends (Gamella 1999):

- 1) Preliminary phase – use is rare and known only to a small group of cosmopolitan people;
- 2) Initial phase – use is spread in a small area (Ibiza and Eastern Mediterranean);
- 3) Popularisation phase – use is popularised with the help of media coverage and its supply and consumption spread to most areas in association with raves and techno music;
- 4) Mass consumption phase – the drug is losing its associations with particular lifestyles and subcultures and is becoming an object of normative consumption;
- 5) Declining phase – the drug has lost status as an innovation and there is a search for new options and an increase in amphetamine use.

There are indications in the UK, Spain and the Netherlands, where use peaked early, that ecstasy is now going out of fashion and use is declining (Anonymous 1999f; Gamella 1999; Plant & Miller 2000; Sheldon 2000). In Australia, where use is still increasing, research with users indicates that ecstasy is used in a wide variety of situations including at home with partners and friends to enhance intimacy and sexual activity, when socialising and meeting new people, while listening to music, even when shopping (Topp *et al* 1997b), although use is still mainly associated with raves and dance parties (McKetin *et al* 1999) suggesting that the normative consumption phase has been reached.

2.4 Pattern of use

Ecstasy is primarily used recreationally, mainly at the weekends in association with social events. A substantial proportion of use is experimental and infrequent, however, studies of samples of users also identify significant numbers of users whose use is regular and intensive. The most detailed information on patterns of ecstasy use comes from studies of users and rave attenders in Australia and the UK (Handy *et al* 1998; Sherlock & Conner 1999; Topp *et al* 1997b).

2.4.1 Quantity and frequency

Topp *et al* found that 89% of their sample of Australian ecstasy users had used at least monthly at some time, usually when they were aged around 19 years (Topp *et al* 1997b). The median number of days ecstasy was used in the last six months was 10 (approximately once every two to three weeks. Thirty seven per cent of the sample had used on one to six days during the last six months (less than monthly), 33% had used on seven to 12 days, 19% on 13 to 24 days and 12% on more than 24 days (ie. more than weekly). In the UK, Handy *et al* found that 75% of their sample used ecstasy weekly (Handy *et al* 1998) while Sherlock and Conner reported, for a self-selected sample of ecstasy users, that 39% used weekly, 27% fortnightly, 22% monthly, and 12% less often (Sherlock & Conner 1999). In the Netherlands, use is reported to stabilise at a maximum of once per week, mainly at weekends (Anonymous 1999d).

One or two tablets (150-300mg) are normally taken at a time but there are reports of greater doses being used, especially by experienced users (Handy *et al* 1998; Sherlock & Conner 1999; Topp *et al* 1997b). One-quarter of an Australian sample had used more than four tablets in a single episode and 35% had binged on ecstasy (used continuously for 48 hours) at some time (Topp *et al* 1997b). Similarly Schifano reported that most (82.2%) ecstasy users in an Italian sample commenced at half to one tablet per occasion of use, but in 25% the dosage increased to more than four tablets on each occasion in subsequent years (Schifano 2000).

2.4.2 Route of administration

Ecstasy is mainly taken by the oral route in most regions of the world. However, injecting has been reported in Australia, Poland, and the USA (Humeniuk 2000; Luna 1999; Moskalewicz *et al* 1999; Topp *et al* 1997b; Topp *et al* 1997c). Topp *et al* (Topp *et al* 1997b) found that 94% mainly swallowed ecstasy, three per cent mainly injected, and two per cent snorted. There was evidence that Australian users had tried a number of routes of administration and Topp *et al* reported that 13% of their sample of Sydney users had ever injected ecstasy (Topp *et al* 1997c). In Poland, the oral route is most common in discos and clubs but injecting of ecstasy was preferred by chronic users and those who were opiate dependent (Moskalewicz *et al* 1999). Similarly, Humeniuk (Humeniuk 2000) report-

ed that ecstasy had been injected by 28% of a sample of injecting drug users and that ecstasy was the third most likely drug to have been injected by this group.

2.4.3 Polydrug use

Polydrug use is almost universal among regular ecstasy users particularly in the industrialised world (Anonymous 1998; Anonymous 1999d; Commission on Narcotic Drugs 1999; Forsyth 1996; Gamella 1999; Handy *et al* 1998; Klee 1999; Lenton *et al* 1997; Luna 1999; Moskalewicz *et al* 1999; Schuster *et al* 1998; Sherlock & Conner 1999; Smart 1999; Topp *et al* 1997b). It appears that ecstasy use is part of a pattern of polydrug use which occurs in a variety of settings (Forsyth 1996; Gamella 1999).

Spanish research found that 75% of ecstasy users also use tobacco and alcohol and that nearly as many also use cannabis (Gamella 1999). Forsyth (Forsyth 1996) found that an average of 10.7 drugs had been used by members of the Scottish dance scene (a total of 51 different drugs was reported). Over 70% had used hallucinogens and stimulants (Forsyth 1996). Similar findings were also reported in England, Wales and Australia (Boys *et al* 1997; Handy *et al* 1998; Lenton *et al* 1997; Sherlock & Conner 1999; Topp *et al* 1997b).

Very few people who use ecstasy in association with a rave or dance party report taking only ecstasy. The vast majority take it in combination with other substances, mainly stimulants and hallucinogens (Boys *et al* 1997; Handy *et al* 1998; Lenton *et al* 1997; Sherlock & Conner 1999; Topp *et al* 1997b). There is a clear distinction between drugs used at dances and parties and those that are not. Ecstasy, amyl nitrite, amphetamine, LSD, cocaine, nitrous oxide, MDA, Ketamine and GHB are most commonly considered party drugs while pharmaceuticals, tobacco, cannabis and alcohol are more likely to be used elsewhere (Boys *et al* 1997; Forsyth 1996; Lenton *et al* 1997; Topp *et al* 1997b).

2.4.4 Planned use

Studies of young people using ecstasy in association with raves in Western Australia showed that drug use in this group is carefully planned and that users try to manage their emotional state by using a variety of drugs in specific combinations and a particular order (Boys *et al* 1997; Lenton *et al* 1997). Most users purchased their drugs many days before the event (Lenton & Davidson 1999). Ecstasy is preferred

for use at a rave and users would save their ecstasy for use at a rave or party more than other drugs. Immediately prior to the event amphetamines and cannabis were the drugs most commonly used by this sample. During the event, amphetamines, LSD and ecstasy were most often used. After the event, most used no more drugs or alcohol but those who did predominantly used cannabis or inhalants (Boys *et al* 1997).

2.4.5 Dependence

Most users appear able to regulate their use of ecstasy and, as stated above, using more than weekly is rare. However, reports from Germany and Australia indicate that a proportion of users meet the criteria for a DSM-IV diagnosis of dependence (Schuster *et al* 1998; Topp *et al* 1997a). In the German study 20% of lifetime users in a community sample were found to meet the criteria for abuse or dependence (Schuster *et al* 1998), while a study of current ecstasy users in Australia found that nearly half the sample met the criteria for ecstasy dependence. These users suffered significantly more ecstasy-related harm than those who were not dependent (Topp *et al* 1997a). Jansen has also described MDMA dependence, based on three case reports (Jansen 1999).

Topp *et al* (Topp *et al* 1997a) analysed the characteristics of the dependence syndrome for ecstasy and found important differences between ecstasy dependence and dependence on alcohol, opiates or amphetamines. The ecstasy dependence syndrome appears to be made up of two independent factors ('compulsive use' and 'escalating use'), unlike other dependence syndromes which are uni-dimensional. In addition, subjects who used ecstasy as infrequently as once a fortnight met the criteria for dependence which was quite different to other drugs where more frequent use was the norm for dependent users. They concluded that the existence of the ecstasy dependence syndrome is problematic and that either the DSM-IV criteria are too liberal for ecstasy, or if ecstasy dependence exists, it is different to the dependence syndrome for other drugs (Topp *et al* 1997a).

Pharmacology

In order to fully understand the health implications of MDMA use, it is necessary to have a clear understanding of how the drug acts. This knowledge allows predictions to be made on likely outcomes which otherwise may not appear for years to come, when the damage to human health becomes evident. It also indicates aspects of drug formulation, drug interactions, environmental conditions, medical conditions or genetic predispositions which may influence the effects of the drug.

Human studies of illicit drugs such as MDMA are somewhat limited by the inherent dangers of investigating adverse effects or addiction potential of drugs in healthy volunteers. Because of this limitation, investigations on the mechanisms of action of these drugs are somewhat dependent on non-human models. The discussion below will use human data when it is available but will also draw on animal models.

3.1 Mechanism of action

The desired effects of MDMA are related to the psychotropic effects of the drug and these are mediated by the action of the drug in the brain. However, MDMA probably also acts on structures outside the nervous system. The undesirable effects of MDMA can also be attributed to a combination of actions on structures within and outside of the brain and central nervous system.

Several authors have investigated the binding affinity of MDMA to important neurotransmitter receptor sites in the brains of experimental animals (Battaglia & De Souza 1989; Pierce & Peroutka 1988). These investigations showed that MDMA has high affinity for serotonin receptors and transport sites.

Serotonin (5-hydroxytryptamine or 5-HT) is a major neurotransmitter in the brain. Serotonin-producing neurones in the brain play a direct role in regulating aggression, mood, sexual activity, sleep, and sensitivity to pain. It is also important in memory and temperature regulation. The role of the serotonin system in the control of mood makes it the target for the successful treatment of depression by drugs such as fluoxetine (Prozac). It is likely to also be the serotonin system that gives MDMA and closely related drugs, such as MDA, their purported properties of heightened sexual experience, tranquillity and conviviality.

When administered as a single dose, MDMA initially enhances the extracellular brain concentrations of serotonin; this eventually results in depletion of the neurotransmitter and hence a decrease in serotonin levels. In addition, MDMA induces a rapid and substantial elevation of another important neurotransmitter, dopamine, which plays an important role in the control of movement, cognition, motivation and reward (Rawson 1999). The release of dopamine in certain areas of the brain is important in mediating the effects of amphetamine and cocaine, and is thought to be the mechanism underlying the stimulant properties of MDMA (Daws *et al* 2000).

3.2 Animal pharmacology

In the rat it has been shown that administration of MDMA results in increases in metabolic rate, evaporative water loss, heart rate, blood pressure, body temperature and locomotor activity (Gordon 1991). These effects are likely to be due to a combination of mechanisms, including centrally mediated effects due to monoamines, such as dopamine and serotonin, and peripheral sympathomimetic actions of MDMA.

In rats, the effect of MDMA is influenced by ambient temperature – Malberg and Seiden found that at ambient temperatures between 20 and 22°C, MDMA had a hypothermic effect, but at ambient temperatures of 28 and 30°C, MDMA had a hyperthermic effect (Malberg & Seiden 1998).

Furthermore, neurotoxicity (assessed in terms of regional 5-HT and 5-HIAA levels) was observed at ambient temperatures of 26 to 30°C but not at temperatures of 20 to 24°C. Hence the effect of the drug is best characterised as a loss of normal control of body temperature.

The influence of ambient temperature is significant given that most reports of ecstasy-related hyperthermia in humans are related to use in dance party or nightclub settings (see section 5.2 and appendix 2) where a high ambient temperature is probable.

Hyperthermia has been induced with serotonin which suggests that the MDMA-induced release of this transmitter may be a cause of the temperature control problems (Loscher *et al* 1990).

3.3 Effect in humans

3.3.1 Controlled administration of MDMA

Much of the reliable information on the pharmacological effect of MDMA in humans was gained from use of the drug in the USA, as an adjunct to psychotherapy, in the early 1980s, prior to legal restrictions. In these studies the drug was used in quiet surroundings, in psychiatric clinics – quite unlike the current typical setting for recreational use. In addition, in therapeutic use the clients were screened for pre-existing conditions and concurrent drug use (Greer & Tolbert 1990). This may have reduced the likelihood of adverse effects. However, the doses used in therapeutic sessions (100-150mg for men and 75-125mg for women) were similar to those taken recreationally.

Greer and Tolbert investigated the effects of 75-150mg of pure MDMA, administered orally, to 29 volunteers in a controlled setting by psychotherapists (Greer & Tolbert 1986). The subjects experienced a sense of well being, calmness and fearlessness. There were few adverse effects, although 28 lost their appetite, 22 had trismus or bruxism, nine had nausea, eight had muscle aches or stiffness, and three had ataxia. Sweating and thirst was common, and water was offered periodically during the session (Greer & Tolbert 1990). Blood pressure and heart rate were both observed to increase after administration of MDMA, but the magnitude of change was not documented. Afterwards, 23 noted fatigue for hours or days, and 11 had insomnia.

Grob administered placebo or MDMA in doses ranging from 0.25 to 2.5mg/kg to 18 normal volunteers with prior experience of ecstasy (Grob 1998). Subjects remained resting in bed and were encouraged to drink fluids throughout the experimental drug session. MDMA was found to induce increases in secretion of cortisol, ACTH and prolactin. Mild temperature elevations (up to 1°F) were observed with mild and high doses of MDMA and two subjects sustained significant blood pressure elevations (peaking at 200/100mmHg in one subject, and 220/120mmHg in the second). Through the use of sophisticated imaging techniques before and after the first MDMA dose, possible alterations of brain neurochemistry and blood perfusion were identified. However, Grob indicates the implications of these changes are unclear. (Brain imaging studies of ecstasy users are discussed further in section 4.1.)

Vollenweider *et al* investigated the effects of MDMA in a double-blind placebo-controlled study (Vollenweider *et al* 1998). This study found that MDMA at 1.7mg/kg, administered to 13 MDMA-naïve healthy volunteers, produced an affective state of enhanced mood, well-being, and increased emotional sensitiveness, little anxiety, but no hallucinations or panic reactions. Mild depersonalisation and derealisation phenomena occurred together with moderate thought disorder, first signs of loss of body control and alterations in the meaning of percepts. Subjects also displayed changes in the sense of space and time, heightened sensory awareness, and increased psychomotor drive. MDMA did not impair selective attention. MDMA increased blood pressure moderately, with the exception of one subject who showed a transient hypertensive reaction. Most frequent somatic complaints during the MDMA challenge were jaw clenching, lack of appetite, feelings of restlessness, insomnia, occasional difficulty concentrating, and brooding.

Cami *et al* conducted a randomised, double-blind, crossover study to assess psychomotor performance and subjective effects of MDMA in eight healthy male volunteers. MDMA was given in 75 and 125mg doses, with amphetamine (40mg) and placebo as reference compounds. They found that the short-term administration of MDMA produced marked euphoria, a slight impairment in the performance of psychomotor tasks, and mild changes in body perceptions without hallucinations (Cami *et al* 2000).

3.3.2 Surveys of users

Although studies involving controlled administration of MDMA provide the most reliable information on the pharmacological effect of MDMA in humans, the setting in which controlled administration occurs is significantly different to the setting for most recreational use. Given that setting and expectations are significant factors in determining the effect of a drug, it is important to also take into account reports from recreational users of the effects of ecstasy. These data are less reliable in that they are generally collected through surveys, thereby relying on participants' recall and perceptions. Furthermore, there is no way of confirming the nature and amount of drugs consumed.

Peroutka surveyed 100 recreational users of MDMA at a university campus concerning the subjective effects of the drug (Peroutka 1990). The most common effect reported was a heightened sense of "closeness" with other people (90% of subjects).

Tachycardia (72%), dry mouth (61%), tremor (42%), palpitations (41%), diaphoresis (38%) and paraesthesias (35%) were the most commonly reported sympathomimetic effects. Bruxism (grinding of teeth) and trismus (jaw clenching) were reported by 75% and 65% of subjects, respectively. Visual hallucinations were reported by 20% of users. Both the sense of "closeness" with other people and the trismus continued into the second day for 22% and 21% of the respondents, respectively. A general sense of anxiety, worry or fear, as well as irritability, on the day following MDMA use were reported by 12% of the subjects. Depression (21%), difficulty concentrating (21%) and headache (17%) were considered to be "negative" aspects of MDMA use occurring on the day after ingestion.

Cohen surveyed 500 people (336 male, 164 female, aged 18 to 25) about the effects of ecstasy (Cohen 1995). Participants were drawn from shopping malls, nightclubs and college campuses. Use of ecstasy ranged from one exposure to over 250 experiences, but over half had a maximum of three exposures to the drug. Following MDMA ingestion, 97% reported euphoria, 91% increased energy, 83% sexual arousal. In terms of acute physical effects, 88% reported pupillary dilation, 54% bruxism, 32% lower back pain and 22% nausea. Bruxism was reported by most users to have been the most disturbing physical side effect. Long-term psychological effects attributed to MDMA use included depersonalisation (54%), insomnia (38%), depression (38%) and flashbacks (27%). Long-term physical effects attributed to MDMA use included lower back pain (48%), neck hypertonicity (48%), joint stiffness (36%), acne/skin rash (31%), frequent headaches (30%), and frequent stomach cramp (24%).

Siegel reports case studies of 44 people (aged 17 to 55) who had used MDMA at least twice during the previous 12 months (Siegel 1986). All had histories of multiple drug use – 56% cannabis; 18% other hallucinogens; 11% cocaine; 5% amphetamines. All used by oral administration, although two had experimented with intranasal and one with intravenous administration. The total dosage taken in a given session averaged 120mg. Specific positive effects reported included: changes in feelings and emotions (80%); enhanced communication, empathy or understanding (68%); changes in cognitive or mental associations (68%); euphoria or ecstasy (63%); changes in perception (44%); and transcendental or religious experiences (11%). Undesirable effects included: muscle tension and/or jaw clenching (100%); increased sweating (91%); blurred vision

(77%); ataxia (77%); nausea (38%); anxiety (15%). Siegel noted that despite the frequency of negative effects as a result of acute intoxication, users continued to rate the overall experience as positive and rewarding. The majority of reported effects disappeared within 24 hours but several users reported prolonged physical and psychological effects. The most common physical effects were muscle tension in the jaw (11%) which continued for two days to six weeks, and blurred vision (7%) which continued for one to three days. The most frequent psychological complaints were fatigue (50%), depression (27%), anxiety (25%) and insomnia (7%) which were reported for periods of one to eight days following MDMA use.

In a survey of individuals attending clubs and "raves" in South Wales, 39.3% of respondents reported that they had experienced negative effects whilst taking ecstasy, most commonly physical sickness (24%), emotional confusion (23%), visual disturbance (19%), paranoia (18%), depression (13%) and ataxia (10%). A greater proportion of females reported negative experiences. The majority (72.9%) stated that taking ecstasy had made them feel closer to their friends (Handy *et al* 1998).

Solowij surveyed 100 ecstasy users (61 males, 39 females), recruited through a 'snowball' peer network technique; 68% of the sample had used ecstasy more than three times; 40% reported regular use of cannabis (Solowij *et al* 1992). Significant findings on the effects of ecstasy included the following:

- seven mentioned having experienced depression acutely as a result of having used ecstasy;
- larger doses were reported to be primarily more hallucinatory;
- successive doses were reported to be less intense and shorter lasting than the first dose taken on each occasion, often with reduced pleasurable effects and increased side effects;
- unpleasant side effects were reported as being experienced 86% of the time;
- the severity of side effects reported was positively correlated with both the total number of doses consumed and the frequency of use;
- residual effects were reported to last up to 24 hours; 12% described the 'coming down' and after effects as severe;

- 28% admitted to having experienced problems related to ecstasy use, predominantly paranoia, panic, loss of reality, loss of control, anxiety, hallucinations;
- 18% reported bad physical side effects such as fainting, decreased respiration, grinding teeth, chewing mouth and jaw clenching; 16% reported nausea and vomiting.

In the survey of 100 recreational users of MDMA undertaken by Peroutka *et al*, 43 subjects had taken two to five separate doses of the drugs (Peroutka 1990). Of these, 21 (49%) reported that the effects of the drug decreased with subsequent doses. In subjects who had taken six or more doses of MDMA, 67% reported a decrease in beneficial effects over time. In general, the subjects reported that the “positive” effects of the drug decreased while the “negative” effects increased with successive doses. An increase in the size of a single dose of MDMA was found to increase the “negative” effects of the drug while decreasing the “positive” effects (Peroutka *et al* 1988). Similar findings were reported by Solowij, based on a survey of 100 ecstasy users (Solowij *et al* 1992).

3.3.3 Summary of effects

Findings of studies using controlled administration of MDMA and surveys of users are consistent, namely immediate positive psychological effects of euphoria, increased energy, and a feeling of closeness to others (Cohen 1995; Peroutka *et al* 1988; Vollenweider *et al* 1998), and negative psychological effects of paranoia, anxiety and depression. Common short-term physical effects are pupil dilation, increased jaw tension and grinding of teeth, loss of appetite, dry mouth, tachycardia, hot and cold flushes, and sweaty palms. Longer term effects reported by users include insomnia, depression, headaches and muscle stiffness.

It has been reported that other ring-substituted amphetamines are only subtly different in effect, although the duration of the experience may be extended, especially in the case of MDA which can last for up to 24 hours (as opposed to six hours for MDMA and MDEA). However, MDA and MDEA lack the empathic effects of MDMA (Handy *et al* 1998). MBDB is also described as being very much like MDMA, but associated with less spontaneity, warmth and clear intimacy (Carter *et al* 2000).

3.4 Pharmacokinetics and metabolism

How drugs are absorbed into our body, distributed throughout our tissues and eliminated from our body is important in determining their likely effects, both positive and negative. Thus, some understanding of pharmacokinetics and metabolism of the drug is important in understanding animal and human pharmacological research on MDMA.

The first step in the elimination of many drugs from the body, and an important determinant of the duration and severity of effects, is chemical breakdown or metabolism of the drug. This mainly occurs in the liver although it can occur in other tissues. After metabolism the metabolic products are excreted from the body, mainly in the urine.

The efficiency of metabolism can be influenced by many factors, including gender, age, disease, co-administration of other drugs, both prescribed and illicit, and genetic variation.

3.4.1 Absorption of MDMA

MDMA, like all amphetamines, is well absorbed from the gastrointestinal tract after it is swallowed. It quickly distributes throughout the body and easily enters the brain.

Following oral administration of MDMA, effects become apparent in about 20 minutes and last for about four hours. A minority of users inject MDMA, resulting in more immediate effects and a slightly shorter duration of action.

In a limited pharmacokinetic study, Verebey administered 50mg of MDMA orally to a single healthy subject (Verebey 1988). This single administration of MDMA resulted in a half-life of MDMA in the blood of 7.6 hours, and a peak plasma concentration of 105.6 ng/ml at two hours. A recent more complete pharmacodynamic/pharmacokinetic study in eight young males given two doses of MDMA resulted in comparable findings: elimination half lives of 7.86 hours for a 75mg oral dose and 8.73 hours for a 125mg dose, with the maximum concentrations in the blood detected at 1.8 and 2.4 hours, respectively (Mas *et al* 1999). In a similar study, de la Torre *et al* obtained data indicating that the relationship between the MDMA dose and blood concentration may not be linear (de la Torre *et al* 2000). This suggests that small increases in dose may produce disproportionate increases in effects and may contribute to the development of acute toxicity.

3.4.2 Metabolism and elimination of MDMA

Some of the metabolic products of MDMA are in themselves bioactive and may contribute to the long-term neurotoxicity (see section 5). An example is MDA, which is also formed in humans and represents one per cent of the recovered dose from urine (Mas *et al* 1999). Consequently, the metabolism of MDMA has been the subject of numerous human and animal studies.

As is the case with many drugs, in the rat, MDMA is metabolised in the liver by a number of cytochrome P450-mediated pathways. One of the enzymes which metabolises MDMA in human liver is an isoform of the cytochrome P450 enzyme, CYP2D6. This enzyme exhibits a genetic polymorphism, such that 5-10% of Caucasians and 20-25% of Asians have low activity of the enzyme and are denoted as poor metabolisers. In poor metabolisers, MDMA will not be broken down as efficiently by the liver and this may result in high blood/brain concentrations of the drug. The unequal expression of the enzymes responsible for the metabolism of MDMA raises the possibility that genetic variation in metabolism may result in individual variability in the intensity of effects of the drug.

