Medical Emergencies and Adverse Events in Ecstasy Users
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Introduction and Overview

This chapter summarizes the literature on medical emergencies and adverse events related to MDMA/ecstasy. Published analyses suggest that most ecstasy pills contain MDMA. However, many other drugs have been detected in these pills, and some pills sold as ecstasy do not contain any MDMA. This chapter does not discuss cases involving drugs sold as ecstasy that were determined to contain no MDMA. Because serious adverse events are rare after illicit ecstasy exposure, they are even less likely in clinical settings. Nonetheless, this chapter may be useful for assessing and minimizing the risks of acute toxicity in clinical studies.

In 1999, there were 2,848 emergency department (ED) cases involving ecstasy in the United States. 78% of these cases also involved other drugs, most commonly alcohol. Most ecstasy-related ED cases occurred in young adults (age 18 to 25), as would be expected given the demographics of ecstasy use in the United States. Given the distribution of ecstasy use among young adults, it can be estimated that 2.9 to 3.6 in 10,000 ecstasy exposures in young adults resulted in an ED visit. A survey of 329 Australian ecstasy users suggests that this estimate is realistic. In this Australian survey, the equivalent of at least 11 ED visits in 10,000 ecstasy exposures occurred. Deaths relating to ecstasy use are poorly documented in the US. Gore (1999) estimated that 0.21 ecstasy-related deaths per 10,000 illicit users occurred annually in England from 1995-96 and 0.87 ecstasy-related deaths per 10,000 illicit users occurred annually in Scotland from 1995-97. Of course, the probability of an ED visit or death after ecstasy use is not evenly distributed among users. Possible risk factors for ecstasy-related medical emergencies or fatalities are discussed at a later point.

Serious adverse effects occurring after ecstasy use are documented in case reports in the medical literature. Before discussing these reports, it is worth considering that they may not indicate the true frequency of various adverse events. First, published case reports are probably often more severe than cases that go unpublished. Second, they probably under-represent adverse effects of ecstasy that do not require emergency treatment. Three reports – two from poison control centers and one from an emergency department (ED) – suggest that most ecstasy-related ED visits result from symptoms that are modest in severity. Signs and symptoms of ecstasy intoxication documented in these reports are similar to those of amphetamines.

We have obtained over 205 published case reports of adverse events in ecstasy users. Some of these reports describe severe forms of common side effects of ecstasy (difficulty urinating, dental problems), motor vehicle accidents, and other injuries due to intoxication. When these reports are excluded, 199 case reports remain. The most common categories of diagnosis are hyperthermia-related syndromes (24.6% of cases), psychiatric complications (22.1% of cases), hepatotoxicity (16.1% of cases), and

hyponatremia (9.5% of cases). Other reported problems include cardiovascular and cerebrovascular, neurological, hematological, respiratory (pneumomediastinum and subcutaneous emphysema), ophthalmic, dermatological, teratological, and dental problems.

Ecstasy-related hyperthermia is described in adverse case reports. While most cases of ecstasy-related hyperthermia were known to have occurred in dance settings, some cases involved individuals who were apparently not involved in "risky" behavior (aside from ecstasy ingestion).

There are reports of hepatotoxicity (liver damage) in ecstasy users. Three *in vitro* studies have confirmed that pure MDMA can damage liver cells and one of these studies found that hyperthermia increases vulnerability to this damage. Although the MDMA concentrations used in these studies are high, they could be attained in individuals taking high doses or having impaired MDMA metabolism (due to pharmacological interactions with other drugs or previous liver damage).

Cases of ecstasy-related hyponatremia (low salt levels) have been reported. The pharmacological effects of MDMA appear to place the user at increased risk of hyponatremia. Consumption of large volumes of water that would normally be safe may lead to symptoms of "water intoxication" after ecstasy ingestion.

The possible dose-dependence of ecstasy toxicity is discussed. It is argued that dose is probably a risk factor for toxicity, but that other risk factors (some of them unknown) are important and may mask the significance of dose. Probable risk factors include exercise, dehydration, over-hydration, and hot or humid settings. More frequent use or greater total lifetime dose may be risk factors for psychological problems. While rare, serious ecstasy toxicity cannot be predicted beforehand, and in many specific cases cannot be explained afterwards. Serious adverse reactions or even death can occur after modest amounts of ecstasy in the absence of known risk factors.

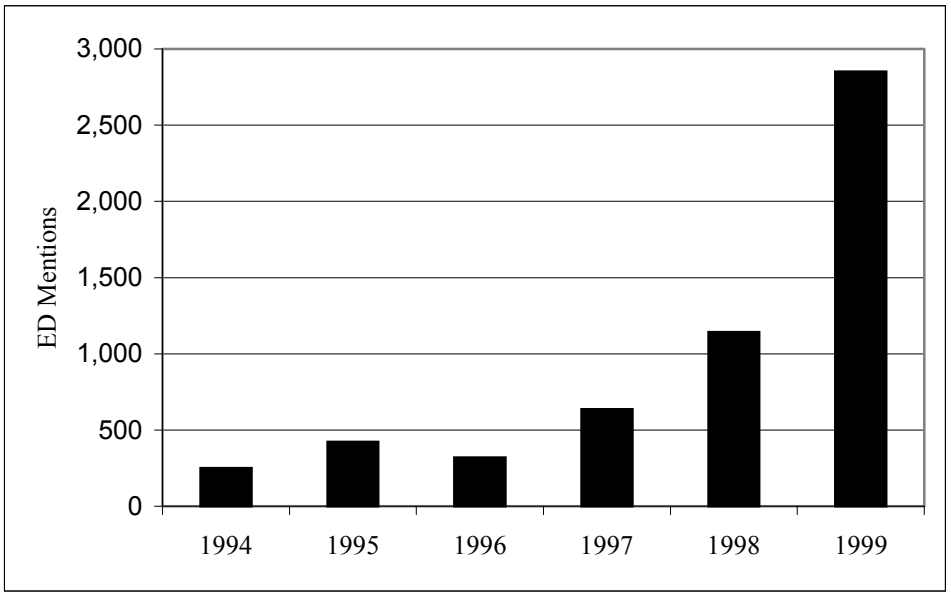
Finally, it is noted that a minority of users can be classified as dependent on ecstasy, using standard criteria.

Emergency Department (ED) Visits After Ecstasy Use

In the United States, the Drug Abuse Warning Network (DAWN) monitors ED cases involving drugs. DAWN produces weighted estimates of drug-related ED cases based on a representative sample of non-Federal, short stay hospitals with 24-hr EDs in the contiguous 48 states. The numbers of ED cases involving ecstasy from 1994 through 1999 are shown in **Figure 6.1**. As can be seen, (statistically significant) increases in cases involving ecstasy have occurred since 1997. Despite these increases, the number of ED cases involving ecstasy in 1999 was significantly lower than those involving either methamphetamine (10,447) or LSD (5,126). 78% of ED cases involving ecstasy also involved other drugs. In 1999, these other drugs included: alcohol (47% of ecstasy cases); marijuana (28%); cocaine (18%); GHB (16%); LSD (11%); methamphetamine

(6%); and ketamine (5%). 80% of cases involved individuals of 25 years or younger. 74% of cases were identified as white/Caucasian.

Figure 6.1: Emergency Department (ED) cases involving MDMA



Source: Office of Applied Services, SAMHSA, DAWN, 1999, (03/2000 update)

Estimating the Frequency of Emergency Department Visits After Ecstasy Use

As described in a previous section, the Monitoring the Future Survey provides annual estimates of the prevalence of ecstasy use among young adults in the United States. Given these data and DAWN estimated ecstasy-related ED cases, it is possible to estimate the frequency with which episodes of ecstasy use result in ED visits. In 1999, 1923 ecstasy ED cases involved individuals of 18-25 years of age, while 347 cases involved younger individuals and 578 involved older adults. The Population Estimates Program of the U.S. Census Bureau states that there were about 26 million individuals age 18-24 in the U.S. in 1999. This suggests that there were almost 30 million 18-25 year-olds in 1999. According to the 1999 Monitoring the Future Survey, 3.6% of adults, ages 19-28, used ecstasy in the last year. Although frequency of ecstasy use is not published in further detail for this group, it is available for 12th grade high school students (see **Table 3.3**). If one assumes that the distribution of annual ecstasy exposures is similar for young adults, then the total number of ecstasy exposures among young adults in 1999 can be estimated. However, there is a need to make assumptions about both novice users and very frequent users. Two estimates are therefore presented. In the low estimate, it is assumed that everyone reporting 1-2 ecstasy exposures in the year only used once and that no individual used more than 40 times in 1999. In the high estimate, it is assumed that individuals reporting 1-2 ecstasy exposures in the year used twice and that no individual used more than 100 times in 1999. It follows that there were approximately 5.4 (low estimate) to 6.7 (high estimate) million episodes of ecstasy use among young adults (ages 18-25) in the United States in 1999. Since there were 1923

ED visits for this age group, this implies that 2.9 to 3.6 in 10,000 ecstasy exposures resulted in an ED visit in 1999.

This estimate is limited by a number of factors. Most importantly, the number of ecstasy-related ED visits reported by DAWN may be over or under-estimated. Toxicology screens vary in their ability to detect MDMA. In a recent survey, approximately 1/3 of 2734 laboratories failed to detect MDMA that was present (Poklis 1999). Second, estimated ecstasy exposures for young adults were derived from patterns reported by 12th graders, and may be inaccurate.