Tucker *et al* have attempted to determine whether a difference in metabolism occurs in humans (Tucker *et al* 1994). Using enzymes prepared from human livers, they found that the metabolism of MDMA was between five and ten times lower in poor metaboliser than in extensive metaboliser livers. To explore whether the genetically deficient metabolism of MDMA in poor metaboliser subjects might help to explain why some users of MDMA seem particularly sensitive to its effects, O'Donohoe *et al* ascertained the genotype of seven cases with a history of MDMA intake and side effects severe enough to necessitate hospital attendance or admission. (The spectrum of symptoms varied from mild intoxication to death.) None of the seven people was homozygous for the CYP2D6, suggesting that poor metabolism was not a contributing factor to the adverse effects they experienced (O'Donohoe *et al* 1998). Schwab *et al* similarly genotyped three patients admitted for MDMA-related hepatotoxicity (Schwab *et al* 1999). Two of these patients developed MDMA-induced fulminant hepatic failure and subsequently required liver transplantation. Hepatotoxicity developed after several months of use without adverse effects (see also section 5.6). The third patient denied drug abuse but MDA and amphetamines were detected in hair samples. All three patients were identified to be extensive

metabolisers. Further investigation of genotypes using larger sample sizes is needed to confirm the negative finding, but on the basis of these studies it appears unlikely that higher plasma concentrations of the drug from genetically impaired metabolism is the basis of adverse reactions to MDMA.

Kreth *et al* approached the question from a different direction. They investigated the kinetics of metabolism of MDMA, MDE and MDA in isolated liver microsomes from an extensive metaboliser subject compared to liver microsomes from a poor metaboliser subject (Kreth *et al* 2000). While they found that CYP2D6 polymorphism is a significant factor in the metabolism of MDE, and probably also MDMA, they also found that considerable metabolism via demethylenation of these compounds does occur in the absence of functional CYP2D6 in a poor metaboliser subject suggesting that other enzymes must be active *in vivo*. Consistent with the lack of correlation between genotype and adverse effects from ecstasy, Kreth *et al* concluded that the CYP2D6 poor metaboliser genotype may not by itself constitute a substantial risk factor for the adverse effects of MDMA and MDE.

3.4.3 Drug interactions

There are two main ways in which other drugs may alter the effects of MDMA:

- (a) by altering the elimination of MDMA from the body – if the elimination rate is slowed, the effect of a given dose of MDMA may be larger and of longer duration than expected;
- (b) drugs with a similar mechanism of action to MDMA may enhance its effect. Such drugs could include amphetamines or other amphetamine derivatives (including medication for treatment of attention deficit disorder and narcolepsy); other stimulants (eg. ephedrine); hallucinogens; weight loss medications; antidepressants (eg. fluoxetine – Prozac); and l-tryptophan, an amino acid used for sedation.

Some of these interactions could result in the "serotonin syndrome" (Sternbach 1991). This is a toxic syndrome resulting from high brain concentrations of serotonin that can be provoked by many drugs which influence this system. The most common cause is interactions between serotonergic agents and monoamine oxidase inhibitors. The serotonin syndrome is characterised by confusion, sweats, hyperthermia, high heart rate and blood pressure and convulsions. The syndrome typically resolves within 24 hours once the suspected serotonergic

agent is discontinued, but confusion can last for days, and death has been reported (Sternbach 1991).

It has been reported that inducers and inhibitors of cytochrome P450 alter the extent to which MDMA elicits some of its actions in the brain (Gollamudi *et al* 1989). Inducers of P450 enzymes include drugs, such as alcohol and the barbiturates; inhibitors include a number of antidepressants, such as fluoxetine. Thus, there is the potential for interactions between MDMA and these drugs. It is possible that the negative and positive effects of MDMA could be altered by concurrent use of other drugs. Indeed, amongst the case studies discussed in section 5, there are three (all fatal) that may have involved interactions between MDMA and inhibitors of P450 enzymes. In one case the subject had been treated with fluoxetine some months previously (Coore 1996); in a second case prescribed fluoxetine was administered concurrently with MDMA (Bingham *et al* 1998); in the third case the subject had recently commenced ritonavir, prescribed as a component of treatment for AIDS (Henry & Hill 1998). Drug interactions cannot be confirmed as a cause of the adverse reactions to MDMA, but these cases support this mechanism as a basis for MDMA toxicity.

Neurotoxicity

There are two reported types of toxicity associated with substituted amphetamines: the acute, and sometimes fatal, toxicity occurring within hours of administration and a more slowly developing neurotoxicity manifested by irreversible destruction of central 5-HT terminals (McCann *et al* 1998). The latter aspect of toxicity of MDMA and related compounds is considered in this section; the acute toxic effects are considered in section 5. The neurotoxic effects of MDMA may be the basis of psychological consequences of ecstasy use. These consequences include emotional disorientation and depression (Handy *et al* 1998). The psychological consequences are also considered in section 5.

MDMA and other similar drugs based on the structure of amphetamine, have been shown to be toxic in animals and humans. It appears however that the type and severity of toxicity is influenced by many factors, such as ambient temperature, exercise, concurrent administration of other drugs and hydration (see also section 5). These variables, when added to the large number of chemical species sold as "ecstasy", or found as contaminants of street "ecstasy", provide a very complex problem for scientists and clinicians alike. Although certain empirically based treatments and preventative actions can be implemented now, it is of utmost importance that research on the basic neuropharmacology of these drugs is pursued vigorously until sufficient understanding of their mechanisms of action can provide the avenue for evidence-based treatments. Information about biological mechanisms is our only hope of predicting toxicity and instituting appropriate public health programs.

4.1 Brain imaging studies

Animal studies have shown that administration of MDMA produces damage to axons and axon terminal fibres containing serotonin (5-HT). Specifically, the administration of MDMA results in reduced density of 5-HT axons in the cortex, hippocampus, and striatum, reduced density of 5-HT uptake sites and reduced concentrations of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), without alterations in the major metabolites of dopamine and noradrenaline (McCann *et al* 2000). Decreases in the density of brain 5-HT axons have been seen in squirrel monkeys more than seven years after MDMA

administration (Hatzidimitriou *et al* 1999). Some regrowth of axons occurs, but this is abnormal and incomplete (Boot *et al* 2000).

Sophisticated brain imaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI), are now being used to demonstrate similar changes in humans.

The initial study of McCann *et al* demonstrated a substantial reduction in the number of 5-HT uptake sites in the brains of young "normal" users of MDMA, three to four months after their last dose. Furthermore, measurable 5-HT deficits occurred in nearly all of the subjects tested (McCann *et al* 1998). These results were confirmed in the subsequent British study of Semple *et al* using slightly different technology (Semple *et al* 1999).

Using PET scanning, Obrocki *et al* identified altered glucose metabolic uptake in brain regions of seven MDMA users, compared to seven subjects with no known history of illicit drug use (Obrocki *et al* 1999). Using MRI and proton magnetic resonance, Chang *et al* evaluated 22 recreational MDMA users and found no evidence for neuronal injury in three brain regions, but observed an elevation, that was related to MDMA use, in the glial marker, myo-inositol, in the white matter. Since glial cells proliferate in response to brain injury or insult, the elevated myo-inositol demonstrates that MDMA use is insulting and causes a reactive process in the brain (Chang *et al* 1999). In a subsequent study, Chang *et al* used SPECT and MRI to investigate cerebral blood flow in 21 abstinent MDMA users compared to 21 age- and gender-matched drug-naïve subjects. Ten of the MDMA users were also assessed following controlled administration of two doses of MDMA. They found a decrease in regional cerebral blood flow in the parietal and dorsolateral frontal brain regions after MDMA administration that is consistent with serotonergically mediated vasoconstrictive effect. This decrease normalises with time and may even increase above baseline at later time points (Chang *et al* 2000).

Reneman *et al* have also focused on the effect of MDMA use on cerebral blood vessels (Reneman *et al* 2000b). Using SPECT, they found significantly lower cortical binding to 5-HT_{2A} receptors in 10 recent

MDMA users (abstinent for one week) as compared with 10 non-user controls and five former MDMA users. Reneman *et al* noted that this finding suggests downregulation of 5-HT_{2A} receptors in recent MDMA users, and that this is consistent with other studies showing that 5-HT release leads to a compensatory down-regulation of postsynaptic 5-HT₂ receptors, whereas 5-HT depletion leads to an up-regulation of 5-HT_{2A} receptors. Reneman *et al* also found that low cortical 5-HT₂ receptor densities were significantly associated with low cerebral blood vessel volumes (implicating vasoconstriction) and high cortical 5-HT₂ receptor densities with high cerebral blood vessel volumes (implicating vasodilatation) in specific brain regions. They note evidence of the involvement of 5-HT and 5-HT₂ receptors in the regulation of brain microcirculation and suggest that MDMA-induced abnormalities in vascular reaction could constitute a basis for increased susceptibility to cerebrovascular accidents (see also section 5.4.1.5).

Dafters *et al* measured resting EEG in 23 recreational MDMA users using a 128-electrode geodesic net system, from which spectral power, peak frequency and coherence levels were calculated (Dafters *et al* 1999). MDMA use in the previous 12 months was positively correlated with absolute power in the alpha (8-12Hz) and beta (12-20Hz) but not the delta (1-3Hz) or theta (4-7Hz) frequency bands. The significance of this is that alpha power has been shown to be inversely related to mental function. MDMA use was found to be negatively correlated with EEG coherence – reduced coherence levels have been associated with dysfunctional connectivity in the brain in disorders such as dementia, white-matter disease and normal aging. This group of MDMA users was also assessed with a battery of cognitive and mood tests – only the card sort test, an indication of frontal function, was weakly negatively correlated with MDMA use (Dafters *et al* 1999).

Gamma *et al* expanded on the work of Dafters *et al* by comparing 15 ecstasy users and 14 ecstasy-naïve controls using EEG, low resolution brain electromagnetic tomography and self-ratings of mood (Gamma *et al* 2000). The study was limited in that the two groups of participants were imperfectly matched with regard to the use of illicit drugs other than ecstasy. However, Gamma *et al* consider the findings provide evidence for both global and localized increases of EEG alpha and beta frequency activity in regular ecstasy users compared with ecstasy-naïve subjects. These differences were state dependent, i.e. present predominantly during eyes open but not eyes closed. Gamma *et al* note that these findings of gen-

erally increased power in ecstasy users might suggest disturbed alertness mechanisms, consistent with reports that ecstasy users show deficits in attention. Ecstasy users in this study also reported a higher occurrence of depressiveness, anxiety and psychovegetative symptoms during EEG measurements. However, it remains unclear whether the observed electrophysiological alterations and symptoms of impaired mood are linked. It is also unclear whether the electrophysiological alterations are related to MDMA-induced serotonergic neurotoxicity, to the use of other drugs or to pre-existing differences.

Kish *et al*, in a recent study, obtained autopsied brain from 11 neurologically normal subjects and one male user of MDMA (confirmed by hair analysis). They found that striatal levels of serotonin and 5-HIAA (but not dopamine) were depleted by 50 to 80 per cent in the brain of the MDMA user (Kish *et al* 2000).

While the studies focus on different aspects of the brain, and many are confounded by use of other drugs and by small subject numbers, nonetheless they are consistent in their findings of changes in the brains of MDMA users. The findings of persisting abnormalities in brain morphology in ex-users, even with moderate use, is consistent with the findings of animal studies.

4.2 Functional studies

Curran and Travill (Curran & Travill 1997) found that, compared to 12 people who reported using only alcohol, 12 users of MDMA showed significant impairments on attentional or working memory. Parrott and Lasky compared 15 regular ecstasy users (use on 10 or more occasions), 15 novice ecstasy users (use on fewer than 10 occasions) and 15 controls who had never taken ecstasy (Parrott & Lasky 1998). All were given cognitive, memory and mood tests before, during and after a Saturday night at a club, during which time regular ecstasy users took an average of 1.80 MDMA tablets, novice users took 1.45 MDMA tablets and control subjects mostly drank alcohol. Two days later, the ecstasy users felt significantly more depressed, abnormal, unsociable, unpleasant and less good tempered than the controls. Memory recall was significantly impaired in ecstasy users, with regular users displaying the worst scores at every test session. Klugman *et al* also report discrete deficits in verbal and non-verbal memory and learning, but not other cognitive functions, in 36 MDMA users compared to 19 people of similar age

who had never used illicit or prescribed psychoactive substances (Klugman *et al* 1999).

Mood, anxiety, aggression, impulsivity and cognition were investigated by Morgan (Morgan 1998) in two separate studies involving three groups: recreational ecstasy users who had also used other illicit substances (MDMA group); polydrug controls who had never taken ecstasy, but otherwise had drug histories and personal characteristics similar to the ecstasy users, and non-drug controls, who had never used illicit drugs. On the basis of the two studies, Morgan found that ecstasy users exhibited elevated impulsivity with those who had taken the most ecstasy having the most elevated trait impulsiveness score. At least 25% of the total sample of 41 ecstasy-using participants reported that they believed that taking ecstasy had made them more susceptible to anxiety, depression, aggression/irritability, and mood swings, and also reduced their ability to concentrate. Morgan noted that some of the elevated trait impulsiveness probably reflects a predisposition that may have led to subsequent use of illicit drugs. However, he believes this does not fully explain the difference between groups.

Parrott *et al* also found impulsivity to be significantly higher in 12 heavy ecstasy users (30-1000 occasions of use) compared to 22 non-ecstasy user controls (Parrott *et al* 2000). In this study the 12 heavy ecstasy users also scored significantly higher than non-ecstasy user controls on a number of items of the SCL-90, an outpatient psychiatric symptom checklist. A group of 16 light ecstasy users (one to 20 occasions of use) generally produced scores that were intermediate between those of the heavy users and the control group. The ecstasy users who participated in this study were polydrug users with significantly higher usage of amphetamine, LSD and cocaine. Parrott *et al* identify this as a potential confounder of the comparison. They also identify the possibility of pre-existing differences between ecstasy users and non-users. Nonetheless, this report supports the presence of psychological problems in a non-clinical sample of young recreational ecstasy users.

In contrast to the preceding two studies, McCann *et al* found MDMA users ($n=30$) had lower scores on personality measures of impulsivity compared to 28 controls (McCann *et al* 1994). In this study MDMA users were also found to have lower scores on personality measures of indirect hostility, and lower levels of 5-HIAA in their cerebrospinal fluid.

In a study comparing abstinent MDMA users and non-users, MDMA users were found to display a

deficit in visual and verbal memory, and higher average monthly doses of MDMA were associated with greater decrements in memory function. Lower cerebrospinal fluid (CSF) concentrations of 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of 5HT and an indirect measure of central 5-HT function, were associated with poorer memory performance (Bolla *et al* 1998).

In a subsequent study, Morgan administered the Rivermead Behavioural Memory test to 25 ecstasy users, 22 polydrug and 19 non-drug controls (Morgan 1999). Participants in the MDMA group recalled significantly fewer ideas (approximately 75% of the number of ideas recalled by participants in either of the other two groups) in both immediate and delayed recall conditions. The two illicit drug-using groups did differ in their estimated IQ scores and their duration of use of LSD (with only LSD a significant correlate) but the difference in recall performance remained statistically significant when this variable was treated as a covariate. Morgan considered this to be evidence that deficits in memory performance in recreational ecstasy users are primarily associated with past exposure to ecstasy, rather than with other legal and illicit drugs consumed by these individuals.

McCann *et al* compared 22 MDMA users, who had not used MDMA for at least three weeks, and 23 control subjects on a variety of cognitive tasks (McCann *et al* 1999). They concluded that MDMA subjects had significant performance deficits on a sustained attention task requiring arithmetic calculations, a task requiring complex attention and incidental learning, a task requiring short term memory and a task of semantic recognition and verbal reasoning. MDMA users were also found to have significant selective decreases in 5-HIAA (a metabolite of 5-HT) levels in the cerebrospinal fluid.

Reneman *et al* compared five people who had used MDMA (lifetime average of 218 tablets) but who had abstained from drug use for two months, with nine healthy controls. Using SPECT (single photon emission computed tomography) they found significantly higher 5-HT_{2A} receptor binding in the occipital cortex of the MDMA users, indicating up-regulation of these receptors. Furthermore, the mean cortical 5-HT_{2A} receptor binding correlated positively with memory performance, assessed by a word-recall test (Reneman *et al* 2000a).

Wareing *et al* tested 10 non-users, 10 current users and 10 previous users of MDMA on measures of central executive functioning, information processing

speed, and on self-report measures of arousal and anxiety (Wareing *et al* 2000). Relative to the control group, both user groups were found to be impaired in some aspects of central executive functioning, particularly with high levels of cognitive demand. Both user groups were found to process information as quickly as non-users, but less accurately. However, a confounding factor in this study is the use of other drugs – all participants in the two user groups, and none in the control group, used at least one other drug in addition to MDMA, predominantly marijuana and amphetamines.

Gouzoulis-Mayfrank *et al*, in a recent study, attempted to control for the effect of cannabis use by comparing 28 abstinent ecstasy users (regular use of psychotropic drugs other than cannabis and regular heavy use of alcohol were exclusion criteria) with 28 persons who had never taken ecstasy and were matched for cannabis use with the ecstasy user group, and 28 persons who had never taken ecstasy and had no previous or current history of regular drug use or regular or heavy alcohol use (Gouzoulis-Mayfrank *et al* 2000). All were assessed with a comprehensive test battery that included tests of attention, memory and learning, frontal lobe function, and general intelligence. All three groups performed within the normal range but ecstasy users performed worse than one or both control groups in the more complex tasks of attention, in memory and learning tests, and in the tasks reflecting aspects of general intelligence. Poorer performance scores or longer reaction times in the working memory, verbal memory, and divided attention tasks were associated with heavier ecstasy and heavier cannabis use. Gouzoulis-Mayfrank *et al* concluded that cannabis use is unlikely to fully account for the poorer performance of ecstasy users, although cannabis use is likely to have affected cognition and to have contributed to some extent. Their data suggests, therefore, that ecstasy use over a period of months or a few years may cause long term impairment of cognitive performance even when ecstasy is taken in typical recreational, and not necessarily very high, doses. Concomitant cannabis use may contribute to the impairment.

Rodgers also attempted to control for the effect of cannabis use. In this study cognitive functioning was examined in three groups: 15 regular users of ecstasy (who had previously also used cannabis but who reported being cannabis-free for at least one month); 15 regular users of cannabis (but cannabis-free for at least one month by self-report); and 15 control subjects who had never taken illicit substances (Rodgers 2000). The battery of tests administered included

computerised reaction time tasks and the Wechsler Memory Scale (revised). A questionnaire to assess participants' subjective rating of their cognitive performance was also administered. Rodgers found performance to be similar across all three groups for measures of reaction time, visual memory, and attention and concentration. Significant impairment was found on measures of verbal memory in both cannabis users and ecstasy users. A significant impairment in performance was found on measures of delayed memory for the ecstasy users compared to both the cannabis group and the control group. As with the study by Gouzoulis-Mayfrank *et al*, this suggests that concomitant use of cannabis may contribute to impairment of cognitive performance but that there is an additional impact on memory performance that appears to be related to ecstasy use. Despite these findings, Rodgers found no differences in subjective ratings of cognitive failures in the three groups.

Thus, there is continuing mounting evidence, by a number of independent research groups, supporting the concept of brain damage as a result of recreational use of MDMA. It appears that the most common functional deficit, so far revealed, is in short term memory, mediated via the 5-HT neurotransmitter system.

4.3 Long-term effects of MDMA

The long term effects of MDMA use in humans are as yet unknown. However, animal studies have suggested an alarming potential for long term harm. In primates, central 5-HT neurons appear exquisitely sensitive to MDMA. Neurodegeneration can occur with a single low dose of MDMA and deficits are still measurable one year later in baboons (Scheffel *et al* 1998). Substantial deficits in brain serotonin have now been demonstrated in squirrel monkeys, seven years after treatment with MDMA (Hatzidimitriou *et al* 1999).

Some human data comes from a study by Gerra *et al*, comparing ecstasy users at three weeks and 12 months following cessation of ecstasy use, with non-user controls (Gerra *et al* 2000). This study assessed prolactin and cortisol responses to the serotonergic agonist, fenfluramine, as indicators of serotonin system function. Prolactin responses were found to be blunted, at three weeks and 12 months after cessation of ecstasy use, whereas cortisol response was blunted at three weeks but largely restored at 12 months. This suggests a degree of recovery, but not complete reversibility, of the neurotoxic action of

MDMA. However, Gerra *et al* note that it is possible that the differences could be attributable to a pre-morbid condition, rather than ecstasy use.

Overall, on the basis of animal and human data, it would appear that brain damage is largely irreversible and does not depend on an extensive history of MDMA use. Hence, it is likely that the incidence of this irreversible neurotoxicity will be high in all users of MDMA. As this population ages, and normal brain function naturally declines, the effects of previous MDMA brain damage may present itself as a range of neurological and/or cognitive disorders.

4.4 Mechanisms of MDMA-induced neurotoxicity

The irreversible neurodegeneration, first demonstrated in rats a decade ago, has been intensively investigated. It is clear that peripherally administered MDMA causes a depletion of brain 5-HT, and a long term neurodegeneration of 5-HT terminals (Commins *et al* 1987).

It would appear that the final mechanism by which peripherally administered MDMA destroys 5-HT terminals involves free radical production within the terminal. Spin trap reagents, such as phenyl-N-tert-butyl nitron (Colado *et al* 1997) or antioxidants, eg. alpha-lipoic acid (Aguirre *et al* 1999), given to animals prior to peripheral MDMA challenge, attenuate MDMA neurotoxicity. However, the chemical species which initiates these cellular events has yet to be identified.

Pharmacologic interventions to attenuate MDMA toxicity have implied a role for 5-HT, dopamine, GABA and perhaps other neurotransmitter systems (Sprague *et al* 1998). However, most if not all of the agents used in these studies have been shown to lower body temperature. Indeed, lowering body temperature by any means has a protective effect on MDMA-induced neurotoxicity (Colado *et al* 1999).

Health consequences

5.1 Review approach

The capacity for analysis of the health consequences of MDMA is limited by the lack of epidemiological studies. The only current source of information is case reports. Analysis of case reports is problematic as firstly, there is no way to determine whether reported cases are representative of the population of MDMA users and, secondly, there is likely to be significant publication bias, with "novel" and severe cases being preferred for publication. Furthermore, there tends to be variability in the nature of data collected and reported, and outcomes assessed for each case report, often reflecting whatever theme is being debated through scientific and medical literature at the time.

Another limitation is variability in information on drug use preceding the episode. Quantification of drugs in blood and urine samples is not always undertaken, and differing intervals between drug use and presentation for treatment influence the possibility and interpretation of testing. The extent and accuracy of reporting of drug use by the patient or observers, and on medical history prior to the adverse event, is also variable (and often limited in cases with fatal outcomes).

A further difficulty in attributing causality of the adverse event to "ecstasy" is variability in the purity of the ingested substance, together with the tendency for MDMA to be used in conjunction with other drugs (Green *et al* 1995; Handy *et al* 1998).

Despite these limitations, consideration of case reports of health consequences occurring subsequent to ecstasy use does provide an indication of the nature and severity of reactions to ecstasy, and outcomes of these reactions. By looking across all reported cases it is possible to go at least some way towards the identification of factors possibly contributing to the development of and outcomes from adverse health effects. Similarities between cases provide a degree of reliability in linking health consequences to ecstasy use, despite limited toxicological confirmation of drug use.

Case reports assessed for this review were located firstly by Medline search, looking for "ecstasy" or "MDMA" in title, subheadings or text. Medline was searched from 1995 to September 2000. Located

papers were considered for all sections of this monograph; only those papers reporting details of cases of health consequences (physical or psychiatric) were included in this section. To ensure reasonable retrieval of reports of cases of health consequences, reference lists of review articles and retrieved reports were handsearched.

5.2 Importance of setting

Although there was substantial use of MDMA in the 1970s, the first reports of deaths involving MDMA use did not appear until around 1987. A subsequent surge in reports of significant health consequences seems to be associated with a change in the setting in which the drug was most commonly used (Green *et al* 1995) – from the clinical psychotherapy setting of the 1970s, to the dance party and rave setting of the 1990s (Henry 1992).

Some MDMA-related complications, such as cardiac arrhythmias and cerebral infarctions, are related to the acute pharmacological properties of MDMA that are shared by a number of amphetamine-type stimulants. Other complications, such as severe hyperthermia with rhabdomyolysis, renal failure and disseminated intravascular coagulation, are more probably related to the use of MDMA in "raves" and dance parties, where individuals participate in extreme physical activity for prolonged periods in a hot, crowded setting (Henry 1992; McCann *et al* 1996). MDMA can produce hyperthermia in quiet surroundings, when taken in sufficient quantity (Green *et al* 1995) but in the setting of "raves" or dance parties, the toxicity appears to be enhanced. It is probably a combination of direct effects of MDMA and the high ambient temperature, sustained physical activity and inadequate fluid replacement, all reducing heat loss and potentiating the direct effect of MDMA on thermoregulatory mechanisms, that creates the greatest toxicity (Green *et al* 1995; Henry *et al* 1992).

5.3 Prevalence of adverse effects

In a survey of individuals attending clubs and "raves" in South Wales, 2.9% of respondents indicated a need for hospital treatment for reasons such as paranoia, overheating and fitting (Handy *et al* 1998). Most cases of acute reactions to ecstasy have mild symptoms – the general pattern on presentation is

that of agitation, tachycardia, hypertension, widely dilated pupils, trismus and sweating (Henry *et al* 1992).

On the basis of a survey of 158 drug users, Williamson *et al* concluded that amphetamine use was associated with significantly more adverse effects, and with more severe adverse effects, than ecstasy or cocaine (Williamson *et al* 1997). In response to questions, 17 (21%) individuals reported having had a bad experience whilst using ecstasy, and 16 (20%) reported having had a bad experience in the last year. The two most common adverse effects were "felt paranoid" (n=6, 7%) and "felt faint/about to collapse" (n=3, 4%). The majority of these bad experiences occurred in clubs (n=13, 77%). The frequency with which adverse effects were reported varied from 21% for panic attacks to 79% for loss of appetite. The majority of effects were considered mild by respondents.

Topp *et al* surveyed 329 people in three Australian cities who had used ecstasy at least three times in the previous six months. In this sample, 71 (22%) had received formal assistance from a health practitioner for an ecstasy-related problem, although in the majority of cases (58) other drugs were also involved. Nine had received first aid at a venue, and eight had presented to a hospital accident and emergency department. Seven per cent were receiving treatment for an ecstasy-related problem at the time of survey (Topp *et al* 1999).

Williams *et al* retrospectively reviewed 48 consecutive MDMA-related cases (47 different patients, 32 males, 15 females) attending the accident and emergency department of a large London hospital between 1 January 1995 and 31 March 1996 (Williams *et al* 1998b). All cases were in the 15 to 30 year age group, with the majority presenting in the early hours at weekends after consuming the drug at a nightclub. The mean number of tablets consumed was two, and almost 40% had prior experience of MDMA. Polydrug use was common with half of the sample having concurrently taken another illicit substance – most commonly other stimulants (amphetamine, cocaine). The most common symptoms were: feeling strange, unwell, dizzy or weak (31.3%); collapse or loss of consciousness (22.9%); nausea/vomiting (22.9%); and palpitations (20.8%). The most common signs elicited were increased pulse rate (66.6%); dilated pupils (37.5%); tachypnoea (20.8%); and raised body temperature (18.5%). Anxiety, agitation, or disturbed behaviour were also commonly found (20.8%). In six instances the

adverse effects were severe – they included delirium (2 cases); seizures (3 cases); and profound unconsciousness (1 case). Complaints of collapse or loss of consciousness were less frequent amongst those who had only taken MDMA. Hyperventilation and increased temperature were more common, and increased blood pressure less common, in those using MDMA only (Williams *et al* 1998b).

This study, combined with data on the frequency of ecstasy use (see section 2) indicates that the prevalence of serious adverse effects arising from ecstasy use is low. Data from the Drug Abuse Warning Network (DAWN) in the USA also indicate that, relative to other drugs, the incidence of ecstasy-related emergency room cases is low (Anonymous 2000). However, as will be discussed in section 5.4, it is the unpredictability of serious adverse effects, the risk of mortality or substantial morbidity, and the young age of those affected (Anonymous 2000), that makes the health consequences of ecstasy use significant.

5.4 Cases of health effects attributed to ecstasy

It should be noted that this analysis of case reports has a high risk of bias arising from preferential reporting of cases with serious or fatal outcomes. The risk of bias is considered likely to be increasing with time. When adverse effects of ecstasy were first detected all cases were considered of interest and worth publishing. With time, and familiarity with the adverse effects, publications are increasingly focusing on selected cases. Some publications, eg. (Lora-Tamayo *et al* 1997) only look at cases with fatal outcomes with the result that estimated mortality rates discussed below are likely to be artificially high. However, in the absence of appropriate epidemiological studies this information remains the best available.

5.4.1 Acute adverse effects

Cases of acute adverse effects subsequent to use of ecstasy were divided into two categories based on whether or not hyperthermia was involved. We identified 69 separate cases of acute reactions to ecstasy involving hyperthermia, summarised in Appendix 1. (Cases were included in this category on the basis of a recorded body temperature above 38°C or a specific statement that the case involved hyperthermia or pyrexia.)

A further 89 cases were identified of adverse effects subsequent to ecstasy use that did not involve hyper-

thermia, or where hyperthermia was not reported. These cases are summarised in Appendix 2. The nature of adverse effects for these cases was more diverse than for the cases involving hyperthermia. This is reflected by the grouping of the cases into a number of subcategories.

These cases of acute adverse effects are considered further below, based on the nature of the adverse effect reported. Section 5.4.1.12 then considers the effect of the dose of drug taken, looking across all instances of acute adverse effects for which toxicology data was reported.

5.4.1.1 Hyperthermia

Of the 69 cases, 17 were female, 52 male; 66 were aged between 16 and 36, with two cases involving accidental ingestion by young children (Cooper & Egleston 1997), and one involving a 53 year-old male (Bedford Russell *et al* 1992; Walubo & Seger 1999). Three cases of hyperthermia were subsequent to intentional overdoses. The overall outcome of the episode was not reported in two cases; of the remaining 67 cases, 32 (48%) resulted in death.

As demonstrated by these cases, hyperthermia is typically accompanied by a number of clinical problems, many probably induced by the hyperthermia (Green *et al* 1995). Of the 69 cases, seizures or convulsions were reported in 39 cases, disseminated intravascular coagulation or some form of coagulopathy in 33, rhabdomyolysis in 27, renal impairment in 16 and liver impairment was reported in 10 cases. (These secondary features may have occurred, but not been detected or reported for other cases.)

Multiple factors can induce convulsions, including brain hypoxia and metabolic disturbances, in particular gross hyponatraemia. Metabolic disturbances include profound metabolic acidosis, hyperkalaemia (which may lead to cardiac arrhythmias), hyperphosphataemia and hyponatraemia.

Disseminated intravascular coagulation results in the depletion of clotting factors and a consequent tendency to abnormal bleeding. This could be manifest as gastrointestinal bleeding, cerebral haemorrhage and bleeding from other parts of the body. Rhabdomyolysis occurs when skeletal muscle breaks down and releases myoglobin. Myoglobin is eliminated in the kidneys. The greater the degree of rhabdomyolysis, the greater the amount of myoglobin released, and the greater the likelihood of renal tubular necrosis leading to kidney failure. Dehydration and reduced blood flow to the kidney are likely to also be contributing factors.

Hypertension has also been described in a high proportion of cases. The likely cause of this is the direct sympathomimetic effect of MDMA.

All of the clinical signs and symptoms are consistent with a malfunction of normal temperature control and water balance, also seen in animal studies (see section 3.2). The specific trigger for the adverse effects is not clear at present but is probably the result of a drug-related, inappropriate physiological response to environmental stress and vigorous exercise. Increased brain extracellular 5-HT is likely to underlie the uncontrolled rise in body temperature, probably through disruption of normal physiologic control of temperature in the preoptic anterior hypothalamus.

The manifestations of hyperthermia associated with an acute toxic reaction to MDMA are those which are seen in heat stroke (O'Connor 1994) – tachycardia, sweating, dehydration, and secondary pathological events (rhabdomyolysis, disseminated intravascular coagulation, acute renal failure, metabolic disturbances) which, in their own right, are associated with an adverse outcome.

It has been suggested that the degree of hyperthermia is predictive of mortality. To investigate this we examined the mortality rate according to the report-

Table 1: Mortality rate and maximum recorded body temperature

| MAXIMUM BODY TEMPERATURE (°C) | NUMBER OF CASES WITH FATAL OUTCOME/TOTAL CASES | MORTALITY RATE |
|-------------------------------|--|----------------|
| ≤ 39.5 | 2/10 | 20% |
| 39.6 - 40.5 | 3/15 | 20% |
| 40.6 - 41.5 | 5/11 | 45% |
| 41.6 – 42.5 | 10/16 | 63% |
| >42.5 | 7/9 | 78% |

ed maximum body temperature (cases found dead were excluded from this analysis):

This data is potentially confounded by bias and the small numbers, but is clearly suggestive of a correlation between body temperature and the risk of mortality. In one fatal case with a temperature of 39.5°C or less, the contribution of ecstasy to the death is uncertain – the subject had taken ecstasy, heroin and amphetamine at a rave, followed by large amounts of alcohol the following day (Squier *et al* 1995).

Overall, the data in Table 1 supports the emphasis placed by others on rapid reduction of temperature as the most important response to hyperthermia related to MDMA use (see section 7.2). It also indicates the importance of educating users on strategies to avoid hyperthermia, and to seek medical assistance promptly if signs of hyperthermia become apparent.

5.4.1.2 Disturbed salt and water balance

We identified 14 cases with features of confusion, reduced consciousness and, in some cases, seizures or convulsions subsequent to ecstasy use and apparently induced by disturbances in salt or water balance. In most cases symptoms resolved as sodium levels were normalised. This is indicated by the recovery of most cases within a few days. However, three of the 14 cases were fatal, apparently due to cerebral oedema associated with excess fluid intake. As with hyperthermia, this indicates the importance of seeking medical assistance as soon as signs of adverse effects become apparent.

In five of the 14 cases it was reported that copious water had been consumed together with ecstasy. In one case it was reported that consumption of a large amount of water was a deliberate attempt to manage unpleasant alterations of perception caused by the ecstasy (Holden & Jackson 1996). In another case water consumption was estimated at 14 litres in response to thirst induced by MDMA (Milroy *et al* 1996). This supports the suggestion that MDMA may result in sensation of thirst even when there is not a water deficit. Alternatively, behavioural disturbance, including stereotyped repetitive actions, may arise from MDMA ingestion (White *et al* 1997). Such an action could include repetitive consumption of water.

The administration of MDMA is associated with inappropriate release of anti-diuretic hormone, arginine vasopressin (Gomez-Balaguer *et al* 2000; Henry *et al* 1998). The antidiuretic effect of vasopressin, and/or kidney failure associated with hyperthermia, would both reduce urine formation, thereby reducing the

body's capacity to excrete fluid consumed and worsening the effects of excessive fluid consumption. Indeed, the first reports of water intoxication and hyponatraemia occurred after dance club owners encouraged users to take dance breaks in a cool room and drink water (Hegadoren *et al* 1999). This advice is still sound for prevention of hyperthermia, but clearly the amount of water consumed needs to be kept within levels able to be handled by the body.

5.4.1.3 Central nervous system effects (seizures)

In 10 cases information indicates the occurrence of some type of fit or seizure, apparently without hyperthermia or hyponatraemia, suggesting a direct effect on the central nervous system. In five of the 10 cases the drug involved was confirmed as PMA while another case involved amphetamine and MDD. The presence of MDMA was confirmed for only one of the 10 cases – that case involved an apparent interaction between MDMA and ritonavir (Henry & Hill 1998).

This group of cases suggests that PMA may have a more potent central nervous system effect, while MDMA appears to have minimal direct central nervous system effects, except where effects are enhanced by interactions with other drugs.

5.4.1.4 Cardiac factors

In some instances cardiac irregularities can be attributed to metabolic disturbances such as hyponatraemia [eg. see (Maxwell *et al* 1993)]. However, there are six cases in which aspects of cardiac function appear to have been the primary factor in the adverse event. All six were fatal. In three cases there appears to be pre-existing cardiac disease – Wolff-Parkinson-White syndrome (Suarez & Riemersma 1988); ischaemic heart disease (Lora-Tamayo *et al* 1997); and an aortic valve abnormality (Bingham *et al* 1998). This suggests that people with existing cardiovascular conditions may have limited capacity to respond to the stimulatory effects of MDMA.

In a case control study, Brody *et al* found that the Valsalva ratio (an index of overall autonomic responsiveness) was significantly smaller in MDMA users than in controls (Brody *et al* 1998). They found eight of 12 users, but none of 12 controls, had defective or marginal Valsalva ratios. Brody *et al* suggest that the finding indicates that parasympathetic cardiovascular tone appears impaired in repeat MDMA users (mean frequency of slightly less than once weekly over the

preceding six months). In their words, the “results are intriguing, and potentially of clinical importance”, but exactly what this finding means is uncertain.

In a study of postmortem pathology of seven ecstasy-related deaths, Milroy *et al* found changes in five of the seven hearts, with the changes reported to be similar to those described in catecholamine-induced myocardial injury (Milroy *et al* 1996).

5.4.1.5 Probable haemorrhages or cerebrovascular accidents

The small number of cases (12) and diversity of clinical features limits the conclusions that can be drawn from this group of acute reactions. However, the cases suggest that sudden inappropriate changes in blood pressure or blood flow associated with ecstasy use can result in cerebral ischaemia (Hanyu *et al* 1995) or blood vessel ruptures, particularly where there are existing weaknesses, such as aneurysms or angioma (Gledhill *et al* 1993; Hughes *et al* 1993). Physical exertion may be a factor, but haemorrhage can also occur in the absence of exercise [eg. (Gledhill *et al* 1993; Jacks & Hykin 1998)]. Intracerebral haemorrhages are also a consequence of abuse of amphetamine and (particularly) cocaine (Harries & de Silva 1992; McEvoy *et al* 1998). This makes it likely that it is the stimulatory effect of MDMA, rather than any unique pharmacological action, that may underlie any association between MDMA use and cerebral haemorrhages. In some cases the drug taken may have been amphetamine rather than MDMA [eg. (Hughes *et al* 1993)].

5.4.1.6 Respiratory factors

In three cases with fatal outcome, respiratory factors appear to have been central to death. In one case the subject had a history of asthma (Dowling *et al* 1987). In the second case death was attributed to inhalation of gastric contents whilst intoxicated (Forrest *et al* 1994), while upper airway obstruction arising from muscle spasms was postulated to have occurred in the third case (Weinmann & Bohnert 1998). These cases indicate that while respiratory difficulties can arise from ecstasy use, MDMA and related amphetamine derivatives do not have a direct effect on respiratory function.

5.4.1.7 Trauma whilst intoxicated

In seven cases use of MDMA or a related amphetamine derivative may have been a factor in behaviour

leading to trauma. Six cases had fatal outcomes: three involved a traffic accident (Dowling 1990; Lora-Tamayo *et al* 1997), two involved falls (Dowling *et al* 1987), (Carter *et al* 2000) while in one case a car was found running in the garage resulting in exhaust fumes in the house (Dowling 1990). In the one non-fatal case in this group the subject received serious burns when a petrol can ignited in the car in which he was travelling (Cadier & Clarke 1993).

In a recently published letter, Davies *et al* report having treated, over a three month period, 16 ecstasy users who had been injured as a result of traffic accidents, all caused by reckless driving. None of the injuries were fatal but ecstasy use was reported to have complicated assessment and treatment (Davies *et al* 1998).

5.4.1.8 Chest pain not related to cardiac factors

Six cases of chest pain due to air in tissues in and around the thoracic cavity were identified and are probably attributable to exercise under the influence of ecstasy, and not the drug itself. In one case intra-alveolar pressure resulting from prolonged, continuous blowing of a whistle whilst dancing was considered to have caused the escape of air into the mediastinum (Pittman & Pounsford 1997). The six cases identified all resolved without intervention, other than analgesia to manage the pain. Several cases of severe chest pain attributed to probable spasm of intercostal muscles as a result of prolonged dancing under the influence of ecstasy have also been reported (Rittoo & Rittoo 1992).

A seventh case is included in this group, on the basis of the patient having attended a doctor for pleuritic chest pain. The patient died following a motor vehicle accident (Dowling *et al* 1987), with the cause of death unclear.

5.4.1.9 Ophthalmic conditions

O'Neill and Dart report three cases of ophthalmic complications that occurred subsequent to ecstasy ingestion. They reported that the distribution of corneal epithelial changes was similar to those seen in conditions that interfere with normal blinking, lid closure and eye position resulting in abnormal exposure of the cornea to the air. They therefore suggested corneal exposure arising from lack of sleep, rather than direct toxic effects of ecstasy, as the likely cause (O'Neill & Dart 1993).

The fourth case of ophthalmic complications involved double vision, attributed to bilateral sixth nerve palsy (Schroeder & Brieden 2000). The link to MDMA use was on the basis of self-report, and the absence of other risk factors.

5.4.1.10 Aplastic anaemia

Three cases of aplastic anaemia subsequent to ecstasy use were identified. The aetiological mechanism by which MDMA might underlie the development of aplastic anaemia is unclear. Marsh *et al* note that in approximately 30% of cases of aplastic anaemia an identifiable factor or agent, such as a drug or virus, may be implicated (Marsh *et al* 1994). Apart from ecstasy use, no other factor could be identified in the three cases reported. In one case a (successful) transplant was undertaken while the other two cases resolved spontaneously.

5.4.1.11 Miscellaneous cases

The miscellaneous category includes 20 cases of adverse effects subsequent to use of ecstasy (MDMA, MDEA, MDA, MBDB or PMA). In some cases there was insufficient detail to definitely include the case in one of the previous categories. Nine cases involved other drugs in addition to ecstasy complicating the clinical picture. These cases do not add significant additional information to this review of acute physical effects of ecstasy.

Another physical consequence of ecstasy use, not included in Appendix 2, is that of toothwear. This reflects the common experience of bruxism (tooth grinding) and trismus (jaw clenching) associated with ecstasy use. The magnitude of effect has been documented by Milosevic *et al* (Milosevic *et al* 1999) who compared incisal and occlusal toothwear in a group of 30 people reporting ecstasy use in the previous six months with a group of 28 people who used other drugs but not ecstasy. Toothwear through the enamel into the underlying dentine occurred in 18 (60%) users but in only three (11%) non-users. The overall mean toothwear score in ecstasy users was 0.63 compared with 0.16 in non-users ($P < 0.001$). Milosevic *et al* noted that the occlusal surfaces were more commonly affected than the incisal, indicating jaw clenching rather than tooth grinding was probably the more significant feature.

Ecstasy use predominantly occurs amongst young people, which raises, as a potential issue, the effects of prenatal exposure. There has been one prospective study which looked at the outcome of 136 pregnan-

cies in mothers who reported using ecstasy during pregnancy (McElhatton *et al* 1999). The rate of miscarriage and the birthweights for term infants were within the range expected, but a higher than average number of congenital birth defects were found in the 78 babies who were born. However, the study looked only at 136 pregnancies, out of an original 302 enquiries involving ecstasy – 31 pregnancies were not completed at the time of publication and 135 were lost to follow-up. This high rate of loss to follow-up may have biased the study towards those who experienced some sort of problem with the birth. A further factor is the effect of other drugs taken in conjunction with ecstasy – of the 136 pregnant women, 74 reported taking ecstasy only. Other drugs used by the remaining 62 women included amphetamine, cocaine, cannabis, alcohol and LSD. McElhatton *et al* themselves note that this case series has insufficient statistical power to confirm a causal relation, but it does indicate an aspect of ecstasy use that should continue to be monitored.

5.4.1.12 Effect of MDMA dose

For 108 of the 158 cases of acute adverse effects drug use was confirmed by analysis of blood and/or urine samples. The drugs detected are indicated in Table 2.

These data should be interpreted with caution because of the small numbers involved and the high risk of bias. Risk of bias is particularly high for the less common amphetamine derivatives (MDEA, PMA, MBDB). The extensive forensic procedures that occur in investigations of sudden deaths means that these drugs are more likely to be detected in cases with fatal outcomes. Hence the mortality rates associated with these drugs in Table 2 are likely to be artificially high.

It is possible to conclude from these data that, although a number of cases of acute adverse effects involved other drugs instead of or in addition to MDMA, MDMA alone can produce adverse effects. Of the 35 cases in which only MDMA was detected, 21 involved hyperthermia and 10 of these (48%) were fatal. A further eight cases involved disturbances of sodium or fluid balance, with three (38%) fatal. The remaining six cases involved cardiac factors (1 fatal), a cerebral haemorrhage (1 non-fatal), respiratory factors (1 fatal), a sudden collapse (fatal), and trauma whilst intoxicated (2 fatal). Given that hyperthermia and disturbances of sodium or fluid balance generally occur when MDMA is used in nightclub or dance party settings, these data suggest that the

Table 2: Drugs detected by analysis of urine and/or blood

| DRUGS | TOTAL CASES | CASES WITH FATAL OUTCOME |
|---------------------------------|-------------|--------------------------|
| MDMA only | 35 | 18 (51%) |
| MDMA + MDA, +/- other drugs | 11 | 6 (55%) |
| MDMA + alcohol, +/- other drugs | 7 | 5 (71%) |
| MDMA + amphetamine | 4 | 2 (50%) |
| MDMA + MDEA, +/- other drugs | 5 | 5 (100%) |
| MDA only | 9 | 4 (44%) |
| MDA + other drugs | 3 | 2 (67%) |
| MDEA only | 5 | 5 (100%) |
| MDEA + other drugs | 7 | 5 (71%) |
| PMA only | 11 | 11 (100%) |
| PMA + MDMA, +/- other drugs | 2 | 2 (100%) |
| PMA + other drugs | 4 | 4 (100%) |
| Amphetamines only | 3 | 0 (0%) |
| Amphetamine + MDBD | 1 | 1 (100%) |
| MDBD + alcohol | 1 | 1 (100%) |

acute adverse effects of MDMA arise from the way it is used, rather than solely an inherent toxic effect of the drug.

This may not be the case with PMA (para methoxyamphetamine). There are two major clusters of deaths associated with PMA: nine cases in Ontario, Canada in 1973 (Cimbura 1974), and six cases in South Australia between 1995 and 1998 (Byard *et al* 1998; Byard *et al* 1999). Media reports (New York Times 30 September 2000, USA Today, 6 October 2000) indicate that a further cluster of PMA-related deaths occurred in Florida, USA and Ontario, Canada in the first half of 2000. Of the 16 published case reports involving PMA, seven involved hyperthermia, five involved seizures, one a cerebral haemorrhage, and three were classed as miscellaneous, largely because of insufficient information. It is notable that in one of the cases reported by Byard *et al*, "ecstasy" use occurred in a home setting over a 12 hour period and a maximum body temperature of 46.1°C was recorded on admission to hospital. This case, together with several others involving ingestion of PMA in home settings, suggests that the adverse effects of PMA may be related more to the action of the drug rather than the way it is used. The higher incidence of seizures associated with PMA is sugges-

tive of a more powerful central nervous system effect.

For 21 of the cases of acute adverse effects where only MDMA was detected, quantitative data from blood toxicology was reported. These data are confounded to some extent in that the time elapsed between drug use and testing is variable but nonetheless these data are useful as an indicator of toxicity. For cases with a fatal outcome serum levels of MDMA ranged from 0.04mg/l to 6.5mg/l. (The lowest levels were in cases of hyponatraemia where testing occurred around 12 hours after drug use.) For those cases with a non-fatal outcome serum levels of MDMA ranged from 0.24mg/l to 7.0mg/l. The similarity of these two ranges supports the conclusion expressed by other commentators, namely that the dose of MDMA is not predictive of the severity of outcome (Hall 1997a; Hegadoren *et al* 1999).