This number must also be interpreted cautiously. First, it is important to recognize that this estimate does not provide a measure of risk for the individual young adult. ED visits are probably not randomly distributed among ecstasy users and some populations are likely at higher risk of adverse event. For example, individuals using higher doses are likely at greater risk of some adverse events. A subsequent section discusses this issue. Second, not all ecstasy-related health problems are treated at an ED. Most obviously, ecstasy-related deaths may not result in ED visits. The use of other health care facilities by ecstasy users is discussed in a following section. Third, the relationship between ecstasy exposures and ED visits reflects the drug use patterns and behaviors of the changing user population as well as the pharmacological characteristics of MDMA. This estimate cannot be seen as a characteristic of the drug in general.

Table 6.1. Relationship Between Ecstasy Exposures and ED Visits in 329 Users

Users		No. of days used in 6 mo.			Possible episodes of ecstasy use in 6 mo.		
		Minimum		Maximum	Minimum		Maximum
37% of 329 =	1	*1*	*to*	*1*	1	to	1
	120	1	*to*	*6*	120	to	720
33% of 329 =	108	*7*	*to*	*12*	756	to	1296
19% of 329 =	62	*13*	*to*	*24*	806	to	1488
12% of 329 =	37	*25*	*to*	*100*	925	to	3700
	1	*100*	*to*	*100*	100	to	100
Total users: *329*			**Total episodes:**		2708		7305
			Minimum no. of ED visits:		*8*		*8*
Minimum rate of ED visits per 10, 000 episodes:					29.5	*to*	11.0

Data taken from Topp et al. 1999. Italicized numbers were directly stated by the authors. Unitalicized numbers show the range of possibilities. It is assumed that each day on which ecstasy was used is a separate episode of use.

This estimate can be compared to the results of a survey of 329 polydrug-using ecstasy users in Australia (Topp et al. 1999). In the survey, users were recruited through

"snowball' sampling and were required to have used ecstasy at least three times in the last 12 months and at least once in the last 6 months. Thus, novice or very infrequent ecstasy users were excluded, in contrast to the nationwide U.S. data relied on for the above estimate. The researchers found that 8 of 329 users had presented to an ED with an ecstasy-related problem in the previous 6 months. Given the data in this report, it can be calculated (see **Table 6.1**) that there were at most 7305 episodes of ecstasy use by these users in this period. Because there were at least 8 ED visits in this time, we can conclude that there were the equivalent of at least 11 ED visits per 10,000 episodes of ecstasy use in this population.

Thus, data from these Australian ecstasy users suggest that the previous estimate of 2.9 to 3.6 ED visits in 10,000 ecstasy exposures is realistic, perhaps even low. There are insufficient data to determine to what extent differences between these estimates are due to the comparison of Australian and U.S. ecstasy users, exclusion of novice and infrequent users from the Australian sample, or the inherent inaccuracy in the estimates.

What Types of Adverse Events Are Most Common?

The adverse case report literature provides data on the range of adverse events in ecstasy users but it does not indicate the true frequency of these events since published case reports over-represent "interesting" or unusual cases. The distribution of different types of acute adverse events after ecstasy use is better estimated by counting consecutive cases from emergency departments (ED) or phone calls to poison control centers. **Table 6.2** summarizes signs and symptoms from a series of 48 ecstasy-related cases presenting in an ED (Williams et al. 1998b). As can be seen, the most common complaints were: feeling strange/unwell/dizzy/weak (31.2% of users); collapse/loss of consciousness (22.9%); and panic/anxiety/restlessness (18.8%). High temperature (defined as >37.1° C) was documented in 18.8% of cases. Dehydration occurred in 4.2%. Management of these ecstasy-related ED cases varied:

> After an initial assessment, 41 (85.4%) cases had an electrocardiogram or continuous cardiac monitoring. In 30 cases (62.5%) the patient received a further period of observation and monitoring (mean 9 hours, range 1-12 hours) in the A&E department. Fifteen cases (31.3%) received fluids (oral eight/intravenous seven) while six (12.5%) had some form of medication administered (diazepam, two, and one each naloxone, activated charcoal, metoclopramide, and antibiotics/paracetamol). Advice/reassurance was recorded as having been given in 14 (29.%) cases. Full resuscitation and intubation were required in one case.

Of these 48 cases, seven required hospital admission, while most were discharged after a period of observation in the ED.

Table 6.2: Features of 48 Sequential Ecstasy-related ED Visits

Clinical features associated with ecstasy only (n=16)			
Complaint/symptom	*No (%)*	*Clinical findings/sign*	*No (%)*
Strange/unwell/dizzy/weak	7 (43.8)	High pulse rate (>100 beats/min)	13 (81.3)
Collapsed/loss of consciousness	1 (6.3)	Dilated pupils	6 (37.5)
Nausea or vomiting	5 (31.3)	Hyperventilation (>20 breaths/min)	6 (37.5)
Panic/anxiety/restlessness	5 (31.3)	Anxiety/agitation/disturbed behavior	4 (25.0)
Palpitations	6 (37.5)	High temperature (>37.1^{o}C)	5 (31.5)
Hot/cold (feeling feverish/shivering)	4 (25.0)	High blood pressure (> 160/95 mm Hg)	0
Sweating	3 (18.8)	Drowsiness	0
Shaking	2 (12.5)	Dehydration	1 (6.3)
Headache	2 (12.5)	Shivering	1 (6.3)
Chest pain	1 (6.3)	Seizure	0
Difficulty breathing	2 (12.5)	Nystagmus	2 (12.5)
Abdominal pain	3 (18.8)	Hallucinating	0
Muscle aches/pains	1 (6.3)	Sweating	1 (6.3)
Visual disturbance	2 (12.5)	Unconscious	0
Thirst	2 (12.5)	Tremulousness	0
Seizure	0	No abnormality found	0
Twitching	0	Other	3 (18.8)
Other	4 (25.0)		