For the nine Canadian PMA-related deaths concentrations of PMA in blood samples ranged from three to 19mg/l and PMA was the only "chemical toxin" found in significant amounts (Cimbura 1974). In six of the seven South Australian PMA-related deaths, other drugs were detected in addition to PMA: amphetamines and methamphetamine (2 cases),

MDMA (2 cases), methamphetamine (1 case) and fluoxetine (1 case). In the six cases involving multiple drugs, serum concentrations of PMA ranged from 0.24 to 3.7mg/l. In the one case where only PMA was detected, the serum level was 4.9mg/l (Byard *et al* 1998; Byard *et al* 1999). In the Spanish PMA-related death, blood concentration of PMA was 5.7mg/l (Lora-Tamayo *et al* 1997). These data are difficult to interpret in the absence of any data from cases with non-fatal outcomes. This makes it impossible to determine whether the apparently high mortality rate associated with PMA reflects the administration of high doses, or whether PMA is inherently more toxic than MDMA.

The lack of correlation between MDMA dose and mortality rate has caused commentators to look for alternative explanations for the occurrence of adverse effects. Suggestions include some form of metabolic myopathy, as has been suggested in the context of those individuals prone to heat stroke (Hall 1997a) and malignant hyperthermia (Denborough & Hopkinson 1997; O'Connor 1994), or individual variability in metabolism of MDMA (see section 3.5.2). However, as yet instances of muscle abnormality or impaired MDMA metabolism have not been identified in any cases of severe reactions (Tehan *et al* 1993) and there appears to be a mix of first time and experienced MDMA users affected, making this explanation unlikely, or at least uncommon.

It has also been suggested that severe reactions might be due to the presence of contaminants in the preparation taken. As indicated by the data in Table 2, it is true that acute adverse reactions are not always due to MDMA alone, but the majority of cases we identified primarily involved MDMA. Furthermore, there are reports of the affected person taking from the same supply as others, who did not experience severe reactions. This suggests that contaminants are also an unlikely explanation (Hall 1997a). It seems most likely that it is the combination of dose, setting and individual behaviour that determines the outcome. Whether this is also true for PMA and other amphetamine derivatives remains unclear.

5.4.2 Liver damage not involving hyperthermia

Severe liver injury can occur shortly after ingestion of ecstasy, in conjunction with acute profound systemic effects. Of the 69 cases of hyperthermia, nine showed signs of hepatitis (jaundice, elevated liver enzymes) and two progressed to liver failure. These

cases of liver damage are probably part of the complex multiple organ system failure that can ensue from hyperthermia.

The 39 cases summarised by Appendix 3 constitute a second pattern of hepatotoxicity, apparently unrelated to hyperthermia (Selim & Kaplowitz 1999). These cases occurred after incidental or regular ingestion of ecstasy with variable latency of days to weeks.

The extent of ecstasy-related liver injury ranges from benign forms mimicking acute viral hepatitis, to severe forms such as liver failure due to massive hepatic necrosis (Andreu *et al* 1998; Ellis *et al* 1996; Fidler *et al* 1996; Jones & Simpson 1999; Milroy *et al* 1996). This is reflected in Appendix 3 with 11 of the 39 cases receiving some form of liver transplant, and one further case being listed for transplant. Six of the 39 cases were fatal, with four of these deaths occurring subsequent to liver transplant or while waiting for a donor organ (1 case). Most of the cases, while severe enough to cause the patient to seek medical advice, did not appear to require specific treatment. For 13 of the 26 cases not requiring liver transplant, treatment responses were not discussed; for eight cases the main response was monitoring with some (conservative) symptomatic management; in four cases prednisolone was administered. Given this pattern, it seems likely, as noted by others, that many cases of ecstasy-related liver damage will be subclinical, and hence escape detection (Jones & Simpson 1999). Indeed, Milroy, in a study of the postmortem findings of seven ecstasy-related deaths, found liver necrosis to be present in all cases, although liver failure was a cause of death in only one case. Liver changes varied from foci of individual cell necrosis to centrilobar necrosis, and massive hepatic necrosis in the case of liver failure (Milroy *et al* 1996).

While the majority of cases of liver damage resolved over a period of weeks to months, recurrence can occur with a resumption of ecstasy use (Andreu *et al* 1998; Fidler *et al* 1996; Khakoo *et al* 1995). Patients who have ecstasy-induced hepatitis should be warned of the risk of recurrence, and the potentially life-threatening nature of liver damage, as well as the risk of developing chronic hepatitis if they resume use of ecstasy (Andreu *et al* 1998; Fidler *et al* 1996).

5.4.2.1 Relative contribution of ecstasy to liver injury

Andreu *et al* reviewed the clinical histories of 62 patients with acute liver failure admitted to an intensive care liver unit in Spain between January 1994

and December 1996 (Andreu *et al* 1998). Five cases (8%) were attributed to ecstasy use. This represented 31% of cases with drug hepatotoxicity. Ecstasy was the second most common cause of liver injury in patients under the age of 25 (20% in this subset).

Jones and Simpson comment that of 342 patients admitted to the King's liver unit in London between 1993 and 1994, only two were due to ecstasy – the majority were due to paracetamol. Similarly, the Scottish Liver Transplant Unit, in six years of operation, treated 350 cases as inpatients, with two of these having acute liver failure due to ecstasy (Jones & Simpson 1999).

5.4.2.2 Mechanism

It has been suggested that liver necrosis subsequent to MDMA might be either a direct action of the drug or metabolites, or could result from ischaemia in the later stages of a severe acute reaction. However, as indicated by the cases in Appendix 3, hepatotoxicity can occur in the absence of a history of hyperthermia (Dykhuizen *et al* 1995; Fidler *et al* 1996). Hypersensitivity to MDMA due to impaired metabolism of MDMA has also been proposed as a mechanism but is not as yet supported by evidence (see section 3.5.2). Contaminants in MDMA are also considered to provide a less than satisfactory explanation, although this remains a possibility (O'Connor 1994).

Andreu *et al* suggest a toxic mechanism of liver damage is most likely because evidence of liver disease begins several days after drug consumption. They note the variability of the delay between last drug exposure and onset of hepatic injury as well as duration of MDMA use and the cumulative amount of drug consumed. They also report that the severity of lesion was not related to the length of exposure or the amount of drug consumed (Andreu *et al* 1998).

General opinion favours an idiosyncratic type of reaction as the explanation (Ellis *et al* 1996; Schwab *et al* 1999). Jones and Simpson note that there appears to be multiple clinical and histological changes with MDMA-induced liver damage, suggesting multiple mechanisms of action (Jones & Simpson 1999).

5.4.3 Psychiatric sequelae

Depression, or low mood, is reported by users as relatively common in the week following ecstasy use (see section 3.3.2). The occurrence of depression subsequent to ecstasy use was documented by

Curran and Travill who compared 12 MDMA users with 12 people who reported having consumed only alcohol. All participants were assessed on the day of consumption (at a club) then re-assessed the following day (day one) and again mid-week (day five).

They found that MDMA users rated elevated mood on day one but significantly low mood on day five, at which point some participants scored within the range for clinical depression. In contrast, the alcohol group showed less pronounced changes, with the lowest point being day two (Curran & Travill 1997). A survey of 469 ecstasy users in the UK also found that 83% said they experienced mid-week 'low mood' and 80% experienced concentration and/or memory problems [cited by (Curran 2000)].

Schifano *et al* used a semi-structured interview to assess 150 consecutive patients, presenting to the Padova (Italy) Addiction Treatment Unit, who had taken ecstasy on at least one occasion (Schifano *et al* 1998). Ninety-five per cent of the sample had experimented with another drug of abuse at least once in their lifetime. Fifty-three per cent were found to be affected by one or more psychopathological problems: the most frequent were depression, psychotic disorders, cognitive disturbances, bulimic episodes, impulse control disorders, panic disorders, and social phobia. Those who were free from any psychopathological problems, compared to the others, had taken a smaller number of MDMA tablets in their lifetime, for a shorter duration, and with a lower frequency. They were less likely to have used alcohol together with ecstasy, but more likely to have used opiates. Longer-term, larger dosage (acute or cumulative) MDMA consumers were found to be at high risk of developing psychopathological disturbances (Schifano *et al* 1998).

Amongst ecstasy users in an Italian survey of 360 young people, 93.6% reported the onset of psychological problems since they began to use MDMA, eg. cognitive disturbances (45.3%), depression (40.7%), craving for carbohydrates and/or chocolate (27.3%) and flashbacks (18%). Another study of 479 people attending discos in the Florence (Italy) area found that 47.2% of MDMA users reported the onset of some psychopathological problems after beginning to use ecstasy, eg. cognitive disturbances (51.2%), depression (28.6%), a craving for carbohydrates and/or chocolate (14.3%), and panic attacks (13.1%). Those who reported these disturbances were more likely to have been using ecstasy for longer, with a higher frequency, and in association with other psychoactive drugs, than those who reported no such symptoms (Schifano 2000).

Our search of published literature resulted in the identification of 44 separate cases of psychiatric sequelae attributed to ecstasy use (Appendix 4). These cases are presented in three groups: altered mental state associated with intoxication (nine cases); suicide (four cases); and persistent or chronic sequelae (31 cases).

One of the nine cases of altered mental state associated with intoxication had a fatal outcome, but in eight cases symptoms appear to have resolved in hours to days. Diazepam was administered in four cases. In three cases concurrent drug use, or the presence of contaminants, appear to be likely factors in the acute psychiatric reactions. These three cases were friends who used together. All experienced a similar pattern of psychiatric symptoms, with a prevalence of persecutory delusions and experiences of bodily changes, which remitted within six days. Urine testing was undertaken for one of the three cases, with MDMA and cocaine being detected. This finding does not exclude the presence of other hallucinogenic amphetamines, or LSD, in the drugs consumed. The concurrent use of cocaine may also have been a factor (Alciati *et al* 1999). In another case the woman affected had used ecstasy in the company of a friend, who was unaffected. The woman affected was concurrently using phenylpropanolamine (Whitaker-Azmitia & Aronson 1989), a non-prescription appetite suppressant, suggesting the possibility of drug interactions as a factor. Two further cases occurred in a man and a woman who used ecstasy together. Treatment was not sought; consequently there was no confirmation of the actual drug ingested. However, both subjects reported the use of ecstasy subsequently without recurrence of symptoms (Whitaker-Azmitia & Aronson 1989). This is suggestive of a contaminant as a factor in these episodes of acute alterations in mental state.

The 31 cases of post-acute sequelae generally comprise persistent episodes of depression, panic disorders, "flashbacks" and delusions. A delay of days to weeks between last ecstasy use and presentation for assessment means that toxicological confirmation of drug use was not possible for any of the cases. On the basis of the drug use history reported, 11 cases appear to have developed subsequent to only a short period of ecstasy use [ranging from a single episode of use (Cohen & Cocores 1997) to four episodes two to three weeks apart (Benazzi & Mazzoli 1991)]. However, 19 cases were related to more prolonged, regular use, eg. several tablets at weekends for six months or more. In 12 cases a history of cannabis use was also reported, and in eight cases a family or

personal history of psychiatric disorders was reported. This suggests that the risk of psychiatric sequelae is greater when other drugs, particularly cannabis, are used in addition to ecstasy, when ecstasy is used repeatedly and at high doses over a period of months, and when there is a family or personal history of psychiatric disorders.

Pallanti and Mazzi discuss three cases of panic disorder apparently triggered by ecstasy, where friends who ingested MDMA at the same time were unaffected. They suggested that the onset of panic disorder was due to a subjective vulnerability of the patients. A temporary stress-related state was suggested as a potential source of susceptibility (Pallanti & Mazzi 1992).

Cohen notes the finding of a correlation between suicide and low levels of cerebrospinal fluid 5-HIAA, the primary metabolite of serotonin. The concentration of 5-HIAA in cerebrospinal fluid has been found to be reduced in those individuals who have had prior exposure to MDMA, although interpretation of this finding is, in some instances, hampered by study design (Grob & Poland 1997). It is not possible to conclude that MDMA is responsible for inducing depression and suicide, but the mooted effect on 5-HIAA levels suggests a possible association (Cohen 1996).

In a study of 89 people in London who had used MDMA, 46 had used the drug more than 20 times, 23 more than 40 times, and five more than 100 times. Roughly a third of the sample reported using the drug at least once a week, with a minority reporting "binge" use, when 10 to 20 tablets might be consumed over a weekend. These patterns of use had been sustained from six months to three years. Polydrug use was common. Nearly 40% reported feelings of "paranoia" and many reported irritability and depression after use. There were also two well described cases of panic attacks occurring on several occasions after prolonged use (Winstock 1991).

Overall, these reports indicate a clear association between ecstasy use and subsequent short-term mood changes. More severe psychiatric sequelae, including depression, panic disorders, psychoses and anxiety, may occur but probably only in those individuals made vulnerable by personal or family history of psychiatric disturbance, by stress or by concurrent use of other drugs.

Prevention

Prevention has traditionally have been classified into three types; primary prevention, which aims to prevent or delay uptake of drug use; secondary prevention, which aims to intervene early in use and prevent associated harm; and tertiary prevention which includes treatment, rehabilitation and relapse prevention. Primary prevention can be further classified as universal, selective or indicated. Universal programmes are those which are delivered to large groups without any screening of risk and protective factors (eg school drug education and mass media campaigns); selective programmes target specific subgroups at higher risk; while indicated programmes target specifically recruited individuals who exhibit early signs of substance use or other specific risk factors (National Institute on Drug Abuse 1997).

6.1 Primary prevention

Primary prevention is directed at stopping, reducing or delaying the initiation of drug use. Programmes should be based on a thorough understanding of the risk and protective factors which influence drug use. These include psychological, behavioural, family and social characteristics (Hawkins *et al* 1995; National Institute on Drug Abuse 2001; Spooner 1999). Prevention programmes may target individuals, peer groups, schools, families or communities. Their effectiveness increases when more than one group is targeted in a comprehensive program (National Institute on Drug Abuse 1997). With the exception of tobacco, prevention literature does not usually focus on individual drugs. There is very little specific literature on ecstasy prevention and that which does exist is focussed on harm reduction. This section will review the principles of prevention, which are applicable to all drugs.

The two most common approaches for the delivery of primary prevention interventions are school-based education and media information campaigns. The effectiveness of these strategies on their own is limited, however, there is consistent evidence regarding the principles of effective programmes (Hawkins *et al* 1995; Midford 2000; Miller & Ware 1989; National Institute on Drug Abuse 1997; National Institute on Drug Abuse 2001; Sherman *et al* 1998).

6.1.1 School drug education

A recent review of school drug education found that many models of drug education are generally unsuccessful at reducing drug use. These include temperance or prohibitionist programmes, information on harmful effects only, fear campaigns and personal development programmes. However, well-conceptualised and implemented evidence based drug education programmes can have some effect in preventing or delaying the onset of drug use. While the effect size is small, the review concluded that there would be significant cost benefit to society from comprehensive, effective drug education programmes (Midford 2000).

Sherman *et al* conducted a major review of effective and ineffective programs for preventing crime, including substance abuse, and identified effective, ineffective, and promising programmes (Sherman *et al* 1998). School drug education programmes found to be effective in reducing substance use included:

- Social competency skills training curricula which teach over a long period of time and include skills such as stress management, problem solving, self-control, and emotional intelligence.
- Clarifying and communicating acceptable norms of behaviour through the use of consistent rules, reinforcement of positive behaviour, and school wide initiatives.
- Training or coaching in thinking skills for high-risk young people using behaviour modification techniques.

The majority of research into prevention has been undertaken in the USA under the auspices of the National Institute of Drug Abuse, which has produced an evidence-based guide to prevention approaches (National Institute on Drug Abuse 2001). This guide identifies a number of principles to increase the effectiveness of school based drug education, suggesting that school based programmes should:

- be culturally and developmentally appropriate,
- promote positive peer influence,
- promote anti drug use social norms,

- foster bonding to the school and the community,
- teach drug resistance skills through interactive teaching and learning methods,
- use a well tested standardised intervention with detailed lesson plans and student materials,
- be ongoing, with sequence, progression and continuity over time,
- target children at all stages of their school life.

The involvement of the target group in the development, implementation and evaluation of programmes has been shown to increase the effectiveness of drug education. This may serve to increase the credibility of the messages, and to ensure that the programme is responsive to the needs and cultural traditions of the target group. Peer-led classes may be more effective than teacher-led classes in some instances (National Institute on Drug Abuse 1997).

6.1.2 Mass media campaigns

The major role for mass media campaigns is in raising awareness, agenda setting and reinforcing anti drug use social norms. They are generally ineffective at bringing about individual behaviour change. Studies of media campaigns have shown that they have greatest impact on increasing knowledge and awareness. The most effective campaigns have been based on a valid model of the antecedents of initiating drug use and the factors which contribute to its continuation (Miller & Ware 1989; Paglia & Room 1998).

Miller and Ware conducted a comprehensive review of the issues involved in mass media drug and alcohol campaigns, drawing on the fields of marketing, communication and social psychology (Miller & Ware 1989). They concluded that the most useful approach to the development of campaigns is a social marketing model targeting the complex determinants of drug use behaviour.

All phases of the campaign should be guided by research and be based on evidence regarding the needs and characteristics of the target group. Pre-campaign research is needed to assess drug use and knowledge, lifestyle, media habits, information sources and perceptions regarding drug use of the target audience. All messages and campaign materials should be based on the identified characteristics

and be pre-tested to ensure that they are effective and capable of addressing local needs. Monitoring and outcome evaluation are also important (Miller & Ware 1989).

A number of principles to increase the effectiveness of mass media campaigns have been identified (Miller & Ware 1989; Paglia & Room 1998):

- careful consideration of audience characteristics
- targeting of clearly defined audience segments
- use of appropriate media, communicators and message content
- specific objectives for each component.
- the use of credible sources of information, concise and simple content, motivation, arousal, entertainment and repetition.
- message strategies which include explicit instructions for change.
- use of multiple media to increase effectiveness and help to promote social norms.
- effectiveness is enhanced when the campaign is linked with other prevention programmes.

Campaigns can be counterproductive if overly fear-arousing messages are used, the information source has low credibility or the campaign promotes messages which are significantly different from community norms. Short-term, one-off campaigns are unlikely to be effective but a series of campaigns over time may create a favourable climate of opinion (Miller & Ware 1989).

6.1.3 Comprehensive community based strategies

The effectiveness of school drug education and mass media campaigns can be enhanced if they are used as components of comprehensive, community based, multi strategy prevention programmes. There is growing support in the literature for prevention to take a broad health promotion approach aimed at individual, social and structural antecedents of drug use (Anonymous 1999e; Commission on Narcotic Drugs 1999; Hawkins *et al* 1995; National Institute on Drug Abuse 1997; National Institute on Drug Abuse 1999; United Nations Office for Drug Control and Crime Prevention 2000).

A number of researchers have reviewed the principles of effective prevention (Commission on Narcotic Drugs 1999; Hawkins *et al* 1995; National Institute on Drug Abuse 1997; National Institute on Drug Abuse 1999; National Institute on Drug Abuse 2001; United Nations Office for Drug Control and Crime Prevention 2000). The identified principles are based on the understanding that drug use is part of wider social problems and is a health behaviour with multiple antecedents (Hawkins *et al* 1995; National Institute on Drug Abuse 1997; United Nations Office for Drug Control and Crime Prevention 2000). While no individual strategy has been found to be effective in the long term there is considerable consistency in the identification of the criteria for effective programmes:

- programmes should target specific settings and cultures
- strategies should be carefully tailored to clearly defined target groups
- include multiple components addressing individuals, families, school, media, community organisations and health providers,
- ensure that components are well integrated and messages are consistent,
- use an evidence based approach incorporating research at all stages of the design, implementation and evaluation of the programme
- involve the community and target groups in defining the problem and finding solutions.
- target groups at higher risk require higher intensity interventions
- strategies applied early in life are more effective for children at higher risk
- Longer term programmes have a longer lasting impact.

Analysis of the cost effectiveness of a comprehensive community based programme based on six-year outcome data concluded that the programme was highly cost effective (Pentz 2000). The programme on which the analysis was based included a school drug education programme, mass media, community organisation and parent involvement programmes.

There are considerable advantages to using a risk and protective factor approach in prevention because there are many commonalities in the antecedents of

substance abuse, crime and mental health problems. Integrated programmes which address these antecedents are likely to have a broader range of outcomes than programmes which focus exclusively on a single problem such as substance abuse (United Nations Office for Drug Control and Crime Prevention 2000). A further advantage is that prevention programmes can make use of existing community service delivery systems (Matthias 1999).

6.1.4 Tailoring prevention to ecstasy use

Prevention programmes targeting ecstasy users need to take into account the reasons young people give for consumption and acknowledge the personal and social functions which ecstasy serves for young people (Boys *et al* 1999).

The positive reasons for using ecstasy appear to be more influential in decisions to initiate or continue use than knowledge or experience of negative effects. Schifano commented on findings of a survey of 360 young people in Italy – 69 football fans, 291 disco-goers. Of ecstasy users, 65% felt they had enough information about MDMA and 85.5% thought that the drug can be dangerous to nerve cells (Schifano 2000). Another survey of 2107 youths attending high schools, a disco and a youth centre in Italy, found 31% of the sample did not think of ecstasy as a drug of abuse and 33% emphasised its positive psychedelic effects. 63% of consumers and 79.5% of non-consumers stated that ecstasy could be dangerous to nerve cells (Schifano 2000). Boys *et al* found that experience of negative effects was not correlated with intentions to use ecstasy in the future (Boys *et al* 1999).

Social context, fashion, and peer group norms appear to be significant influences on the initiation and maintenance of ecstasy use (see section 2.3). Prevention programmes targeted at influencing these factors, such as peer interventions and the promotion of alternative trends and fashions to provide group identity, may be of benefit in preventing ecstasy use.

6.2 Secondary prevention

Even the best primary prevention efforts are unlikely to be 100% effective – a degree of initiation of drug use is inevitable. For those who do initiate drug use, secondary prevention is relevant. With this target group secondary prevention is of two types: (1) inter-

ventions to encourage cessation of drug use before it becomes problematic (see section 7.1); and (2) education to help users minimise the risks of adverse effects from drug use.

Obvious measures to prevent the harms of ecstasy 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 (Green *et al* 1995).

Guidelines for the conduct of dance parties have been developed in a number of countries (Fromberg 1998; Kamieniecki *et al* 1998; Spruit 1999). The protocols make recommendations regarding ventilation and air temperature, the provision of sitting out facilities, provision of free water to patrons, and the provision of preventive and harm reduction information regarding ecstasy and other drug use (Fromberg 1998; Kamieniecki *et al* 1998).

Those who use the drug should be advised to wear loose clothing, to drink liquid to facilitate thermoregulation, and to have regular breaks from dancing (Henry 1992). However, because of the possibility of hyponatraemia, only moderate amounts of liquid should be ingested. Hyponatraemia can be acutely life threatening; consequently the importance of seeking medical attention promptly for non-resolving symptoms should be emphasised (Parr *et al* 1997).

Because of the wide range of substances marketed as ecstasy (see section 1) testing of tablets has been undertaken in some countries as a harm reduction measure. Large scale testing of ecstasy tablets at parties and agencies of the Drugs Information and Monitoring System has been undertaken in the Netherlands since 1992. The results of testing are used to provide information to users and as the basis of harm reduction campaigns (Fromberg 1998; Spruit 1999). A benefit of such ecstasy testing programs is the opportunity to monitor trends in supply and rapidly respond to changes in the market. Testing of tablets is undertaken in the USA by the Dance Safe organisation in the context of a comprehensive harm reduction program involving volunteers from within the rave and dance party community (Dancesafe 2000). This program uses ecstasy testing kits, which are limited in their capacity to provide accurate and detailed information about contents and dose.

Testing of ecstasy tablets has some value in enabling users to avoid more toxic substances such as PMA, but it is important that users are aware that use of MDMA by itself can result in adverse effects. Testing

of tablets should, therefore, always be accompanied by secondary preventive education.