Clinical features associated with ecstasy and other drugs and/or alcohol (n=32)			
Complaint/symptom	*No (%)*	*Clinical findings/sign*	*No (%)*
Strange/unwell/dizzy/weak	8 (25.0)	High pulse rate (>100 beats/min)	19 (59.4)
Collapsed/loss of consciousness	10 (31.1)	Dilated pupils	12 (37.5)
Nausea or vomiting	6 (18.8)	Hyperventilation (>20 breaths/min)	4 (12.5)
Panic/anxiety/restlessness	4 (12.5)	Anxiety/agitation/disturbed behavior	6 (18.8)
Palpitations	6 (18.8)	High temperature (>37.1^{o}C)	4 (12.5)
Hot/cold (feeling feverish/shivering)	3 (9.4)	High blood pressure (> 160/95 mm Hg)	6 (18.8)
Sweating	3 (9.4)	Drowsiness	3 (9.4)
Shaking	4 (12.5)	Dehydration	1 (3.1)
Headache	4 (12.5)	Shivering	1 (3.1)
Chest pain	3 (9.4)	Seizure	2 (6.3)
Difficulty breathing	2 (6.3)	Nystagmus	0
Abdominal pain	1 (3.1)	Hallucinating	1 (3.1)
Muscle aches/pains	3 (9.4)	Sweating	0
Visual disturbance	1 (3.1)	Unconscious	1 (3.1)
Thirst	1 (3.1)	Tremulousness	1 (3.1)
Seizure	3 (9.4)	No abnormality found	3 (9.4)
Twitching	1 (3.1)	Other	6 (18.8)
Other	3 (9.4)	Missing data	1 (3.1)

Table reproduced from (Williams et al. 1998b)

Two publications have described ecstasy-related calls to a poison control center. The earlier report describes 37 consecutive ecstasy-related calls to the National Poisons Information Centre in Ireland from January 1991 to June 1992 (Cregg and Tracey 1993). Symptoms were described as relatively mild in most cases, although 1 death due to ecstasy-related congestive heart failure in a 17-year-old male was recorded. Serious signs and symptoms included coma (5.4% of cases), hypokalaemia (2.7%), convulsions (2.7%), and cardiorespiratory arrest (2.7%). In a retrospective survey of 191 ecstasy-related calls handled by the New York City Poison Control Center from 1993-1999 (Rella et al. 2000), 73% of calls involved minor or no toxicity. Of the 27% (52/191) of calls involving moderate to major toxicity, 7 patients were hyperthermic (one died) and three had electrolyte abnormalities, including hyponatremia.

These three reports suggest that most acute adverse events involving ecstasy are modest in severity. Aside from typical MDMA effects (such as dilated pupils, hypertension, tachycardia, and excitement), symptoms and signs of ecstasy toxicity are varied. From these reports, no single mechanism or syndrome seems obviously responsible for the majority of ecstasy-related ED visits. From these reports, signs and symptoms of ecstasy toxicity appear fairly similar to those reported from amphetamines (Chan et al. 1994; Derlet et al. 1989; Richards et al. 1999). One exception to this may be hyponatremia, which is relatively common in ecstasy users but does not appear to be associated with other amphetamines. There are limitations to using EDs and poison control centers as sources of information. Both types of facilities likely also treat more acute, rather than chronic, problems. Therefore it is important to consider use of other types of health care facilities by ecstasy users.

Use of Other Health Care Services by Ecstasy Users

Ecstasy users are likely to use health care services other than EDs for some ecstasy-related problems. In particular, ecstasy-related problems that are chronic in nature and are not life-threatening are likely to be treated at other facilities. The incidence of these chronic problems is difficult to assess. In the survey of 329 Australian polydrug-using ecstasy users, 22% had received formal assistance for an ecstasy-related health problem, although other drugs were also involved in most (58%) of these cases (Topp et al. 1999). When only those problems which were considered ecstasy-related are included, the percentages of users in this survey accessing non-emergency health care services were: 8.8% for a general practitioner, 3.3% for a ‘natural therapist’, and 1.5% for a psychiatrist. Thus, this survey suggests that a substantial minority of ecstasy users seek health care for ecstasy-related problems.

Although the specific reasons for seeking health care are not given, the incidence of various potentially ecstasy-related problems is given for the overall sample in this study. Significant minorities of users reported symptoms lasting beyond the short-term recovery period such as weight loss (17.3% of users), depression (24.3%), irritability (20.4%), energy loss (19.4%), difficulty sleeping (16.1%), anxiety (14.0%), and dental problems (12.2%). Of course, it cannot be conclusively established that these symptoms were caused by ecstasy use. The individuals in this survey also may not be representative of

ecstasy users in general. In addition to seeking relief from possible ecstasy effects, users may have also sought formal health care for assistance in decreasing ecstasy use. 25% of users in this survey wanted to reduce their ecstasy use. Ecstasy dependence is discussed in a subsequent section.

Deaths After Ecstasy Use

There are few available data on MDMA-related deaths in the United States. DAWN collects data on drug-related deaths from medical examiners in large metropolitan areas. However, participation in this program is voluntary and is not based on a statistical sampling. Furthermore, for comparing data across years, DAWN only includes reports from medical examiners who provided data for at least 10 months in every relevant year. Therefore, DAWN counts of MDMA-related deaths do not represent the U.S. as a whole, merely a consistent but unrepresentative subset. DAWN recently reported that 27 deaths involving MDMA occurred between 1994 and 1998 (DAWN 3/2000 update). MDMA-related deaths ranged from 1 in 1994 to 9 in 1998, with no apparent trend in numbers after 1995 when 6 deaths were reported. These numbers may be useful for illustrating potential trends, but are clearly not comprehensive.

Table 6.3: Estimated Annual Ecstasy-related Death Rate in England and Scotland

	Scotland	England
Number of ecstasy-related deaths		
Total in 1995-97 for Scotland, and in 1995-96 for England	11	18
Annual	3.7	9.0
Population (age 15-24)	600×10^3	6000×10^3
Number of ecstasy users (age 15-24) in 1996		
Total	42×10^3	420×10^3
Regular users	18×10^3	180×10^3
Sporadic users	24×10^3	240×10^3
First-time users (estimate A)	7×10^3	70×10^3
First-time users (estimate B)	12.8×10^3	128×10^3
Annual ecstasy-related death rate per 10,000 users		
All users	0.87	0.21
Sporadic users	1.54	0.38
First-time users (estimate A)	5.29	1.29
First-time users (estimate B)	2.89	0.70

Table adapted from Gore, 1999.
Estimate A assumes the number of new first-time users was constant each year. Estimate B assumes that number increased.

Because reliable data are not available on ecstasy/MDMA-related deaths, it is not possible to estimate the death rate of ecstasy users in the U.S. There are apparently more complete data available on ecstasy-related deaths in Scotland and England. By 1996, at least 53 ecstasy-related deaths had occurred in the U.K. (anonymous 1996). One publication (Gore 1999) has ventured estimates of death rates in young ecstasy users in Scotland and England. These estimates are reproduced in **Table 6.3**. It must be cautioned that, as always, estimated ecstasy-related deaths may over or under-estimate actual MDMA-related deaths. Letters responding to the calculation by Gore have pointed

out difficulties in such estimates, including the varying and unknown contents of illicit ecstasy pills (Lind et al. 1999; Ramsey et al. 1999).

Hyperthermia

The most commonly reported category of ecstasy-related adverse event involved hyperthermia (overheating). Any case in which body temperature equaled or exceeded 38º C or was stated as involving hyperthermia was classified in this category. Hyperthermia occurred in 25.1% (50/199) of the cases identified in the literature. The presence of MDMA was confirmed in the majority of these cases (70.0%). Of the 50 cases involving hyperthermia in the ecstasy literature, 62.0% (31/50) occurred in a dance or party setting. Hyperthermia occurred in other settings in 14% (7/50) of cases. Location was unknown in 24% (12/50) of cases. This section will discuss possible mechanisms and risk factors for ecstasy-related hyperthermia, including dose-dependant drug effects, setting of use, and user behaviors. Three rare, potentially relevant, drug-induced hyperthermic syndromes will be discussed. Finally, symptoms that can be caused by sustained hyperthermia, such as rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation, will be mentioned.

Hyperthermia in the presence of neurologic disturbance, such as delirium, stupor, or convulsions, has high risk of mortality or lasting morbidity. Mortality rates from heat stroke vary from 30-80%, depending on the maximum temperature reached, the durations of hyperthermia and unconsciousness, and the health of the individual. Mortality occurred in 42.0% (21/50) of cases of ecstasy-related hyperthermia. Of the 49 cases where body temperature is available in the literature, individuals who recovered from ecstasy-related hyperthermia tended to have lower body temperature than fatalities. Initially recorded body temperatures were 41.1° ± 1.8° C in fatalities versus 40.3° ± 1.5° C in survivors. However, this difference is not statistically significant, partially because data are skewed by case reports describing unusually high body temperatures in survivors (Logan et al. 1993; Mallick and Bodenham 1997).