6.3 Tertiary prevention

This third level of prevention is effectively treatment. The aim of tertiary prevention is to minimise the extent of damage when a condition has occurred. Tertiary prevention comprises both treatment administered in response to acute adverse effects, such as hyperthermia, and interventions aimed at encouraging a reduction in or cessation of drug use. These aspects are covered by sections 7.2 and 7.1, respectively.

Treatment

7.1 Interventions directed at using behaviour

In general ecstasy users do not present for treatment, except in instances of adverse effects serious enough to require medical assessment, or in instances of significant concomitant use of alcohol or other drugs. This is likely to largely be a reflection of typical patterns of use of ecstasy. It also determines the type of interventions that can be considered for ecstasy users.

As indicated in section 2.4, ecstasy is generally used infrequently, in small amounts (1 to 2 tablets a time, taken orally), in association with social events. This pattern of intermittent use, that is usually self-limited, supports a view of ecstasy as being relatively benign and certainly does not suggest the need for treatment directed at ecstasy use.

The occasional occurrence of significant adverse effects, particularly the highly publicised deaths of young people in the UK and Australia subsequent to ecstasy use, have negated the benign image of ecstasy to some extent and have triggered primary prevention initiatives directed, in particular, at the youth dance party culture (see section 6). However, apart from prevention, no attention has been given to the development of interventions specifically targeting ecstasy users. This raises the question of whether specific interventions are needed.

While the majority of ecstasy users take small doses infrequently, a proportion use more frequently (monthly to weekly) and/or use larger amounts. There may also be a trend of increasing use by injection rather than orally (Topp *et al* 1999). Topp *et al* found it was young, female, polydrug users and those who binged on ecstasy (ie. administered high doses to maintain intoxication over a period of hours to days) who were most likely to report physical, psychological, financial, relationship, and occupational problems which they attributed, at least in part, to their ecstasy use (Topp *et al* 1999). Those who inject ecstasy are also likely to be at increased risk of harm arising from the more rapid onset of effects and higher peak levels in the blood following injection, thereby increasing the effect on the cardiovascular system and the liver, and the possibility of physical trauma from loss of control during the 'rush' (Hunt *et al* 1993). Those who inject ecstasy are also at risk

of vein damage and blood-borne viruses due to their injecting behaviour. These groups of ecstasy users therefore constitute targets for preventive interventions.

In the absence of research into specific interventions for ecstasy users, the closest approximation is interventions for users of other psychostimulant drugs, ie. cocaine, amphetamine and methamphetamine. It is cocaine dependence that has been the subject of most research in this area. While cocaine and amphetamines are related to MDMA, it should be noted that there are substantial differences in the context and patterns of use, as well as pharmacology. Furthermore, it is now generally accepted that cocaine and amphetamine use can progress to a dependence syndrome, while the existence of ecstasy dependence remains questionable (Topp *et al* 1997a).

Considerable research effort has been directed towards the identification of effective pharmacotherapies for cocaine users. To date these efforts have been largely unsuccessful and even if an effective pharmacotherapy were found, any transfer to the treatment of ecstasy users is questionable because of the differing pharmacology of the drugs – cocaine acts primarily through dopamine (Rawson 1999) whereas MDMA acts through serotonin (see section 3.1). Hence pharmacotherapies for ecstasy users should be innovative and specific to the action of MDMA. Selective serotonin reuptake inhibitors (SSRIs), if taken concurrently with MDMA, have been shown to block the usual subjective effects of MDMA (Stein & Rink 1999). However, administration of SSRIs (eg. fluoxetine, citalopram) subsequent to MDMA may potentiate the effects of the released serotonin, worsening any adverse effects (Green *et al* 1995) and limiting their value as a treatment agent.

The non-pharmacological interventions which have demonstrated the most efficacy in treating psychostimulant users are relapse prevention (particularly for heavy users), cue exposure/response prevention, and possibly multifaceted behavioural therapy (Kamieniecki *et al* 1998). Contingency management approaches may also be of value (Rawson 1999).

These types of more intense psychological interventions are appropriate to those with problematic drug use behaviour. However, as discussed previously, this

group is likely to constitute a minority of ecstasy users who are likely to be polydrug users, and hence may require additional interventions appropriate to whatever other drugs are being used.

There remain the issues of attracting users into treatment and intervening prior to the development of problematic use. An approach that is well suited to these purposes is that of brief intervention (Barry 1999). Brief interventions aim to investigate a potential problem and motivate an individual to begin to do something about their substance use. The basic goal of a brief intervention is to reduce the risk of harm that could result from continued substance use. Brief interventions on their own can promote behaviour change, or they can act as the first stage of more intense treatment. Furthermore brief interventions are applicable to individuals from a wide range of cultures and backgrounds, and they can be used in a variety of settings, both opportunistic or within specialised substance abuse treatment.

Potential settings for opportunistic use of brief interventions to address ecstasy use include emergency departments of hospitals, subsequent to attendance for acute adverse effects; support services at major events such as dance parties; primary health care (doctors and dentists may detect ecstasy use in the context of other consultations); law enforcement settings (subsequent to being found in possession of an illicit drug); and computer based applications (the target group is likely to be high level internet users).

These strengths identify the potential value of brief interventions in addressing ecstasy use, but brief interventions need to be structured and much of the evidence of their effectiveness relates to alcohol abuse. It is desirable for there to be development, and evaluation through structured research, of brief interventions appropriate to ecstasy users and the various context(s) for delivery of the interventions.

7.2 Responses to conditions induced by ecstasy

7.2.1 Adverse effects of intoxication

In the case of cocaine and methamphetamine, uncomplicated intoxication requires only observation and monitoring for several hours in a subdued environment until symptoms subside (Rawson 1999). This approach of reassurance and monitoring appears to also be appropriate to ecstasy intoxication (Henry

1992). For example, Williams *et al* reviewed 48 consecutive MDMA-related cases presenting to a large London hospital (see also section 5.3), six of which entailed severe adverse effects (Williams *et al* 1998b). After initial assessment, 41 cases (85.4%) had an electrocardiogram or continuous cardiac monitoring. In 30 cases (62.5%) the patient received a further period of observation and monitoring (mean nine hours) in the accident and emergency department. Fifteen cases (31.3%) received fluids (eight oral, seven iv.). Six had some form of medication administered (diazepam in two cases; naloxone, activated charcoal, metoclopramide, antibiotics/paracetamol in one case each). Advice and reassurance was recorded as having been given in 14 cases (29%). Full resuscitation and intubation were required in one case. Eight (16.6%) were discharged home immediately; 20 (41.7%) were discharged after observation and monitoring; 10 (20.8%) discharged themselves; seven (14.6%) required hospital admission (the reasons for admission were not reported).

Adverse effects associated with cocaine and methamphetamine intoxication that indicate a need for intervention include psychosis, hyperthermia, uncontrolled hypertension and seizures (Rawson 1999). The analysis of reported cases of acute adverse effects related to ecstasy use in section 5.4 suggests that hyperthermia and hyponatraemia are the most significant complications necessitating intervention. In both conditions the treatment response needs to be rapid and intense if significant morbidity and mortality are to be averted. In the case of hyperthermia, the patient may deteriorate rapidly towards multiple organ failure, requiring intensive support of cardiovascular, respiratory and renal systems (Hall 1997a). This requires admission to an intensive care unit.

The cases reviewed in section 5.4.1.1 show clearly that mortality rate increases with increasing degree of hyperthermia. The duration of hyperthermia is also considered to be an important determinant of mortality (Hall 1997a; O'Connor 1994). The recommended medical response to acute reactions with hyperthermia therefore comprises rapid cooling with intensive monitoring (Hardern & Tehan 1995). Sedation to slow down and stop agitated movements may also be appropriate (Rawson 1999). Rehydration, treatment of metabolic acidosis and support of failing organ systems are also typical requirements (Hall 1997a). Alkalinisation of the urine prevents renal damage by myoglobin – on this basis, alkalinisation is recommended by some as an early measure (Murthy *et al* 1997). However, alkalinisation

of the urine reduces renal clearance of amphetamines and is associated with the risk of adverse effects in critically ill patients. Consequently the use of alkalinisation is controversial. It is recommended that urine output is used as the major determinant of adequacy of resuscitation.

There has been considerable discussion in the literature of the use of dantrolene. This discussion has tended to rely on comparisons between ecstasy-induced hyperthermia and heat stroke, malignant hyperthermia and the serotonin syndrome. Dantrolene is the drug of choice with malignant hyperthermia, but is not effective in heat stroke. However, it should be noted that severe heat stroke involves an overwhelming of normal thermoregulatory mechanisms, while MDMA reactions appear to involve an abnormality of thermoregulation (Hall 1997a). Another argument against dantrolene was that it is a peripherally acting muscle relaxant with no central effects, whereas hyperthermia subsequent to ecstasy use is attributed to central thermoregulatory mechanisms. However, Tehan noted that skeletal muscle is nonetheless a major site of increased metabolic activity induced by ecstasy, giving grounds for dantrolene use (Tehan 1993). Another aspect raised (Watson *et al* 1993) is that each 20mg vial of dantrolene contains mannitol (3g) and is reconstituted in solution with pH 9.5. Consequently the use of dantrolene also results in alkalinisation of the urine. As mentioned above, this is usually recommended in rhabdomyolysis but also reduces renal clearance of amphetamine.

As experience of ecstasy-induced hyperthermia has accumulated, it is becoming apparent that dantrolene (1mg/kg *iv.*, repeated up to 10mg/kg) is of value in achieving rapid control of body temperature (Hall 1997a). For the cases of ecstasy-induced hyperthermia that we identified, five of 26 (19%) clearly identified as having received dantrolene, compared to six of 17 (35%) clearly not administered dantrolene, had fatal outcomes. This suggests some advantage, in terms of reduced risk of mortality, arising from the use of dantrolene. The UK National Poisons Information Service advocates the early use of dantrolene in ecstasy-induced hyperthermia.

Despite its apparent benefits, use of dantrolene in ecstasy-related hyperthermia is likely to be limited to some extent by its cost and availability. Dantrolene for intravenous administration is typically held by intensive care departments of major hospitals for the treatment of malignant hyperthermia associated with anaesthesia. As such reactions to anaesthesia are

rare, there is little need for substantial stocks to be held. Each 20 mg vial of dantrolene costs in the vicinity of US\$37. A typical initial dose of 1mg/kg, for a 60 kg person, would therefore cost US\$111, and if the recommended maximum dose of 10mg/kg were required, the cost would exceed US\$1000. This needs to be weighed against the probability of dantrolene reducing the duration of intensive hospital care, which in itself is expensive (around US\$1000 per day), and the life-threatening nature of hyperthermia. In the context of limited health resources, the high cost of dantrolene and intensive care emphasises the importance of secondary and tertiary prevention measures, including education of users, to prevent the occurrence of hyperthermia and to intervene quickly with physical cooling measures when it does occur.

The use of neuroleptics requires care because of the theoretical risk of producing the neuroleptic malignant syndrome and the possibility of precipitating seizures (Green *et al* 1995). Delirium, agitation and seizures should be controlled with increments of diazepam in the first instance, in preference to chlorpromazine (Alciati *et al* 1999; O'Connor 1994). In cocaine users it has been found that diazepam is less effective if administered after the commencement of seizures (Rawson 1999).

Rehydration, while recommended, needs to take into account any existing hyponatraemia (Hegadoren *et al* 1999; Henry 2000).

Activated charcoal has been administered in some cases and is considered to be helpful in cases of amphetamine ingestion (Hardern & Tehan 1995). However, the value of activated charcoal, and gastric lavage, will depend on the time elapsed since ingestion of drugs.

7.2.2 Hepatotoxicity

The cases presented in section 5.4.3 indicate that many cases of ecstasy-induced liver damage will resolve without intervention, and simply require monitoring. However, patients developing jaundice or with evidence of hepatic failure, particularly encephalopathy and prolongation of the international normalised ratio, or both, should be referred to a specialised liver unit. Liver transplantation may represent the only chance of recovery should they progress to fulminant liver failure (Ellis *et al* 1996; Jones & Simpson 1999).

Auxiliary liver transplantation is a procedure in which part of the native liver is left in situ. The transplanted

liver provides a temporary support until the native liver has recovered. When native liver function has been regained, immunosuppression can be tapered then stopped permanently. The auxiliary liver may be removed, or left to atrophy (Chenard-Neu *et al* 1996). Chenard-Neu *et al* followed 30 patients with fulminant hepatic failure who received auxiliary liver transplantation in 12 European centres. Two of the 30 cases were ecstasy-induced. After follow-up of three to 36 months, 19 (63%) survived and 13 (43%) had resumed normal native liver function, with interrupted immunosuppression. (Reported one-year survival rates following full liver transplantation for fulminant hepatitis between 1987 and 1995 were between 54 and 70%.) One of the two ecstasy-related cases received a second auxiliary liver transplant for primary non-function of the first graft. Both survived but with incomplete regeneration of the native liver and remained graft dependent 18 and five months after transplant (Chenard-Neu *et al* 1996).

Concluding remarks

8.1 Preventing harms

Given the recent increased prevalence of ecstasy use, and its use predominantly by young people, it is considered desirable for increased attention to be given to ecstasy in primary prevention education programs. To support this, appropriate information should be provided to agencies and organisations responsible for school education to enable its integration into drug education programs within health curricula.

Any mass media information campaigns addressing ecstasy use should be supported by other approaches, such as community-based strategies. Messages should be informative, supported by evidence, and appropriate to the target audience. Scare campaigns presenting unrealistic messages of dramatic harms attributed to ecstasy should be avoided. Such approaches are counterproductive.

Secondary prevention efforts should also be increased. Secondary prevention comprises early intervention for those who are using, with a view to preventing progression to problematic use, as well as measures to reduce the risks of adverse effects occurring.

Hyperthermia and hyponatraemia are the most significant, and potentially life threatening, adverse effects associated with ecstasy use. Given that both appear to arise largely as a result of the setting of use and individual behaviour, they constitute good targets for secondary prevention initiatives. Obvious measures include the provision of free water and temperature control at venues, together with education to increase the knowledge of users, venue operators and support staff, about the importance of controlling body temperature and fluid intake, how to recognise early signs of adverse effects, and the importance of seeking medical assistance promptly. A number of countries have developed guidelines for dance parties and nightclubs that support this approach. Such guidelines are recommended as a useful secondary prevention approach.

Testing of ecstasy tablets has some value in enabling users to avoid more toxic substances, such as PMA, but it is important that users are aware that use of MDMA by itself can result in adverse effects. Testing of tablets should therefore always be accompanied by secondary preventive education.

Secondary prevention should also include strategies to prevent progression to problematic drug use. Psychosocial approaches are most appropriate for this purpose. Given that ecstasy users will generally be identified opportunistically, brief interventions are well suited for secondary prevention purposes. It is desirable that specific brief interventions suitable for ecstasy users and the contexts in which the interventions are likely to be delivered, are developed.

Tertiary prevention entails the delivery of effective treatment when adverse effects do occur to limit the degree of harm to the individual. Treatment responses to adverse effects related to ecstasy use are largely symptomatic – quick control of temperature and attention to salt and water imbalances are most important.

8.2 Future directions in research

As outlined above, it is desirable that specific brief interventions suitable for settings where ecstasy users are likely to be detected (eg. emergency rooms, dentists, law enforcement) are developed and tested. This would support enhanced secondary prevention efforts.

Systems of emergency room monitoring should be developed and implemented to monitor the prevalence of adverse effects. The Drug Abuse Warning Network (DAWN) in the USA provides a useful model of such monitoring. An added advantage of this sort of system is that it also has the capacity to identify emerging patterns of drug use and related problems. For example, data from DAWN indicates the significance of mixing drugs, and recent increases in GHB-related problems in parallel with MDMA. Data shows the young age of users experiencing adverse effects.

Given that medical responses to ecstasy-related adverse effects are largely determined by the symptoms, there is probably little need for specific information or guidelines for hospital personnel on treatment of ecstasy users. However, medical personnel may find it useful to be informed on the pattern of adverse effects experienced by ecstasy users and their responses to different treatment approaches. It is recommended that the needs of medical personnel for such information, and most appropriate ways to deliver such information, be assessed and responded to as appropriate.

This report identifies the absence of controlled epidemiological studies and the consequent difficulties in quantifying risks of ecstasy. It is recommended that such studies be designed and initiated to establish prevalence of harms associated with ecstasy use, and particularly to assess long-term functional consequences of ecstasy use.

Another area where our knowledge is currently limited relates to the capacity of ecstasy to produce dependence. Furthermore, if ecstasy dependence does exist what are the central features, how should it be assessed, and does it have any diagnostic significance. That is, does it predict risk of adverse effects or appropriate treatment responses?

Although animal and cellular studies have contributed much to our understanding of the effects of amphetamine derivatives, there is still much to do. Due to the unpredictability of adverse effects of these drugs and the very large number of possible chemical manipulations that can be made by illicit chemists, we are still not capable of predicting the outcome of administration in individuals. It would appear that environmental factors are important but these have not been fully explored. The role of genetic variation has not been examined to any great extent. Further cellular and animal studies are essential if we are to gain sufficient knowledge of the mechanisms of action of these drugs to predict the likely adverse effects in a given situation. This indicates the importance of continued basic research in this area.

Our general understanding of the pharmacology of MDMA and related amphetamine derivatives should continue to be developed. This report identifies a small number of cases of adverse effects apparently arising from interactions between MDMA and other drugs (fluoxetine, ritonavir). Data reviewed also indicate that a wide range of drugs are commonly used in conjunction with ecstasy. Improved understanding of the potential for interaction between these drugs may help to avert or respond to other possible interactions. Further analysis of toxicological data in fatal and non-fatal cases of adverse effects would also help to determine relative toxicity of various amphetamine derivatives.

Appendix

Acute reactions to ecstasy involving hyperthermia

Note: temperature reported under clinical features is the maximum body temperature recorded.

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|--|--|--|-------------------------|
| 21, M | Inhaled half of 3 "caps". History of asthma. PMA detected - see text section 5.4.1.12. | Disoriented, spasms, rigid; perspiration, dilated pupils, convulsions, jaw rigidity; 42.8°C; cardiac arrest. | Not reported | Fatal 3 hours after admission | Cimbura 1974 |
| 19, M | 17-40 "hits" iv and orally. Known drug addict. PMA detected - see text section 5.4.1.12. | Bulging eyes, convulsions, agitation, sweating, jaw rigidity; 42.8°C; cardiac arrest. | Not reported | Fatal 3 hours after admission | Cimbura 1974 |
| 30, M | No information. PMA detected - see text section 5.4.1.12. | Sweating, dilated pupils, extreme rigidity; 42.8°C; cardiac arrest. | Not reported | Fatal one hour after admission | Cimbura 1974 |
| 35, M | Ingestion observed but amount not reported. MDA 2.3mg/l in blood; no other drugs or alcohol detected. | Erratic behaviour, marked pyrexia (temperature not reported). | Dead on arrival | Fatal | Lukaszewski 1979 |
| 32, M | Party; MDA in empty capsule in pocket and tissues at autopsy. | 41°C; comatose; seizures; acidosis; repeated cardiac arrests. | Intubation; lavage; naloxone. | Fatal | Simpson & Rumack 1981 |
| 32, F | 100-150mg MDMA; home; serum MDMA 7.0mg/l. | 41.6°C; hallucinations; renal failure; DIC; rhabdomyolysis; hepatitis. | Cooling; iv fluids; frusemide; haloperidol and diazepam. | Discharged day 5. Bouts depression, low energy for 6 months. | Brown & Osterloh 1987 |
| 16, F | 1 tab ecstasy, nightclub; serum MDMA 0.424mg/l. | Convulsion, 42°C, DIC, metabolic acidosis, cerebral oedema. | Blood products; dobutamine; noradrenaline; sodium bicarbonate; frusemide & mannitol. | Fatal at 36 hours | Chadwick 1991 |
| 18, M | 3 tabs ecstasy, concert; serum MDMA 1.26mg/l. | 43°C, seizures, renal failure, DIC, rhabdomyolysis. | Diazepam; intubation, ventilation; iv fluids; dantrolene; blood products. | Fatal at 5 hours | Campkin & Davies 1992 |
| 23, M | 3 tabs ecstasy; club; serum MDMA 0.20mg/l, amphetamine 0.1mg/l. | 40°C; convulsion; unconscious; renal failure; DIC; rhabdomyolysis. | Blood products; haemofiltration. | 33 days in hospital; full recovery. | Fahal <i>et al</i> 1992 |
| 18, M | 3 tabs ecstasy, nightclub; serum MDMA 0.36mg/l. | 41.8°C; unconscious; arrhythmias and asystole. | Not reported | Fatal at 2.5 hours | Henry <i>et al</i> 1992 |

Appendix 1

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|---|---|--|----------------------------|
| 17, M | 2 tabs ecstasy, party; MDMA detected in blood. | 41°C; comatose, seizures; DIC | Not reported | Fatal at 11 hours | Henry <i>et al</i> 1992 |
| 18, M | 5 tabs ecstasy, party; MDMA detected in blood. | 42.1°C; coma; GI bleed | Not reported | Fatal at 11 hours | Henry <i>et al</i> 1992 |
| 20, M | Party; serum MDMA 1.16mg/l, amphetamine 0.10mg/l. | 40°C; seizures; renal failure; rhabdomyolysis, DIC [haemophiliac]. | Not reported | Fatal at 60 hours | Henry <i>et al</i> 1992 |
| 21, F | Party; serum MDMA 0.11mg/l. | 41°C; seizures; renal failure; DIC; rhabdomyolysis; jaundice. | Liver transplant after 4 days | Fatal at 18 days due to graft rejection. | Henry <i>et al</i> 1992 |
| 19, F | 2 tabs "amphetamine"; nightclub; serum MDMA 0.97mg/l. | 39.7°C; vomiting; comatose; raised AST, thrombocytopenia. | Forced diuresis, chlorpromazine | Recovered | Henry <i>et al</i> 1992 |
| 20, M | 3 caps ecstasy; nightclub; serum MDMA 0.24mg/l. | 40°C; agitated; renal failure; DIC; rhabdomyolysis. | Did not require haemodialysis. Other measures not reported. | In hospital 21 days. Recovered. | Henry <i>et al</i> 1992 |
| 19, M | Nightclub; MDA, amphetamines in blood and urine. | 43.3°C; comatose; DIC; rhabdomyolysis. | Ventilation; rapid cooling; iv saline; blood products; mannitol. | Fatal | Screaton <i>et al</i> 1992 |
| 19, M | MDMA (1st use); nightclub. | 41°C; coma; renal damage; DIC; rhabdomyolysis. | Rapid cooling; ventilation; blood products; mannitol, bicarbonate; surgery for compartment syndrome both legs. | Recovered but walking impaired by leg muscle loss. | Screaton <i>et al</i> 1992 |
| 19, M | 3 tabs MDMA; nightclub. | 40°C; coma; rhabdomyolysis; mild coagulopathy. | Rapid cooling; alkaline diuresis. | Self-discharge at 30 hours | Screaton <i>et al</i> 1992 |
| 24, M | 200mg MDMA, nightclub. | 40.2°C; unconscious, convulsions, hypotensive, hyperkalaemia; rhabdomyolysis; coagulation disorder. | Diazepam (ineffective), thiopentone; intubated, ventilated, sedated; glucose & insulin infusions; physical cooling, dantrolene. | Symptoms resolved over 2 days. In hospital 2 weeks for psychiatric assessment. | Singarajah & Lavies 1992 |
| 20, M | 5 tabs ecstasy, rave; serum MDA 1.51mg/l, ethanol 0.2g/l, MDMA 0.5mg/l. | 41.4°C; convulsion; rhabdomyolysis; metabolic acidosis. | Fluids; dantrolene, diazepam; ventilation; activated charcoal. | Recovered after 72 hours | Woods & Henry 1992 |
| 23, M | 1 tab ecstasy, amphetamine; serum MDMA 0.20mg/l, amphetamine 0.1mg/l | 40°C; convulsion; renal failure; DIC; rhabdomyolysis. | Oxygen, chlorpromazine, iv fluids, propranolol, frusemide, haemofiltration. | 33 days in hospital. Recovered. | Barrett & Taylor 1993 |