Many cases of ecstasy-related hyperthermia are likely the result of an interaction of drug effects, setting of use, and user behavior. In rodent studies, MDMA has been shown to dose-dependently impair thermoregulation, leading to hyperthermia in most settings (Broening et al. 1995; Colado et al. 1995; Dafters 1994; 1995; Daws et al. 2000; Gordon et al. 1991). Drug-induced vasoconstriction likely plays a role in hyperthermia by slowing heat loss from the body (Fitzgerald and Reid 1994; Gordon et al. 1991). High ambient temperatures (as can be sometimes found at dance events) and exercise can be expected to increase body temperature. Ambient temperature has been linked to risk of death in overdose from other stimulants. A retrospective review of cocaine overdoses in New York City analyzed the maximum daily temperature and the number of unintentional cocaine overdoses over a three-year period. It found a threshold peak temperature of about 31.1° C (88° F) above which daily deaths from cocaine overdose increased dramatically (Marzuk et al. 1998). A number of studies of athletes and amphetamines suggest that these drugs can prolong ability to exercise, possibly by delaying fatigue or masking pain (Clarkson and Thompson 1997). MDMA may also

increase desire or ability to exercise beyond one's normal limits. MDMA has been shown to decrease fluid consumption when fluid-deprived animals are given access to water (Dafters 1995) or sweetened ethanol solution (Bilsky et al. 1990). Thus, MDMA intoxication may mask thirst, preventing dehydrated individuals from rehydrating. Dehydration impairs sweating and therefore cooling. In a rat study, dehydration increased MDMA-induced hyperthermia (Dafters 1995).

However, it does not appear that ecstasy-related hyperthermia can be entirely attributed to warm settings, dance, and dehydration. 14.0% (7/50) of cases of ecstasy-related hyperthermia described in the literature occurred in settings other than dances or parties. These other settings included homes (5 cases), pubs (1 case), and jail (1 case). Dehydration is also not necessary for hyperthermia. In the 48 ecstasy-related ED cases summarized by Williams et al. (1998), high temperature was reported in 18.8% of cases, while dehydration occurred in only 4.2%.

A number of case reports describe hyperthermic syndromes that rapidly developed after ecstasy ingestion in individuals who were apparently not exercising (Brown and Osterloh 1987; Demirkiran et al. 1996; Henry et al. 1992). In one case, blood concentration of MDMA was very high (6.5 mg/L), suggesting impaired MDMA metabolism or overdose, despite the modest estimated dose of 100-150 mg MDMA (Brown and Osterloh 1987). In another case, adverse symptoms began within 15 minutes of drug ingestion and resembled neuroleptic malignant syndrome (Demirkiran et al. 1996). Although MDMA was not specifically identified in biofluids, it was detected in another tablet reportedly from the same batch consumed by the patient. These cases suggest that ecstasy hyperthermia may sometimes be one of several rare drug-induced hyperthermic syndromes. These syndromes are all described below.

Malignant Hyperthermia (MH). Malignant hyperthermia is a hypermetabolic state that is due to one of several inherited muscle-cell membrane disorders. MH has varied clinical presentation including rhabdomyolysis, muscle pain, and markedly elevated core temperature. When triggered in a clinical setting by anesthetics, signs of MH include tachycardia, dysrhythmia, cyanosis, generalized muscle rigidity, and (of course) hyperthermia. In addition to anesthetics, other possible triggers of MH are exercise in heat, infections, and neuroleptic drugs. MH is triggered by a rapid and sustained increase in myoplasmic Ca^{2+}. Ca^{2+} is stored in the sarcoplasmic reticulum and released in a process controlled by at least three structural proteins. The amount of released Ca^{2+} controls the strength of skeletal muscle contraction. In MH, regulation of Ca^{2+} fails and sustained increases in free Ca^{2+} lead to muscle tension and heat production. Testing for susceptibility to MH involves taking muscle fibers from the thigh by biopsy and measuring their response to halothane and, separately, caffeine. Although several gene mutations have been associated with MH, others have yet to be discovered. It is therefore not possible to screen for MH susceptibility by DNA testing. Treatment of MH typically involves ice, fans, cooling blankets, and dantrolene (a drug that decreases heat production by relaxing muscles through blocking myoplasmic Ca^{2+} release).

Serotonin Syndrome. Serotonin syndrome is a potentially fatal toxic syndrome that is thought to result from excessive 5HT release with common symptoms including restlessness, confusion, myoclonus, hypereflexia, hyperthermia, sweating, shivering, tremor, and diarrhea. In animal studies, increased extracellular 5HT does not necessarily lead to serotonin syndrome, suggesting other neurotransmitters may be involved. $5HT_{1A}$ and, to a lesser extent, $5HT_2$ receptors are thought to mediate many symptoms of serotonin syndrome since drugs acting as antagonists at these receptors decrease these effects in animals. It has also been suggested that serotonin syndrome may be due to 5HT release inhibiting DA release, leading to NMS, although this hypothesis has not been confirmed. Serotonin syndrome occurs most commonly when two agents that increase serotonin levels by different mechanisms are taken together. For example, simultaneous administration of a monoamine oxidase inhibitor and L-tryptophan has led to serotonin syndrome in many cases. Less often, a high dose of a single serotonergic agent may also cause serotonin syndrome. Treatment of serotonin syndrome is primarily supportive. Although animal studies suggest that nonspecific 5HT antagonists or propranolol (a ß-andrenergic blocker that is also a $5HT_{1A}$ antagonist) may be useful, results have been mixed in humans.