Appendix 1

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|--|--|--|-----------------------------|
| 21, F | "Single exposure of ecstasy" at a dance hall. Amphetamine derivatives in urine. | Collapsed. 39°C, respiratory insufficiency, seizures. CPK elevated; no myoglobinuria; liver insufficiency. | Intubation, sedation and ventilation until second day. No further detail reported. | Discharged day 10 | Ijzermans <i>et al</i> 1993 |
| 23, M | 4 tabs ecstasy, amphetamines, nightclub; MDMA metabolites in urine. | 42°C; agitated; fluctuating consciousness; metabolic acidosis; DIC (day 2), acute confusional state with paranoid delusions, hallucinations. | Dantrolene, diazepam, labetalol; gastric lavage, activated charcoal, ventilation, inotropic support; haloperidol. | 3 days intensive care, 5 days in hospital; recovered. | Logan <i>et al</i> 1993 |
| 19, F | Ecstasy, party. MDMA in blood. | 40°C; convulsions; tachycardia; cerebral oedema; coagulation defect. | Diazepam; dantrolene; intubated, ventilated; single dose mannitol (20g); blood products when coagulopathy worsened. | Temperature normal in 10 hours; 3 days intensive care, 14 days in hospital; recovered. | Nimmo <i>et al</i> 1993 |
| 20, M | 18 tabs ecstasy, 5 pints beer, home; serum MDMA 4.05mg/l, ethanol 1.2 g/l | 38.6°C; vomiting, convulsing. | Paralysis, sedation, ventilation; dantrolene; active cooling; gastric lavage; rehydration. | Extubated at 48 hours, self-discharge following day. | Roberts & Wright 1993 |
| 20, M | 2 tabs ecstasy, nightclub; serum amphetamine 0.28mg/l, MDEA detected. | 40.2°C; agitation, stuporose; DIC, rhabdomyolysis; metabolic acidosis. | Fluids; diazepam; anaesthetised and ventilated; dantrolene; active cooling; activated charcoal, bicarbonate, dobutamine, calcium chloride. | 18 days in hospital, recovered | Tehan <i>et al</i> 1993 |
| 16, M | Nightclub; MDMA detected in blood. | 42°C; hypotensive, tachycardia; convulsion; DIC, hyperkalaemia, renal insufficiency, rhabdomyolysis. | Intubated, ventilated; diazepam, dantrolene, blood products, noradrenaline, haemofiltration, dextrose. | Fatal day 6 | Watson <i>et al</i> 1993 |
| 18, M | Unknown tablets, danced 5 hours. MDA detected in vomitus, blood and urine. | 41°C; vomiting, hallucinations; tachypnoeic, agitated, increased muscle tone. | Dantrolene; monitored 48h in intensive care. | Recovered | Watson <i>et al</i> 1993 |
| 26, M | Swallowed tablets to conceal from police. MDA detected. | 40°C; vomited, semiconscious, increased muscle tone, metabolic acidosis, seizure; renal insufficiency. | Diazepam, dantrolene, sodium bicarbonate, fluids. Self-discharge after 72 hours. | Full recovery at one month follow-up | Watson <i>et al</i> 1993 |
| 20, M | Several tabs ecstasy, not dancing. MDA detected. | 40.5°C; leg cramps, headaches; developed lower lobe pneumonia. | Dantrolene, antibiotics | Self-discharge after 48 hours | Watson <i>et al</i> 1993 |

Appendix 1

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|---|---|--|---------------------------|
| 20, M | 200mg ecstasy; MDMA detected in blood. | 40.2°C; agitation; DIC; hypoglycaemia | Diazepam; sedated and ventilated; active cooling; inotropic support; dantrolene. | Discharged at 7 days with evidence of neurological disability. | Webb & Williams 1993 |
| 18, F | Speed, ecstasy, alcohol at rave. History of ecstasy, alcohol use. Amphetamine and MDA in urine. | 42°C; Glasgow Coma Scale 3, aspiration pneumonia; hypokalaemia; rhabdomyolysis; hepatocellular damage, coagulation defect. | Assisted ventilation 24 hours. No other detail reported. | Recovery implied, but not specifically reported. | Jones <i>et al</i> 1994 |
| 20s, M | Found sweating and rigid at rave. Drug use uncertain. | Convulsion, vomited; unconscious; rigidity round mouth; 42°C, pupils dilated; metabolic acidosis, hyperkalaemia, aspiration gastric contents. | Halothane induction, intubated, suctioned, diazepam, ventilated; ice packs, cold iv fluids, dantrolene, antibiotics. | Ventilated for 30 hours. Rapid recovery. Discharged after four days. | Walsh <i>et al</i> 1994 |
| 36, M | 1 tab ecstasy, beer, copious water | 36.2°C, to 39.7°C at 12 hours; convulsions; aspiration pneumonia; rhabdomyolysis 18 hours after admission. | Diazepam, chlorpromazine for seizures; antibiotics, hydrocortisone for pneumonia; forced alkaline diuresis when rhabdomyolysis developed. | Recovered over 5 days. | Lehmann <i>et al</i> 1995 |
| 30, M | Ecstasy, heroin, amphetamine at rave, large amounts alcohol following day. | Unconscious, vomited, convulsion; 38.5°C; rhabdomyolysis; chest infection; no hepatic or renal failure or DIC. | Not reported | Fatal at 5 weeks. Bilateral necrosis of globus pallidus on autopsy. | Squier <i>et al</i> 1995 |
| 24, M | 25 tabs MDMA at rave. | Collapsed. Agitated, aggressive. 41.2°C, tachycardia, hypotensive. | Diazepam, sodium bicarbonate, dantrolene; intubated, ventilated; active cooling, mannitol and crystalloid for diuresis; insulin and dextrose for hyperkalaemia; activated charcoal. | Extubated after 36 hours. Recovered. | Wake 1995 |
| 22, M | Ecstasy by self-report | 5 day history fever (>39°C) from day after drug use; seizure; acute inflammatory CNS disease | Ventilation; prednisolone, amoxicillin/gentamicin, mannitol, analgesia. | Recovered over 10 days | Bitsch <i>et al</i> 1996 |

Appendix 1

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|--|---|--|---|------------------------------------|
| 18, F | 1 tab ecstasy, nightclub; serum MDA 0.246mg/l | 40.3°C; vomiting, hallucinations, convulsion; DIC, jaundice, renal impairment, rhabdomyolysis | Dantrolene; cold sponging; diazepam | Fatal at 9 days | Coore 1996 |
| 22, M | Rave; marijuana, alcohol, 2_ tabs ecstasy. Blood MDMA 0.55mg/l, MDEA 0.49mg/l, MDA 0.24mg/l. | Bizarre behaviour, vomiting, shaking, hyperventilating; convulsions; 41.8°C; metabolic acidosis, DIC. | Intensive treatment (not specified) | Fatal 17 hours after admission | Cox & Williams 1996 |
| 17, M | 10 tabs ecstasy, alcohol, nightclub; serum MDMA 2.3mg/l, alcohol 0.8g/l | 42°C; delirious; coagulopathy, metabolic acidosis, hyperkalaemia, atrioventricular block | Fluids; cooling; ventilation; temporary cardiac pacing wire; dantrolene | Fatal at 6 hours | Dar & McBrien 1996 |
| 19, F | 1 tab ecstasy, apres ski | 38.5°C; vomiting; seizure; disoriented; possible rhabdomyolysis | Gastric lavage; iv fluids; bromocriptine; dantrolene | Oriented at 4 days, 11 days in hospital. Recovered. | Demirkiran <i>et al</i> 1996 |
| 25, M | 1 tab ecstasy | 39°C; agitated; sinus tachycardia with QT interval prolongation | Rehydration | Vital signs normal at 24 hours; QT normal in 4 days | Drake & Broadhurst 1996 |
| 21, F | Ecstasy, LSD; party; serum MDMA 0.11mg/l | 41°C; convulsion; unconscious; DIC, renal failure, liver failure | Ventilation, paralysis and sedation; haemofiltration; blood products; liver transplant day 4 | Died of sepsis 13 days after transplant | Ellis <i>et al</i> 1996 |
| 19, M | 3 tabs ecstasy, party; serum MDMA 0.38mg/l | 42°C; unconscious; DIC; liver damage | Ventilation; rehydration; dantrolene | Ventilated 6 days, 15 days in hospital; recovered. | Ellis <i>et al</i> 1996 |
| 26, M | 1 tab ecstasy, pub | 41°C; seizures; DIC, renal failure, rhabdomyolysis, respiratory distress | Diazepam; ventilated, anaesthetised; active cooling; inotropic support; dantrolene; blood products | Self-ventilating at day 17. Recovered. | Hall <i>et al</i> 1996; Hall 1997b |
| 21, M | Collapsed at rave. Blood MDMA 4.2mg/l, amphetamine 1.4mg/l. | Agitation, unconscious, 44°C, cardiac arrest. | Not reported | Fatal | Milroy <i>et al</i> 1996 |
| 20, M | Not reported. Blood MDMA 0.09mg/l, MDA 0.13mg/l. | Found unconscious in bed. Rigidity, 39.5°C, elevated liver function tests, cerebral hypoxia. | Not reported | Fatal after 4 days | Milroy <i>et al</i> 1996 |
| 30, F | 1 tab ecstasy (1st use), large amounts water, rave. | 39°C (over 24 hours); seizures, confused, agitated; hyponatraemia. | Not reported | | Box <i>et al</i> 1997 |

Appendix 1

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|--|---|--|---|
| 19, M | 3 tabs ecstasy, nightclub; MDMA detected in blood and urine | 42.9°C; seizures; myoglobinuria but no renal impairment | Diazepam; anaesthetised and ventilated; cooling; dantrolene; intravenous fluid; adrenaline, bicarbonate. | 6 days in hospital, recovered | Mallick & Bodenham 1997 |
| 25, F | 3 tabs MDMA | 41.9°C; convulsion; hypoglycaemia; coagulopathy, rhabdomyolysis | Active cooling; dantrolene; chlormethiazole, dextrose; supportive therapy. | Recovered | Montgomery & Myerson 1997 |
| 21, M | 7 tabs ecstasy, 2g amphetamine, alcohol; nightclub; serum MDMA 0.75mg/l, MDA 0.025mg/l | 41°C; unconscious; mild coagulopathy, hypocalcaemia, DIC, pulmonary oedema, jaundice, renal failure | Rapid cooling, ventilation, dantrolene, mannitol and bicarbonate, haemodialysis or haemofiltration | 60 days intensive care, 80 days in hospital; normal renal function day 45, liver function 50 days after discharge. | Murthy <i>et al</i> 1997 |
| 25, F | 1 tab ecstasy, alcohol; party | 41.9°C; seizure, unconscious; elevated creatine kinase but normal renal function | Diazepam, dantrolene, glucose, platelets; intensive care | 2 weeks in hospital; creatine kinase still elevated at discharge. | Williams & Unwin 1997 |
| 35, M | 5 tabs, 1 "line" ecstasy over 5 hours, club house; amphetamine 1.6mg/l, methylamphetamine 0.23mg/l, PMA 1.7mg/l in blood. | Hot, sweating, signs of delirium, jaw locked; found dead 4 hours after last ecstasy. Body temp 41.2°C when found. | None | Fatal | Byard <i>et al</i> 1998; James & Dinan 1998 |
| 22, F | 3 tabs ecstasy, methamphetamine dance clubs; PMA 1.32mg/l, MDMA 0.3mg/l in blood. | 42.5°C; unconscious, fitting; DIC, rhabdomyolysis, hyperkalaemia | Not reported | Fatal at 12 hours | Byard <i>et al</i> 1998 |
| 23, M | Multiple tabs ecstasy, friend's house; PMA 3.7mg/l, amphetamine 0.26mg/l, methamphetamine 3.1mg/l in blood. | Collapsed; felt hot; cardiac arrest soon after arrival at hospital; kidney damage, rhabdomyolysis detected at autopsy. | Not reported | Fatal | Byard <i>et al</i> 1998 |
| 26, F | 5 tabs ecstasy in 12 hours, home; PMA 2.2mg/l, MDMA 0.82mg/l, methamphetamine 0.09mg/l in post-mortem blood. | Felt hot, agitated, difficulty breathing; 46.1°C on admission, cyanosis, fits, hyperthermia, cardiac arrhythmias. | Not reported | Fatal 30 minutes after admission. | Byard <i>et al</i> 1998 |
| 20, F | 2 tabs MDMA; serum MDMA 2.3mg/l | 41.7°C; unresponsive, cyanotic; tachycardia, seizures | Chewing gum suctioned from oropharynx; diazepam, dextrose, phenobarbital, vecuronium, activated charcoal. | Fatal at 4.5 hours | Mueller & Korey 1998 |

Appendix 1

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|-----------------------------|--|---|--|---|-----------------------------------|
| 23, M | Hotel room; serum PMA 2.0mg/l, methyl-amphetamine 0.36mg/l | Found dead; 39°C | | Fatal | Byard <i>et al</i> 1999 |
| 19, M | Ecstasy, several doses over 30 hours; rave party; MDMA detected in urine, blood alcohol 110mg/dl | 39°C; incoherent, agitated, disoriented | Intravenous fluids, dantrolene | Resolved over 72 hours | Rochester & Kirchner 1999 |
| 19, M | Numerous tabs ecstasy at disco. MDMA and MDA in blood and urine. | Respiratory difficulty, uncoordinated movements, hypertonia, 40.6°C. DIC, cardiac arrest. | Artificial ventilation; heparin and blood products. | Fatal around 14 hours after admission. | Fineschi <i>et al</i> 1999 |
| 20, M | Numerous tabs ecstasy at disco. MDMA, MDA and MDEA in blood and urine. | "Felt feverish", 40°C (armpit). Found dead 8 hours later, pillow soaked with blood. | | Fatal | Fineschi <i>et al</i> 1999 |
| 19, M | Drug used unknown. MDEA in blood. | Found unconscious near disco. 40.5°C; convulsions, progressive hypotension | Treated in intensive care unit; detail not reported. | Fatal 24 hours after admission. | Fineschi <i>et al</i> 1999 |
| 19, M | 4 tabs ecstasy | 43°C; hyperkalaemia; metabolic acidosis; myoglobinuria; renal failure; rhabdomyolysis; DIC; bilateral gluteal compartment syndrome. | Intubation and ventilation; dantrolene; active cooling; dextrose and insulin infusions; haemofiltration; forced alkaline diuresis; laparotomy; bilateral thigh and gluteal fasciotomies. | Recovered, after 37 days intensive care. At 1 year, walking and functioning normally. | Ferrie & Loveland 2000 |
| Accidental ingestion | | | | | |
| 1, M | Serum MDMA 0.70mg/l | 38.5°C; agitation; convulsions | Diazepam and haloperidol ineffective. Chlormethiazole infusion. | Full recovery. Discharged after 4 days. | Bedford Russell <i>et al</i> 1992 |
| 2, F | 1 tab ecstasy, partially removed by mother; MDMA in stomach contents and urine. | 39°C; seizure, agitated. | Tepid sponging; oxygen; paracetamol; diazepam; gastric lavage | Recovered | Cooper & Egleston 1997 |

Appendix 1

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|-----------------------------|---|--|--|---|-----------------------------|
| Intentional overdose | | | | | |
| 19, M | Unknown tablets at home (suicide intent). Plasma MDEA 20.2mg/l at admission. No other drugs detected. | Vomiting, paranoid ideas; agitated, mydriasis, sweating, hypertension, 42.5°C, convulsions, cardiac arrest; rhabdo-myolysis, DIC. | Not reported | Fatal several hours after admission | Iwersen & Schmoldt 1996 |
| 30, M | 50 tabs ecstasy, 10 tabs oxazepam, alcohol over 4-5 hours; home; serum MDMA 1mg/l | 38.7°C; comatose, convulsions; | Ventilated; gastric lavage; activated charcoal; dantrolene; pancuronium bromide | Recovered over 2 days | Ramcharan <i>et al</i> 1998 |
| 53, M | Psychiatrist, arrested for possession of marijuana and narcotics. History of gastritis and platelet disorder. Serum MDMA 3.05mg/l. No other drugs detected. | Found on floor 8 hours later, breathing heavily. Semicomatose, diaphoretic, 'decorticate posturing'; 41.8°C; pneumothorax, metabolic acidosis, DIC, rhabdomyolysis, respiratory distress, liver failure. | Fluids, active cooling, activated charcoal, naloxone, frusemide, nitroprusside, intubated, ventilated; transferred to intensive care 12 hours after arrest; dantrolene. Intensive case continued with haemodialysis. | Fatal 5 days after admission. Considered suicide – handwritten will dated day of arrest found in back pocket. | Walubo & Seger 1999 |

Appendix

Acute adverse effects not involving hyperthermia

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|-----------------------------------|--|---|--|--|-----------------------------|
| Disturbed salt and balance | | | | | |
| 17, F | 1.5 tabs ecstasy (1st use); MDMA and MDA in urine | Body temperature normal; seizures 4 hours after drug use; hyponatraemia | None reported | Recovered over 54 hours | Maxwell <i>et al</i> 1993 |
| 17, F | 1 cap ecstasy; MDMA detected in plasma; danced continuously, drank about 5 litres water. | Body temperature normal; poor response; prolonged QT interval on ECG; possible hyponatraemia | Conservative management | Recovered over 18 hours | Maxwell <i>et al</i> 1993 |
| 23, F | Alcohol, ecstasy | Vomited; abnormal behaviour, drowsy; hyponatraemia | Observation | Recovered over 24 hours | Kessel 1994 |
| 24, F | 1 tab ecstasy, small amount alcohol at rave party. Serum MDMA 0.05mg/l 10 hours after ingestion. | Seizures, vomiting; dilated pupils, profuse sweating, agitated; fluctuating consciousness; hyponatraemia, elevated serum creatine kinase. | Fluid restriction, cautious infusion 1.8% sodium chloride; iv fluids from day 2, dopamine, sodium bicarbonate. | Marked improvement from day 2 as serum sodium normalised. Full recovery in 3 days. | Satchell & Connaughton 1994 |
| 20, F | 1 tab ecstasy at rave with large amount water; MDMA detected in blood | Convulsion about 9 hours after drug use; confused; cerebral oedema | Ventilated; mannitol and dexamethasone | Recovered over 4 days | Holden & Jackson 1996 |
| 15, F | Ecstasy, alcohol; party; MDMA detected in blood | Body temperature normal; semi-conscious; hyponatraemia, moderate cerebral oedema | Fluid restriction | Recovered over 24 hours | Matthai <i>et al</i> 1996 |
| 16, F | MDMA, alcohol, amphetamines; party; MDMA and MDA detected in blood | Body temperature normal; semi-conscious; hyponatraemia, cerebral oedema | Fluid restriction | Recovered over 24 hours | Matthai <i>et al</i> 1996 |
| 20, M | Collapsed at disco. Estimated intake 14 litres water. Blood MDMA 0.04mg/l. | Thirst, convulsions, 36°C, high blood pressure, low sodium, unconscious. | Not reported | Fatal | Milroy <i>et al</i> 1996 |
| 20, F | 1 tab ecstasy over 2 nights, nightclub; MDMA in urine | Normal temperature; comatose, vomiting; metabolic acidosis, hyponatraemia | Water restriction, 0.9% sodium chloride intravenously. | Began to communicate after 48 hours; recovered | Nuvials <i>et al</i> 1997 |

Appendix 2

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|--|--|---|--|-----------------------------|----------------------------------|
| 15, F | MDMA, dance party; serum MDMA 0.05mg/l | 32.8°C; vomited, respiratory arrest; tachycardia; pulmonary oedema, cerebral oedema, hyponatraemia | Ventilated; noradrenaline; intravenous fluids; frusemide, mannitol | Fatal at 5 days | Parr <i>et al</i> 1997 |
| 19, F | Ecstasy, beer; nightclub; amphetamines in urine | Vomiting 8 hours after drug use; collapsed; mild cerebral oedema, hyponatraemia | Activated charcoal, fluids, frusemide | Full recovery over 48 hours | Ajaelo <i>et al</i> 1998 |
| 26, M | 1 tab ecstasy with large volume water, home | Temp normal; seizures; hyponatraemia, pulmonary oedema | Diazepam, slow infusion sodium chloride and frusemide | Full recovery after 5 days | Holmes <i>et al</i> 1999 |
| 27, F | 2 tabs ecstasy, copious water; nightclub; serum MDMA 0.18mg/l | Respiratory arrest; pulmonary oedema; hyponatraemia; cerebral oedema | Ventilated; frusemide, noradrenaline | Fatal at 15.5 hours | O'Connor <i>et al</i> 1999 |
| 18, F | 3 tabs ecstasy, small amount alcohol, over 6 hours, rave. Amphetamines detected in urine. | Decreased consciousness, hallucinations, delirium, myrdriasis. CPK elevated, increased urine osmolarity and natriuresis with decreased natraemia and plasma osmolarity. | Frusemide, hypertonic saline serum, water restriction. Considered to be inappropriate antidiuretic hormone secretion induced by ecstasy. | Recovered over eight hours | Gomez-Balaguer <i>et al</i> 2000 |
| Central nervous system effects (seizures) | | | | | |
| 20, M | "MDA" twice by injection and orally, party. Had been drinking. PMA detected – see text section 5.4.1.12. | Perspiring, hyperactive, convulsive, "stopped breathing". | Dead on arrival at hospital | Fatal | Cimbura 1974 |
| 17, M | 1.5g "MDA" during evening. PMA detected – see text section 5.4.1.12. | Bulging eyes, shaking, "thrashed around". | Dead on arrival at hospital | Fatal | Cimbura 1974 |
| 22, M | 12-13 "hits" orally during afternoon, by injection in evening. PMA detected – see text section 5.4.1.12. | Confused, convulsions. | Dead on arrival at hospital | Fatal | Cimbura 1974 |
| 17, M | "MDA" by injection. History heroin and amphetamine use. PMA detected – see text section 5.4.1.12. | Extreme agitation, convulsions. | Dead on arrival at hospital | Fatal | Cimbura 1974 |
| 18, M | Ecstasy | Seizure; tachycardia [history of fit 1 month previously, after ecstasy] | None | Self-discharge | Sawyer & Stephens 1992 |

Appendix 2

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|------------------------|--|---|--|---|-------------------------------|
| ?, M | Ecstasy | Drowsy, headache; probable seizure; hyperkalaemia | Activated charcoal, observation | Discharged next day | Sawyer & Stephens 1992 |
| 23, M | Multiple doses ecstasy, dancing continuously. MDA detected. | Seizure, vomited; apyrexial, sweating profusely, agitated, unresponsive. | Intubated, ventilated; sodium bicarbonate. | 48 hours intensive care, self-discharge 24 hours later. | Watson <i>et al</i> 1993 |
| 24, M | 3 tabs ecstasy, friend's house; PMA 4.9mg/l in post-mortem blood. | Found dead. Probable convulsions. | None | Fatal | Byard <i>et al</i> 1998 |
| 32, M | 2.5 tabs ecstasy, alcohol. Blood MDMA 4.56mg/l, ethanol 0.24g/l. Uneventful MDMA use before starting ritonavir (AIDS). | Unwell 4 hours after arriving at club. Progressed to convulsion, cardiorespiratory arrest. | Resuscitation unsuccessful | Fatal. Ritonavir likely to reduce metabolism of MDMA. | Henry & Hill 1998 |
| 19, F | Amphetamine powder, 1 tab ecstasy over 2 hours, nightclub. Blood amphetamine 2.1mg/l, MDD 0.435mg/l. | Aggressive, difficulty speaking and standing. Fits, cardiac arrest. Body temperature not recorded - no signs of hyperthermia. | Resuscitation attempted | Fatal 11 hours after drug use. Cause of death uncertain - possible cardiac arrhythmias. | Carter <i>et al</i> 2000 |
| Cardiac factors | | | | | |
| 18, F | 150mg ecstasy, alcohol; serum MDMA 1mg/l, ethanol 40mg/dl | Collapsed; ventricular fibrillation | Resuscitation attempted | Fatal | Dowling <i>et al</i> 1987 |
| 21, M | 300mg ecstasy, 65mg propoxyphene, several drinks; serum MDEA 2mg/l | Unconscious; enlarged heart - idiopathic cardiomyopathy | Resuscitation attempted | Fatal | Dowling <i>et al</i> 1987 |
| 34, M | Ecstasy; MDMA in blood and urine | Ventricular fibrillation, day after use [history of Wolff-Parkinson-White syndrome] | Resuscitation attempted | Fatal | Suarez & Riemersma 1988 |
| 25, M | Not reported. Traces MDMA and MDA in urine. | Sudden (witnessed) collapse in street. Brought in dead. | | Fatal. At autopsy foci of necrosis in heart, liver. | Milroy <i>et al</i> 1996 |
| 39, M | Post-mortem blood MDMA 0.6mg/l, MDEA 0.22mg/l, amphetamine 0.22mg/l, MDA 0.12mg/l, ethanol 0.54g/l. | Sudden death when dancing at a disco. | | Fatal. At autopsy coronary arteries occluded, old infarction in left ventricle. | Lora-Tamayo <i>et al</i> 1997 |
| 30, M | Prescribed temazepam, fluoxetine. Used amphetamine, ecstasy. | Fluid overload, renal failure, pulmonary oedema, 10 days after ecstasy use | Haemodialysis, prednisolone | Fatal. Cardiac arrest - congenitally abnormal aortic valve, enlarged left ventricle. | Bingham <i>et al</i> 1998 |