Neuroleptic Malignant Syndrome (NMS). NMS is a very rare potentially fatal extrapyramidal syndrome associated with muscle ("lead pipe") rigidity, autonomic dysfunction, and altered mental state. NMS typically develops when a drug blocks dopamine receptors or decreases extracellular dopamine levels. Decreased dopaminergic levels in the striatum causes muscle tension, which, along with altered hypothalamic functions, leads to hyperthermia. Most commonly, NMS occurs during the administration of neuroleptics. In addition to dose-related variables, risk factors for developing NMS are thought to include high ambient temperature, dehydration, and agitation. Treatment of NMS involves dopamine agonists such as bromocriptine or apomorphine.

There is not sufficient evidence to establish whether cases of ecstasy-related hyperthermia are sometimes one of these three drug-induced hyperthermic syndromes. There is overlap in the symptoms of these syndromes and correct diagnosis ultimately relies on understanding the cause of the syndrome, which remains unknown in cases involving ecstasy. Based on the pharmacology of MDMA, which includes increased synthesis and release of dopamine, serotonin syndrome seems more likely than NMS. Demirkiran et al. (1996) discuss this issue and conclude that ecstasy-related hyperthermia is more likely serotonin syndrome than NMS. Among other considerations, serotonin syndrome has a more rapid onset after drug administration than NMS, which often occurs in clinical practice 3 to 9 days after a patient's medication is changed. Testing for malignant hyperthermia proved negative in a case of MDE-related hyperthermia (Tehan et al. 1993).

On the other hand, two reports analyzing muscle changes in ecstasy users presenting with hyperthermia have drawn conflicting conclusions. One report describes an ecstasy user presenting with pain and swelling in the left buttock, oliguria, and elevated CK. The authors conclude that the microscopic muscle changes in this user were characteristic of

NMS (Behan et al. 2000). However, it is not clear why NMS should lead to localized muscle swelling, since muscle contractions are due to CNS abnormalities. Another report described muscle changes in three deceased hyperthermic MDMA or MDE users that were considered typical of malignant hyperthermia (Fineschi et al. 1999). In these individuals, immunohistochemistry revealed hypercontracted fibers with disruption of cell architecture. Given the divergent conclusions is these two reports, it does not appear that hyperthermic syndromes can be diagnosed by microscopic muscle changes. Finally, an *in vitro* study found that MDMA potentiated halothane- or caffeine-induced muscle contractions (Denborough and Hopkinson 1997). However, the concentrations of MDMA (2 mM) used were very high and of questionable physiological relevance (Hall 1997a). Overall, it remains unclear whether some cases of ecstasy-related hyperthermia are due to serotonin syndrome, NMS, or malignant hyperthermia. It is possible, perhaps even likely, that fulminant ecstasy-related hyperthermia has different causes in different individuals.

Treatment of ecstasy-related hyperthermia is discussed in several publications (Dar and McBrien 1996; Henry 2000; MacConnachie 1997; Rochester and Kirchner 1999; Walubo and Seger 1999). This typically involves supportive measures and facilitation of cooling with fans, ice, etc. Intravenous saline solution is used to correct hypovolemia, which often corrects tachycardia and hypotension. Anticonvulsants, such as diazepam, are sometimes required. The use of dantrolene is controversial and it is not clear if it is effective (Hall 1997a; Singarajah and Lavies 1992; Stone 1993; Tehan 1993; Watson et al. 1993; Webb and Williams 1993).

Sustained hyperthermia can lead to multiple organ and system failure. In adverse case reports, hyperthermic ecstasy users commonly present with or develop tachycardia, hypotension, rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation (DIC). These last three syndromes are discussed below.