Appendix 2

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---|---|---|---|--|---------------------------|
| Probable haemorrhages or cerebrovascular accidents | | | | | |
| 30, F | Ecstasy, speed, at party. | Sudden onset headache, dysphasia, right hemiparesis; BP 100/60; haematoma left fronto-parietal region by CT scan. | Conservative | Resolved – cerebral angiography 6 weeks later normal. | Harries & de Silva 1992 |
| 20, M | Soft drink 'spiked' with ecstasy, public house. | Grand mal seizure few hours later; BP 170/90; large frontal haematoma by CT scan. | Emergency craniotomy (unsuccessful). | Fatal | Harries & de Silva 1992 |
| 16, M | Cider 'spiked' with ecstasy | Right hemiparesis, expressive dysphasia; BP 130/70; haematoma in left hemisphere by CT scan. | Conservative | Resolved – cerebral angiography 4 weeks later normal. | Harries & de Silva 1992 |
| 32, F | 1 tab ecstasy | Large left-sided CVA. | Not reported | Good recovery. Mild expressive aphasia at 6 weeks. | Teggin 1992 |
| 25, F | 2.5 tabs ecstasy, home; serum MDMA 0.21mg/l | Severe headache, vomiting, 5.5 hours after drug use; subarachnoid haemorrhage from aneurysm | Surgery | Full recovery | Gledhill et al 1993 |
| 21, F | Ecstasy. Drug analysis detected amphetamine 0.07mg/l, but no MDMA. | Headache, dizziness, paraesthesiae right arm. Next morning incontinent, unable to speak. Intracerebral haemorrhage by CT scan. | Mannitol, dexamethasone; craniotomy to remove clot – small angioma found. | Speech returned; partial recovery of power in right arm and leg. | Hughes et al 1993 |
| 35, M | Ecstasy, cannabis | Normal temperature; right hemiparesis, dysphagia; left cerebral infarct | | Prolonged rehabilitation. Residual disability. | Manchanda & Connolly 1993 |
| 22, F | 1 tab MDMA (1st use); dance party – no fluids | Headache (persisting 12 days), photophobia, nausea. Cerebral venous sinus thrombosis | Intravenous heparin, repeated lumbar puncture for 4 weeks | Resolved at 3 months | Rothwell & Grant 1993 |
| 28, M | 2 tabs ecstasy (first time user). Denied use of other drugs, including alcohol. | Severe frontal headache, vomiting 1 hour after ecstasy; persistent right hand weakness. Cerebral infarction by CT scan 10 days later. | No specific treatment | Gradual improvement | Hanyu et al 1995 |

Appendix 2

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|----------------------------------|--|--|--|--|-----------------------------|
| 36, F | 1 tab ecstasy, home. Post-mortem blood PMA (0.24mg/l), fluoxetine (0.1mg/l). | Felt hot with headache. Found dead following morning. Intracerebral haemorrhage at autopsy. | None | Fatal | Byard <i>et al</i> 1998 |
| 22, F | 1 tab ecstasy, nightclub (sitting down) | Loss of central vision in left eye, persisting 2 days; retinal haemorrhage | None | Resolved over 3 months | Jacks & Hykin 1998 |
| 23, M | Ecstasy (1st use) | Severe epigastric pain, vomiting; rupture of short gastric artery. | Surgery – basis of rupture uncertain | Full recovery | Williams <i>et al</i> 1998a |
| Respiratory factors | | | | | |
| 32, M | Post-mortem blood MDMA 1.1mg/l | Found dead, adrenaline inhaler in hand | | Fatal – attributed to asthma | Dowling <i>et al</i> 1987 |
| 21, M | Party where ecstasy available; cannabis. Post mortem blood MDA 8.5mg/l, MDMA 2.1mg/l, MDEA 3.5mg/l, amphetamine 0.3mg/l. | Found dead in bed – considered “normal” 7 hours prior. Temazepam and other tablets (found to contain 60mg MDA or 45mg MDEA) beside bed. | | Fatal. Cause of death inhalation of gastric contents whilst intoxicated. | Forrest <i>et al</i> 1994 |
| 19, M | 10 tabs ecstasy in 8 hours at home; (assay 130mg MDEA per tab). History MDEA use by hair analysis. MDEA 12mg/l femoral vein serum, 22mg/l heart serum. | Profuse sweating, trembling, severe muscle spasms, aggressiveness, hallucinations, difficulty breathing, retching, salivating; collapsed. Body temperature not recorded, but no marked increase. | Resuscitation attempted. Cause of death may have been upper airway obstruction due to muscle spasms. | Fatal | Weinmann & Bohnert 1998 |
| Trauma whilst intoxicated | | | | | |
| 22, M | MDMA only drug detected in blood | Found dead by electricity tower. Injuries consistent with electrocution and fall. | | Fatal – suicide considered unlikely. | Dowling <i>et al</i> 1987 |
| 25, M | Blood ethanol 0.23g%, MDEA 0.33mg/l | Multiple injuries from car accident after running red light | | Fatal | Dowling 1990 |
| 49, M | Cocaine, MDMA (blood 1.4mg/l) | Found dead at home, car running, exhaust fumes in house. | Standard burns treatment, complicated by episodes of renal failure and grand mal fit. | Fatal. Uncertain if suicide or accident. | Dowling 1990 |
| 19, M | 18 months ecstasy, up to 15 tabs/day. Last use several tabs ecstasy, 2g amphetamine in 48 hours. | Serious burns after petrol can ignited in car. Features of paranoia and hyperactivity. | | Recovered | Cadier & Clarke 1993 |

Appendix 2

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|--|---|--|--|---|-------------------------------|
| 21, M | Autopsy blood MDEA 1.07mg/l, MDMA 0.17mg/l, MDA 0.18mg/l, ethanol 0.71g/l. | Traffic accident while driving from one disco to another. | | Fatal | Lora-Tamayo <i>et al</i> 1997 |
| 26, M | Autopsy blood contained MDEA 2.44mg/l, MDA 0.15mg/l, ethanol 0.88g/l. | Traffic accident | | Fatal | Lora-Tamayo <i>et al</i> 1997 |
| 33, M | History attempted suicide. Blood ethanol 15mg/100ml, MDD 1.2mg/l. | Found dead. Injuries in keeping with fall from height. | | Fatal | Carter <i>et al</i> 2000 |
| Chest pain not related to cardiac factors | | | | | |
| 25, M | Post-mortem blood MDEA 0.95mg/l, butalbital 0.8mg/l | Motor vehicle accident after GP attendance re pleuritic chest pain | Resuscitation unsuccessful | Fatal. Athero- sclerotic heart disease at autopsy. | Dowling <i>et al</i> 1987 |
| 17, M | 2 tabs ecstasy, party 12 hours prior. | 37.9°C; vomiting; chest pain; air in mediastinum and retroperitoneal space. | Analgesia, intravenous fluids, antibiotics | 7 days in hospital; recovered | Levine <i>et al</i> 1993 |
| 22, M | 1g speed, 1g ecstasy | Temperature normal; epigastric & cervical pain, painful swallowing. Retropharyngeal emphysema. | No specific treatment | Resolved over 4 days. | Onwudike 1996 |
| 20, M | 1 tab ecstasy | Sudden onset chest pain; air in mediastinum. | Analgesia, intravenous fluids | Resolved over a few days | Rezvani <i>et al</i> 1996 |
| 18, M | 1 tab ecstasy, party | Sudden onset chest pain; mediastinal and surgical emphysema | Conservative | Resolved | Rezvani <i>et al</i> 1996 |
| 17, F | 1_ tabs ecstasy, party, 2 days prior. Danced continuously 8 hours, while blowing whistle. | Chest pain, swollen neck. No vomiting, trauma, coughing. Air in mediastinum, pneumothorax by chest x-ray. | Observation, paracetamol | Discharged after 24 hours. Improvement after 3 days, then lost to follow-up. | Pittman & Pounsford 1997 |
| 28, F | 1 tab ecstasy, 1 tab speed; nightclub | Chest pain, anxiety 18 hours after drug use; air in pericardium and mediastinum. | Analgesia, monitoring | 4 days in hospital; recovered over 4 weeks | Ahmed <i>et al</i> 1998 |
| Ophthalmic conditions | | | | | |
| 31, F | 1 tab ecstasy, party, 2 days prior. Prescribed methadone; previous ecstasy use. | 1 day ocular pain, blurred vision. Corneal epithelial erosions; right corneal infiltrate (sterile). | Topical chloramphenicol | Settled rapidly. | O'Neill & Dart 1993 |

Appendix 2

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|-----------------------------|---|---|--|---|-----------------------------|
| 18, M | 1 tab ecstasy, 36h prior. | 1 day painful blurring of vision. Corneal erosions. | Chloramphenicol | | O'Neill & Dart 1993 |
| 19, M | 3 tabs ecstasy previous evening | 12 hours painful, watery, photophobic left eye. Corneal erosions. | Chloramphenicol, double padding of left eye. | Resolved rapidly. | O'Neill & Dart 1993 |
| 17, M | 2 tabs MDMA, 24 hours prior; 2 month history 1-2 tabs MDMA every 1-2 weeks. | Double vision, paresis arms and legs, mild sleepiness. Bilateral sixth nerve palsy. | None – ceased MDMA use | Resolved within 5 days | Schroeder & Brieden 2000 |
| Aplastic anaemia | | | | | |
| 21, M | 12 months use ecstasy, LSD, cocaine every 2-3 months. Last ecstasy 1 week prior. | 1 month flu-like illness; spontaneous bruising, epistaxis, gum bleeding. Severe aplastic anaemia | Monitored. | Spontaneous recovery. Blood count normal after 2 months. | Marsh <i>et al</i> 1994 |
| 18, F | Ecstasy on 2 occasions in 2 months prior. | 11 day history general malaise. Non-severe aplastic anaemia. | Monitored. Bone marrow transplant considered but not undertaken. | Spontaneous recovery. Blood count normal after 2 months. | Marsh <i>et al</i> 1994 |
| 19, M | Ecstasy (1st use) | Severe aplastic anaemia 2 weeks after ecstasy use. | Immunosuppressive therapy (unsuccessful); peripheral blood progenitor cell transplant. | Discharged 44 days after transplant. | Clark & Butt 1997 |
| Intentional overdose | | | | | |
| 25, M | 40 tabs MDEA, 12g heroin (oral), home (suicide attempt); serum MDEA 1.4mg/l, heroin 0.1mg/l | 36.4°C; agitated, confused; respiratory insufficiency | Gastric lavage; sedated, ventilated; diazepam, fentanyl; acidification of urine; supportive care, clonidine. | 11 days in hospital (7 in psychiatric ward); recovered | Jorens <i>et al</i> 1996 |
| 27, F | MDEA in blood (1.2mg/l), urine (1.9mg/l) and bile (3.6mg/l). Traces of diazepam and metabolites. | Cardiac and respiratory arrest, severe trismus, muscle contraction (intubation not possible). | Tracheostomy; resuscitation attempted. | Fatal – considered to be suicide (had attempted suicide 13 days prior). | Arimany <i>et al</i> 1998 |
| 19, M | 40 tabs ecstasy, home; serum MDMA 4.3 mg/l, MDA 0.23 mg/l, ethanol 1.3g/l | 37°C; confused, able to be roused; retrograde amnesia; creatine kinase, myoglobin elevated | 70g activated charcoal; frusemide; intravenous fluids. | Self-discharge at 24 hours | Regenthal <i>et al</i> 1999 |
| Miscellaneous | | | | | |
| 17, F | Bar; MDA, secobarbital detected at postmortem | Comatose, spastic movements. | | Fatal | Reed <i>et al</i> 1972 |
| 22, M | "MDA" orally and probably iv. History of alcohol and drug misuse. PMA detected – see text section 5.4.1.12. | Hallucinations, semi-conscious, violent. Taken by ambulance to 3 different hospitals; dead on arrival at third. | | Fatal 4 hours after last dose | Cimbura 1974 |

Appendix 2

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|--|--|--|--|--|
| 18, M | 6 or 7 capsules "MDA" over 4 hours. History of alcohol, cannabis, LSD use. PMA detected – see text section 5.4.1.12. | Twitching, extreme restlessness reported. Found dead. | | Fatal | Cimbura 1974 |
| 24, M | 2 tabs methaqualone (600mg), 0.5+0.7g white powder over 3.5 hours. Methaqualone (2mg/l) and MDA (10mg/l) in blood. | One hour after last drug sweating profusely, speaking irrationally. Unresponsive 3.5 hours after last drug; ambulance called. | Resuscitation unsuccessful | Fatal | Poklis <i>et al</i> 1979 |
| 35, M | LSD, valium, MDMA; serum MDMA 6.5mg/l | Sudden collapse. No anatomical cause of death at autopsy. | Resuscitation attempted | Fatal | Bost 1988; Dowling 1990 |
| 35, M | Unknown. Autopsy MDMA in heart (10.9mg/l) & femoral blood (2.8mg/l). Blood ethanol 0.21% w/v. | Initially observed intoxicated. Found dead 2 hours later, empty wine bottle nearby. | | Recorded cause of death toxic effects of MDMA and ethyl alcohol. | Rohrig & Prouty 1992 |
| 23, F | _ tab ecstasy, danced continuously 36 hours. MDA detected. | Fracture-dislocation of right ankle, generalised muscle tenderness. | Surgery postponed 24 hours until creatine kinase normal. General anaesthetic without depolarising neuromuscular blocking agents. | Recovered | Watson <i>et al</i> 1993 |
| 19, M | 15 tabs ecstasy over 36 hours | 24 hour history urine retention | Urinary catheter inserted | Resolved over 36 hours | Bryden <i>et al</i> 1995 |
| 22, M | occasional cocaine user (several months since last use). | 11 hours after ecstasy felt restless, difficulty turning head, dysphagia. Acute dystonic reaction to ecstasy. | Anticholinergic treatment (biperidene lactate, 10mg i.m.) | Symptoms resolved over 2 weeks. Symptom free at 8 month follow-up. | Priori <i>et al</i> 1995 |
| 37, M | Ecstasy, rave party. Prior use LSD, amphetamines, cannabis. | Headache, abdominal pain, vomiting, seizure. Unconscious, hypertensive, apyrexial, impaired renal function, coagulation abnormalities. | Ventilation, labetalol, sodium nitroprusside 2 days. Dialysis dependent for 5 months. Anti-hypertensive medication maintained. | 4 years later renal function remains abnormal, anti-hypertensive drugs still required. | Woodrow <i>et al</i> 1995; Woodrow & Turney 1999 |
| 19, M | 2 tabs MDMA, rave party | Body temperature normal; frank haematuria, elevated creatine kinase | No specific treatment | Discharged – probably exercise related | Sultana & Byrne 1996 |

Appendix 2

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|---|--|--|--------------------------------|
| 24, M | 2 tabs ecstasy; Collapsed and died at disco. Blood MDEA 0.187 mg/l, amphetamine 0.453mg/l. | Temperature | Forced alkaline diuresis followed by oral water diuresis | Fatal | Milroy <i>et al</i> 1996 |
| 29, M | Autopsy blood MDMA 4.07mg/l, MDA 0.49mg/l, morphine 0.38mg/l, ethanol 0.92g/l, alprazolam 0.1mg/l. | Death in open space | Maximum doses levodopa, pramipexole | Fatal | Lora-Tamayo <i>et al</i> 1997 |
| 30, M | Autopsy blood MDMA 0.98mg/l, morphine 0.15mg/l, ethanol 0.38g/l. | Death in open space with syringe alongside. Acute pulmonary oedema. | | Fatal | Lora-Tamayo <i>et al</i> 1997 |
| 27, M | Autopsy blood MDMA 8mg/l, MDA 1.2mg/l, benzoylccgonine 0.13mg/l, ethanol 0.9g/l, amphetamine 0.18mg/l. | Found dead. Setting not reported. Acute pulmonary oedema, pulmonary haemorrhage. | | Fatal | Lora-Tamayo <i>et al</i> 1997 |
| 19, M | Autopsy blood MDEA 4.32mg/l, MDMA 0.49 mg/l, MDA 0.29mg/l, amphetamine 0.2mg/l, dipyrone 1.36mg/l. | No information. | | Fatal | Lora-Tamayo <i>et al</i> 1997 |
| 21, M | Known pill user. Blood PMA 5.7mg/l. | Dead on arrival at hospital. Visceral shock lesions. | | Fatal | Lora-Tamayo <i>et al</i> 1997 |
| 31, M | Unknown. History psychological problems. Autopsy blood MDEA 3.1mg/l. | Found dead, 3 days after last seen alive. | | Fatal | Tsatsakis <i>et al</i> 1997 |
| 33, M | Quarter tab ecstasy, alcohol; party | Diarrhoea, aches 7 hours after drug use, dark urine 3 days later; elevated creatinine kinase without renal failure | | Discharged after 5 days, Creatine kinase levels near normal 30 days later. | Williams & Unwin 1997 |
| 29, M | History MDMA use | Parkinsonism | | No improvement | Mintzer <i>et al</i> 1999 |

Appendix

Cases of liver damage not involving hyperthermia

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|---|---|--|----------------------------|
| 20, M | 3 months 1-2 tabs ecstasy at weekend; 4 weeks since last use | Acute hepatitis – dark urine for 3 weeks, jaundice for 10 days | Monitoring only | Full recovery at one month | Gorard <i>et al</i> 1992 |
| 29, M | MDMA on 7 occasions; also used psilocybe, cocaine, cannabis | Cholestatic jaundice, peripheral oedema, ascites. | Not reported | Slow recovery over 3 months | Henry <i>et al</i> 1992 |
| 19, M | 1 tab ecstasy, 3 weeks prior. | 2 weeks flu-like illness, diarrhoea, jaundice. AST 1509 U/l, bilirubin 170 mmol/l. | Not reported | Slow recovery (>14 days) | Henry <i>et al</i> 1992 |
| 19, M | MDMA, last dose 1 week prior. | Increasing jaundice, vomiting, confusion. Bilirubin 400 mmol/l. | Liver transplant | Successful | Henry <i>et al</i> 1992 |
| 27, F | MDMA on 3 occasions. | 3 severe episodes relapsing hepatitis, each following MDMA. Bilirubin 400 mmol/l. | Not reported | Recovered | Henry <i>et al</i> 1992 |
| 20, M | 3 month history regular MDMA use; 2 year history LSD, cannabis | Jaundice 2 weeks after last use. AST 2600 U/l, bilirubin 530 mmol/l. | Not reported | Fatal | Henry <i>et al</i> 1992 |
| 20, M | 10 month history MDMA use | Jaundice, tender hepatomegaly. Bilirubin 40 mmol/l. | Not reported | Recovered | Henry <i>et al</i> 1992 |
| 19, M | 3 month history MDMA, increasing to 4 tabs/week | Pruritis, jaundice. AST 659 U/l, bilirubin 181 mmol/l. | Not reported | Slow recovery | Henry <i>et al</i> 1992 |
| 27, F | Past iv drug use. Admitted to ecstasy use after 3rd episode jaundice. | Symptoms 8-15 days after ecstasy use. Unwell, jaundiced, palmar erythema, liver edge palpable. AST 1717 umol/l, bilirubin 471 umol/l. | No specific treatment | Resolved over 3 weeks | Shearman <i>et al</i> 1992 |
| 18, F | Regular use ecstasy, 1-2 tabs at weekends. | Encephalopathy, no hepatomegaly. AST 1025 umol/l, ALT 1390 IU/l, bilirubin 480 umol/l. | Conservative. 2 months hospitalisation. | >50 days for liver function tests to resolve. Recovered. | de Man <i>et al</i> 1993 |

Appendix 3

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|--|--|--|---|-----------------------------|
| 24, F | 4 month history ecstasy, 1 tab/fortnight. | Fatigue, upper abdominal pain, leading to subacute liver failure, encephalopathy grade III, ascites, coagulation disorders. AST 436 IU/l, ALT 540 U/l, bilirubin 445umol/l | Initially conservative. Liver transplant following deterioration. | Discharged from hospital after 16 days. | Ijzermans <i>et al</i> 1993 |
| 18, F | 6 month history 1-2 tabs ecstasy at weekends. | 6 week history fatigue, leading to jaundice, ascites, encephalopathy grade II. ALT 1360 IU/l, AST 1025 IU/l, bilirubin 480umol/l. | Conservative | 2 months in hospital. Complete recovery at 6 months. | Ijzermans <i>et al</i> 1993 |
| 25, F | 2 month history ecstasy at weekends, last use 10 days prior. Alcohol use limited. | 3 week history fatigue, 3 days jaundice. Urine & stools normal. Liver slightly enlarged, tender. Bilirubin 329umol/l, ASAT 529U/l, ALAT 1157 U/l. Acute hepatitis by liver biopsy. | No specific treatment | Improved over 10 days | Oranje <i>et al</i> 1994. |
| 24, M | Drank beer "spiked" with ecstasy 3 days prior. [Insulin-dependent diabetic.] | Jaundiced after 2 days lethargy, anorexia, nausea, vomiting. Peak AST 950 U/l, bilirubin 346umol/l. | Monitoring | Resolved in 1 month | Dykhuizen <i>et al</i> 1995 |
| 22, M | 10-15 units alcohol over weekend; history cannabis & mushroom use; unknown amount ecstasy. | Jaundiced 4 weeks after ecstasy. Liver palpable, not tender. Peak AST 1410 U/l, bilirubin 371umol/l. | Prednisolone, 10 days | Resolved in 3 months | Dykhuizen <i>et al</i> 1995 |
| 23, M | 1 year history 4 tabs ecstasy, 5-10 units alcohol per week. | 1 month history jaundice, malaise, pale stools, dark urine. Jaundiced. AST 639 U/l, bilirubin 75umol/l at admission. Hepatitis by liver biopsy. | No specific treatment | Resolved over 5 weeks | Dykhuizen <i>et al</i> 1995 |
| 22, F | 4 month history ecstasy use, 1 tab/week | 2 episodes of jaundice, pruritis, dark urine, pale stools; 2nd with abdominal swelling, pain. AST (1) 2314 (2) 413 IU/l, ALP (1) 145 IU/l, (2) 253, bilirubin (1) 53 (2) 410 uM. | (1) No specific treatment. (2) Prednisolone (severe hepatic fibrosis). | (1) Resolved. Lost to follow-up. Continued ecstasy use. (2) Liver function improved but extensive fibrosis. | Khakoo <i>et al</i> 1995 |

Appendix 3

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|--|---|---|--|-------------------------------|
| 33, ? | Detail of ecstasy use not reported. | Jaundice. Grade IV encephalopathy. Bilirubin 642 umol/l. | Mechanical ventilation, haemofiltration pre-operatively. Auxiliary liver transplant. | Survived. Full immuno-suppression and functional auxiliary graft after >18 months. | Chenard-Neu <i>et al</i> 1996 |
| 19, ? | Detail of ecstasy use not reported. | Jaundice. Grade IV encephalopathy. Bilirubin 500 umol/l. | Auxiliary liver transplant. | Survived. Full immuno-suppression and functional auxiliary graft after >5 months. | Chenard-Neu <i>et al</i> 1996 |
| 18, F | Regular ecstasy user. | 4 week history jaundice, malaise, pale stools, dark urine. AST (1) 1575 (2) 3160 U/l, bilirubin (1) 277(2) 452 U/l. | Monitored 3 weeks until confusion developed. Paralysis, ventilation, sedation for Grade II encephalopathy. Listed for transplant. | Died before donor organ available. | Ellis <i>et al</i> 1996 |
| 36, F | 1 capsule ecstasy 10 days prior. | 6 day history nausea, lower back pain, vomiting, jaundice. Encephalopathy 10 days later. AST 828 U/l, bilirubin 406umol/l. | Ventilated; liver transplant 15 days after presentation. | Died 25 days after transplant. | Ellis <i>et al</i> 1996 |
| 21, F | 4 month history ecstasy use, up to 5 tabs at weekends. | General malaise, pain with vomiting, pale stools. Pain in right upper quadrant of liver. Stones in gall bladder. AST 760 U/l, bilirubin 44umol/l. | Monitored | AST settled over 2 weeks. Discharged well. | Ellis <i>et al</i> 1996 |
| 22, M | Regular use ecstasy, amphetamine. | 7 day history malaise, nausea, pale stools, dark urine. AST 1191 U/l, bilirubin 311 umol/l. | 10% dextrose to maintain blood sugar, for 3 days. | Recovered. | Ellis <i>et al</i> 1996 |
| 22, F | 6 month history ecstasy use. | 3 week history jaundice, nausea, vomiting. Developed grade II encephalopathy. Bilirubin 343 after 2 weeks. | Auxiliary left partial orthoptic liver transplant. | Died 30 days after transplant. | Ellis <i>et al</i> 1996 |
| 24, F | 2-4 tabs ecstasy over 6 weeks. | 1 week history non-specific illness, jaundice. Grade III encephalopathy. AST 721 U/l, bilirubin 407 umol/l. | Reduced liver graft. | Discharged well after 5 weeks. | Ellis <i>et al</i> 1996 |

Appendix 3

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|---|--|---|-----------------------------------|
| 19, M | 5 month history ecstasy increasing to 4 tabs on 2 nights/week. | Nausea, dark urine, pale stools, jaundice. ALT 745 U/l, bilirubin 131umol/l. | Not reported | Resolved over 6 weeks. Recurrence after further use of ecstasy. | Fidler <i>et al</i> 1996 |
| 18, F | 3 month history ecstasy increasing to 1.5 tabs/week. Last use 2 days prior. | 2 episodes jaundice, dark urine, pale stools. (2) Encephalopathy, fluid retention. ALT (1) 2435 (2) 2000 U/l, bilirubin (1) 96 (2) 201 umol/l. | 1st episode: monitoring only. 2nd episode prednisolone and spironolactone. | Recovered over 3 weeks. Remains well, not using ecstasy. | Fidler <i>et al</i> 1996 |
| 23, M | Regular, heavy ecstasy use, even after onset of jaundice. | Progressive jaundice and liver failure. | Not reported | Fatal. Massive hepatic necrosis at autopsy. | Milroy <i>et al</i> 1996 |
| 18, F | 2 month history ecstasy use at weekends. Last use 2 days prior. | Lethargy, vomiting, abdominal pain, stools discoloured, icterus, dark urine. Bilirubin 263 umol/l, ALT 1530 U/l. Encephalopathy grade IV day 7. | Orthotopic liver transplant | 6 weeks in hospital. Full recovery. | Brauer <i>et al</i> 1997 |
| 18, M | Used ecstasy over several months | Progressing hepatic failure. | Auxiliary liver transplant | Survived. Auxiliary graft removed at 6 weeks. | Cited by Brauer <i>et al</i> 1997 |
| 18, M | 8 month history ecstasy, 1-2 tabs/week. Last use 8 days prior. | Abdominal pain, weight loss, vomiting, jaundice. SGOTO 756U/l, SGPT 1450U/l, GGT 164U/l, bilirubin 7.5mg/dl. | Initially symptomatic. Auxiliary liver transplant after 15 days. Transplant removed at 6 months. | Liver function normal at 11 months | Hellinger <i>et al</i> 1997 |
| 23, F | Detail of ecstasy use not reported | Subacute liver failure, encephalopathy grade I-II. AST 370 U/l, bilirubin 320 mol/l. | Auxiliary partial orthotopic liver transplant | Died 31 days after transplant | Pereira <i>et al</i> 1997 |
| 18, M | 1 month history ecstasy 1 tab/week | Symptoms not reported. Peak ALT 2623 U/l, AST 1755 U/l, bilirubin 21mg/dl. | Not reported | Recovered over 3 months | Andreu <i>et al</i> 1998 |
| 19, M | 1 year history ecstasy use, 1 tab/fortnight | Symptoms not reported. Peak ALT 5282 U/l, AST 4800 U/l, bilirubin 38.9mg/dl. | Not reported | Recovered over 12 months | Andreu <i>et al</i> 1998 |
| 17, M | Ecstasy on 2 occasions | Symptoms not reported. Peak ALT 2870 U/l, AST 2160 U/l, bilirubin 24.7mg/dl. | Not reported | Recovered over 4 months | Andreu <i>et al</i> 1998 |

Appendix 3

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|--|--|--|---|----------------------------|
| 19, M | 2 month history ecstasy 1 tab/week | Symptoms not reported. Peak ALT 3640 U/l, AST 2770 U/l, bilirubin 27mg/dl. | Not reported | Recovered over 8 months. Recurrence after further use of ecstasy. | Andreu <i>et al</i> 1998 |
| 20, M | 6 month history ecstasy 1-2 tabs/week. Last use 15 days prior. | Symptoms not reported. Peak ALT 2918 U/l, AST 2970 U/l, bilirubin 21.9mg/dl. | Not reported | Recovered over 3 months | Andreu <i>et al</i> 1998 |
| 20, F | _ tab ecstasy, 7 days prior. MDMA detected in urine. | Asthenia; icteric skin & sclera; liver enlarged & tender. Liver enzymes elevated. Developed reddish papules over face. | Cholestyramine; fat-reduced diet; metronidazole ointment (for rash). | Resolved over 3 weeks | Wollina <i>et al</i> 1998 |
| 20, M | 1 tab ecstasy | 6 days fatigue, jaundice. Liver enzymes elevated. Developed thrombotic thrombocytopenic purpura. | Prednisolone, plasma exchange | Full recovery at 4 months | Schirren <i>et al</i> 1999 |

Appendix

Psychiatric sequelae

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|--|---|---|---|---|---------------------------------|
| Altered mental state associated with intoxication | | | | | |
| 50, M | 1 tab MDMA, 15mg phenelzine (MAOI). MDMA in urine. [History depression, angina.] | Marked hypertension, diaphoresis, altered mental state, hypertonicity. | Diphenhydramine (ineffective), activated charcoal, magnesium sulphate; supportive care. | All symptoms resolved over 15 hours. | Smilkstein <i>et al</i> 1987 |
| 26, F | 1st use MDMA. 3 year history phenylpropanolamine (non-prescription anorexic). | Nausea, ataxia, vertigo, fear of imminent death, tachycardia, hyperventilation. | Diazepam | Released after 3 hours | Whitaker-Azmitia & Aronson 1989 |
| 25, M | Prior use ecstasy with positive effects | Unnatural fear, spatial disorientation, tachycardia, sweaty palms, difficulty speaking. | None sought | Resolved. No recurrence despite further ecstasy use. | Whitaker-Azmitia & Aronson 1989 |
| 22, F | Used ecstasy with case above | Dysphoria, shortness of breath, fear of being trapped. | None sought | Resolved. No recurrence despite further ecstasy use. | Whitaker-Azmitia & Aronson 1989 |
| 22, M | 4 month history ecstasy 4-7 times a week, prolonged moderate cannabis use. | 3 separate episodes drug-induced psychosis with delusions, bizarre behaviour. | No treatment for 1st or 3rd episodes; trifluoperazine, flupenthixol for 2nd episode. | Symptoms remitted over days each time | Creighton <i>et al</i> 1991 |
| ?, M | Blood MDEA 0.22mg/l, amphetamine 0.75mg/l, alcohol 0.46. | Psychotic state, strange behaviour; locked himself in room, stabbed himself to death. | None | Fatal | Iwersen & Schmoldt 1996 |
| 21, M | 6 month history ecstasy, cannabis on weekends. [No personal or family history psychiatric illness.] | Delirium; creatine kinase elevated | Diazepam, forced diuresis | Psychiatric symptoms remitted at 42 hours. Biochemistry normal at 6 days. | Alciati <i>et al</i> 1999 |
| 21, M | 3 tabs ecstasy; opioid dependent (methadone maintenance); MDMA and cocaine in urine. [Family history of schizophrenia.] | Delirium; elevated creatine kinase | Diazepam | Symptoms remitted over 5 days | Alciati <i>et al</i> 1999 |
| 22, M | 8 month history MDMA, cocaine on weekends. [Family history of paranoid and personality disorder.] | Confused; delusions and hallucinations 30 hours after drug use. | Diazepam | Symptoms remitted over several hours | Alciati <i>et al</i> 1999 |

Appendix 4

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------------------------------------|---|--|--|---|-------------------------------|
| Suicide | | | | | |
| ?, F | History drug abuse, personality disturbance. Frequent reference to ecstasy but urine test inconclusive. [No personal or family history of major psychiatric illness.] | Agitated, distressed; affect labile, mood depressed; rapid speech, mild thought disorder; paranoid delusional beliefs. | Antipsychotic medication (little immediate benefit). | Suicide, day 3 | Ellis & Schimmel 1989 |
| 17, M | 1 tab ecstasy at rave, 1st use. | Depression 3 hours after use, lethargy, agitation, dysphoria after 2 days. | Treatment not sought | Suicide | Cohen 1996 |
| ?, F | Injected ecstasy over 3 day period. | Found stuporous. Arrested. Suicide by hanging whilst in detention, 2 days later. | At autopsy MDMA found in femoral blood (0.58mg/l). | Recorded as suicide | Rohrig & Prouty 1992 |
| 17, M | Took "pills". Blood MDMA 0.23mg/l, methamphetamine 0.35mg/l. | Became agitated, threw himself out of window. | | Fatal | Lora-Tamayo <i>et al</i> 1997 |
| Persistent or chronic sequelae | | | | | |
| 34, M | 2 syringes + half teaspoon MDMA in 48 hours. Being treated for opiate, benzodiazepine dependence. | Agitation, hypertension, 2 days after use. Paranoia, auditory hallucinations 5 days later. | Haloperidol, phenobarbital | Not reported | Hayner & McKinney 1986 |
| 23, M | 1 tab ecstasy on 4 occasions, 2-3 weeks apart | Depression with suicidal ideation, persistent 45 days after last drug use. | Cognitive psychotherapy, S-adenosyl-L-methionine | Gradual improvement | Benazzi & Mazzoli 1991 |
| 22, F | Ecstasy 2 times over 1 week, 1 month prior to presentation. Regular cannabis use. | Episodes of hallucinations, flashbacks, fear, anxiety | Not reported | Not reported | Creighton <i>et al</i> 1991 |
| 17, F | 1 tab ecstasy, party. [Serious assault after party.] | Visual illusions at time of use, episodes of fear and flashbacks subsequent 3 months. | Not reported | Not reported | Creighton <i>et al</i> 1991 |
| 18, F | MDMA 3 times in 2 years. 3rd dose >600mg. [History alcohol & drug use, conduct disorder, major depression.] | 2 days after 3rd use fatigued, depressed mood; panic attacks, persisting for 5 weeks. | None reported | Symptoms gradually decreased over 3 months. | McCann & Ricaurte 1991 |

Appendix 4

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|--|---|--|--|--------------------------|
| 19, M | MDMA weekends 2.5 years. Last use 1.5g MDMA + hallucinogenic mushrooms in 2 days. History cannabis and LSD use, depression. | 8 month history hallucinations, perceptual distortions, poor memory, insomnia, headache, paranoid, anxious. | Amitriptyline unsuccessful. Changed to fluoxetine. | No psychiatric complaints while maintained on fluoxetine. | McCann & Ricaurte 1991 |
| 24, M | 4 year history MDMA use, 100-300mg/dose, 1-14 days between doses. Also cannabis. [No family history psychotic disturbance.] | Assaulted mother. Chronic atypical psychosis. | Fluphenazine decanoate, clothiapine, promazine | Aggression but not mental state improved at 3 months. | Schifano 1991 |
| 23, M | MDMA [no family history of psychiatric conditions]. | Episodes anxiety then intense depression over several weeks; panic disorder. | Lorazepam, haloperidol unsuccessful. Alprazolam provided relief. | "Close to normal" while maintained on medication. | McCann & Ricaurte 1992 |
| 27, M | MDMA 20 times in 10 months. First attack after 2 pints beer, 1 dose MDMA. [No family history of psychiatric illness.] | 2 month history panic attacks plus avoidance behaviours. | Tranlycypamine (monoamine oxidase inhibitor), tapered over 4 months; avoidance of drugs and alcohol. | Symptom free during 6 month follow-up. | Pallanti & Mazzi 1992 |
| 21, M | MDMA 3 times in 6 months. First attack after 2 doses MDMA at party. [No family history psychiatric illness.] | 4 week history panic attacks plus avoidance behaviour. | Fluvoxamine, amitriptyline | Attacks ceased after 3 months, drugs tapered. Symptom-free in 8 month follow-up. | Pallanti & Mazzi 1992 |
| 28, M | Cocaine, ecstasy, every 2 months for 2 years. | 8 week history panic attacks and avoidance behaviours. | Fluvoxamine | Symptoms diminished in 2 months, drug tapered. Remained well 6 month follow-up. | Pallanti & Mazzi 1992 |
| 48, M | 6 occasions ecstasy use | Major depressive disorder, refractory to tricyclic antidepressants, 2 months after ecstasy use. | Amitriptyline, tranlycypromine | Full recovery | Teggin 1992 |
| 17, M | 5 month history MDMA use, 1-2 tabs/week at raves; occasional cannabis. [No personal or family history psychiatric disorder.] | Paranoid psychosis, diagnosed 5 days after last use. | Chorpromazine, 24 hours inpatient, day patient 5 months. | At 5 months symptoms less intrusive. MDMA use stopped. | Keenan <i>et al</i> 1993 |

Appendix 4

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|--|--|---|----------------------------|
| 18, M | _ tab ecstasy 4 times, weekends. 5 month history cannabis use. Undisplaced frontal skull fracture 2 months prior. [Family history psychiatric illness.] | Arrested (disturbed, aggressive) 48 hours after last ecstasy use. Bizarre behaviour, aggressive outbursts, auditory hallucinations, paranoid delusions, disoriented. | Haloperidol, diazepam, carbamazepine had little effect. Changed to clopenthixol acetate. | Gradual resolution over 2 months. Mental state normal at follow-up. | Williams <i>et al</i> 1993 |
| 21, M | 6 month history ecstasy 1-2 times a week and regular cannabis use. | 2 days rapid mood fluctuations, suicidal ideation, grandiose delusions, commencing 12 hours after ingestion of 2 tabs ecstasy. | Chlorpromazine | Gradual improvement over 3 weeks | Cassidy & Ballard 1994 |
| 17, M | 4-5 month history ecstasy 2-3 times a week and regular cannabis. [No personal or family history of psychiatric disorder.] | 3 week history paranoid psychosis and delusional disorder. | Not reported | Not reported | Cassidy & Ballard 1994 |
| 28, M | MDMA at weekends, 18 months, to 20 tabs/night. [History of amphetamine psychosis, family history of schizophrenia.] | Attempted to strangle wife; prominent delusions of infidelity. Diagnosed schizophrenic. | Haloperidol | 2 relapses in 7 months after discharge despite refraining from drugs. | McGuire & Fahy 1994 |
| 22, M | 2 years MDMA use, to 3-4 tabs/night; intermittent use cocaine, LSD, cannabis. [No history of psychosis.] | Paranoid delusions, delusions of bodily change, 2 weeks after last drug use. | Sulpiride partially effective. | Remained an inpatient after 3 months. | McGuire & Fahy 1994 |
| 19, M | MDMA use <1 week. History of 'bad trips' (LSD), visual illusions (cannabis). | Visual illusions, hallucinations, palinopsia, depersonalisation 4 weeks after MDMA. | Fluoxetine | Gradual improvement over 2 years. | McGuire <i>et al</i> 1994 |
| 19, M | 26 week history of MDMA use | Persecutory delusions, auditory hallucinations 14 weeks after ceasing MDMA. | Not reported | Not reported | McGuire <i>et al</i> 1994 |
| 38, M | 1 year history MDMA use. [Family history of depression.] | Depression, morbid jealousy 3 weeks after stopping MDMA. | Limited response to fluoxetine. Changed to amitriptyline. | Improved | McGuire <i>et al</i> 1994 |
| 20, M | 5 months MDMA, 2-5 tabs/day. 5 years occasional cannabis. [Personal history conduct disorder. Family history personality disorder.] | Suicidal intent 1 week after last MDMA. Grandiose and persecutory delusions. | Trifluoperazine. Noncompliant. | Recurrence 2 months later. | McGuire <i>et al</i> 1994 |

Appendix 4

| SUBJECT | DRUG USE | CLINICAL FEATURES | TREATMENT | OUTCOME | REFERENCE |
|---------|---|---|--|--|-----------------------------|
| 18, F | MDMA, 1-2 tabs at weekends, discontinued after 6 months. | 12 month history visual illusions, hallucination, palinopsia, persisting despite cessation MDMA. | No effect from chlorpromazine and dothiepin. Counselling. | Some improvement | McGuire <i>et al</i> 1994 |
| 18, F | 18 week history MDMA use | Panic attacks, visual illusions and flashbacks 4 weeks after last MDMA. | Beta-blockers | Gradual improvement | McGuire <i>et al</i> 1994 |
| 22, F | 3 year history MDMA use. [Family history panic disorder.] | Panic attacks, depersonalisation, derealisation, visual illusions 6 weeks after last MDMA. | Fluoxetine | Resolved after several months | McGuire <i>et al</i> 1994 |
| 24, M | Ecstasy; history LSD use. Delusional episode after use of ecstasy + LSD 1 month prior. [No personal or family psychiatric history.] | 4 day history delusions, bizarre speech and behaviour, commencing immediately after use. | Haloperidol – ceased after 6 doses because of dystonic reaction. | Symptoms improved but persistent ideas of reference at 1 month follow-up | Series <i>et al</i> 1994 |
| 23, F | 2 month history ecstasy, 1-2 tabs at weekends; also cannabis, amphetamines, LSD. [Family history of depression.] | 7 week history persistent depressive symptoms, commencing 4 days after MDMA use. | Lofepamine, psychological measures | Gradual improvement over 2 months | Series <i>et al</i> 1994 |
| 22, F | 6 year history sporadic ecstasy use, plus alcohol, few exposures to cannabis | Persistent depressive episodes | Lorazepam, psychotherapy, cessation ecstasy | Improved | Cohen 1996 |
| 17, M | 1 tab ecstasy (1st use); other drug use denied. | 2 month history memory lapses, depersonalisation, residual paranoia, depression, headache, blurred vision, suicidal ideation. | Sertraline, clonazepam | Held in remission by medication. [Possible temporal lobe epilepsy kindled or exacerbated by MDMA.] | Cohen & Cocores 1997 |
| 26, F | _ tab MDMA, rave; history (not current) cocaine, heroin use. [No family history of seizures or psychiatric disorders.] | Psychotic episode 3 days after MDMA use, possibly subsequent to generalised seizure. | Clozapine; occupational therapy for memory disorder. | Psychotic episode resolved, clozapine tapered. Some memory problems at 9 months. | Spatt <i>et al</i> 1997 |
| 21, M | 5 month history MDMA use; rising to 7 tabs/day. [No personal or family history psychiatric disorders.] | Acute panic attack and subsequent panic disorder. | Alprazolam for acute panic attack. Paroxetine and alprazolam for ongoing panic disorder. | Attacks diminished over 3 months. Paroxetine tapered over 2 months. Symptom-free at 6 month follow-up. | Windhaber <i>et al</i> 1998 |

Glossary of terms and abbreviations

| | |
|----------------------------|---|
| 2CB | 4-bromo-2,5-dimethoxyphenethylamine ("venus", "nexus", "bromo-mescaline") |
| 4-MTA | 4-methylthioamphetamine |
| 5-HIAA | 5-hydroxyindoleacetic acid, a metabolite of serotonin |
| 5-HT | see serotonin |
| 5-hydroxytryptamine | see serotonin |
| AST | aspartate transaminase |
| Ataxia | failure of muscular coordination; irregularity of muscle action |
| ATS | amphetamine-type stimulant |
| Bruxism | grinding of teeth, especially during sleep |
| Dextrorotatory | turning the plane of polarisation, or rays of light, to the right |
| Diaphoresis | perspiration, especially profuse perspiration |
| DIC | disseminated intravascular coagulation |
| DOM | 2,5-dimethoxy-4-methylamphetamine |
| EMCDDA | European Monitoring Centre for Drugs and Drug Dependence (for further information see http://www.emcdda.org) |
| Enantiomer | one of a pair of compounds having a mirror image relationship (see also isomers) |
| Entactogen | an ability to "touch within" (Riedlinger & Riedlinger 1994) |
| F | female |
| GI | gastrointestinal |
| Hallucination | a sense perception (sight, touch, sound, smell, or taste) that has no basis in external stimulation |
| Hallucinogen | an agent that is capable of producing hallucinations |
| Hyperkalaemia | an excess of potassium in the blood |
| Hyperphosphataemia | an excess of phosphates in the blood |
| Hyperthermia | greatly increased body temperature |
| Hypertonicity | having increased muscle tone or tension |
| Hyponatraemia | deficiency of sodium in the blood; salt deficiency |

| | |
|-------------------------|---|
| Hypothermia | low body temperature |
| Isomers | chemical compounds that have the same molecular formula but differ in the way their atoms are linked, or have the same structure but different configurations (see also enantiomer) |
| iv | intravenous |
| Levorotatory | turning the plane of polarisation, or rays of light, to the left |
| LSD | lysergic acid diethylamide |
| M | male |
| MBDB | 3,4-methylenedioxyphenyl-2-butanamine ("methyl-J", "Eden") |
| MDA | 3,4-methylenedioxyamphetamine |
| MDEA | 3,4-methylenedioxyethylamphetamine ("Eve") |
| MDMA | 3,4-methylenedioxymethamphetamine ("Adam", "XTC", "E") |
| mg | milligram |
| ml | millilitre |
| Neurotransmitter | a substance released at the synapse of a neuron that induces activity in susceptible cells |
| Oliguria | diminished urine secretion in relation to fluid intake |
| PMA | paramethoxyamphetamine |
| PMMA | paramethoxymethamphetamine |
| Psychedelic | pertaining to or causing hallucinations, distortions of perception, and, sometimes, psychotic-like behaviour; also, a drug producing such effects |
| Racemic | optically inactive, being composed of equal amounts of dextrorotatory and levorotatory isomers |
| Serotonin | 5-hydroxytryptamine or 5-HT; present in blood, central nervous system and other tissues; stimulates smooth muscle and serves as a central neurotransmitter |
| Tachycardia | abnormally rapid heart rate |
| Trismus | motor disturbance of the trigeminal nerve, especially spasm of the masticatory muscles, with difficulty in opening the mouth |
| ug | microgram |
| UK | United Kingdom |
| UN | United Nations |
| UNDCP | United Nations International Drug Control Programme (for further information see http://www.undcp.org) |
| US or USA | United States of America |

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