Rhabdomyolysis. Rhabdomyolysis is a clinical syndrome resulting from muscle degeneration and the release of muscle proteins into the extracellular fluid. In ecstasy users, muscle degeneration is probably most often due to sustained hyperthermia or prolonged exercise but can also be caused by muscle compression in an unconscious individual. Rhabdomyolysis was reported in 38.0% (19/50) of hyperthermic ecstasy users. In addition, rhabdomyolysis was identified in three users who were not known to have been hyperthermic (Bertram et al. 1999; Sultana and Byrne 1996; Williams and Unwin 1997), although hyperthermia may have occurred before these individuals received medical assistance. Mortality occurred in 36.4% (8/22) of cases of ecstasy-related rhabdomyolysis. Possible risk factors for rhabdomyolysis in methamphetamine users are discussed by Richards et al. (1999) and include hyperthermia, decreased nutrition, dehydration, exhaustive physical exercise, tobacco smoking, and alcoholism. These may also be risk factors in ecstasy users. Symptoms of rhabdomyolysis include muscle pain, weakness, and brown ("Coca-Cola" colored) urine. The release of damaged muscle contents can lead to potentially fatal electrolyte imbalance, acute renal failure, and disseminated intravascular coagulation. Rhabdomyolysis was associated with acute

renal failure in 50.0% (11/22), and with disseminated intravascular coagulation in 63.6% (14/22), of published cases.

Acute Renal Failure (ARF). Acute renal failure can occur when myoglobin that was released from damaged muscles precipitates and blocks renal tubules. Dehydration facilitates the development of ARF. ARF leads to an accumulation of metabolic waste products, damaging tissues and impairing organ functioning. ARF occurred in 24.0% (12/50) of cases of ecstasy-related hyperthermia. ARF also occurred in one case in which there was rhabdomyolysis but no evidence of hyperthermia (Bertram et al. 1999). Chronic renal failure led to death in one ecstasy user who was treated too late to detect possible hyperthermia (Bingham et al. 1998). Treatment of ARF in ecstasy users is discussed by Cunningham (1997).

Disseminated intravascular coagulation (DIC). DIC is a systemic blood coagulation disorder involving the generation of intravascular fibrin and the consumption of procoagulants and platelets. In DIC, endothelial or tissue injury leads to release of procoagulant cytokines and tissue factors. When these factors are exhausted, coagulation is no longer possible and generalized bleeding occurs. Acute DIC is characterized by generalized bleeding, which leads to hypoperfusion, infarction, and end-organ damage. Fever and a shock–like syndrome with tachycardia and hypotension may occur. Symptoms of DIC include bleeding nose or gums, cough, shortness of breath or difficulty breathing, confusion, and fever. DIC occurred in 50.0% (25/50) of cases of ecstasy-related hyperthermia. Mortality occurred in 60.0% (15/25) of cases of ecstasy-related DIC.

Psychiatric Problems in Ecstasy Users

Psychiatric problems were reported in 22.1% (44/199) of case reports. The presence of MDMA was confirmed in only a minority of psychiatric case reports (9.1%, 4/44), generally due to the elapsed time between last ecstasy exposure and psychiatric assessment. For purposes of analysis, psychiatric problems in ecstasy users may be categorized into psychotic and affective symptoms (such as panic, anxiety, or depressed mood). However, not all case reports can be easily categorized as cases mood or anxiety disorders or psychosis because some cases have atypical symptoms. In addition, cases in which symptoms were absent until after ecstasy use could be reasonably classified as organic mental disorders.

Interpreting the role of MDMA in case reports of psychiatric problems in ecstasy users is difficult. When psychiatric complications occur in ecstasy users, it is impossible to determine whether ecstasy use nonspecifically triggered the onset of psychiatric complications in vulnerable individuals in whom problems could have been triggered by other stressors. Alternatively, certain patterns of ecstasy exposure could cause psychiatric complications in healthy individuals with no other risk factors. Finally, early symptoms of an undiagnosed psychiatric disorder could lead individuals to use ecstasy. It is impossible to fully separate the relative contributions of individual vulnerability and drug exposure in most case reports.

Given repeatedly, other amphetamines are able to cause psychotic symptoms or frank psychosis in volunteers who have been screened for pre-existing psychotic disorders (Angrist 1994). The symptoms of stimulant psychosis typically disappear or greatly diminish with withdrawal from drug use, but are likely to re-occur if drug use is reinitiated. MDMA may cause acute psychotic symptoms in some cases. In rodents, some patterns of MDMA administration cause behavioral sensitization, which is considered to be an animal model of stimulant psychosis (Kalivas et al. 1998; Spanos and Yamamoto 1989).

Psychotic symptoms were the most commonly reported psychiatric complication in the literature, occurring in 66.0% (29/44) of cases. Psychotic symptoms commonly included delusions of persecution, ideas of reference, depersonalization, and derealization. Most cases (79.3%, 23/29) with psychotic symptoms occurred in "regular" or "experienced" users, and only 2 cases were known to involve new users. In 48.3% (14/29) of cases with psychotic symptoms, a personal and/or family history of psychiatric problems was documented. Outcome has generally been poor in cases of psychotic symptoms in ecstasy users. In 34.5% (10/29), full recovery was reported. In 20.7% (6/29), symptoms were only partially controlled or the patient was known to have relapsed. No improvement was evident in 17.2% (5/29). Outcome was not stated in 27.6% (8/29) of cases. History of psychiatric illness did not appear to predict outcome. While 50% of those fully recovering had known personal and/or family history of psychiatric illness, none of the 5 cases without improvement had any known history.

In a few cases, psychotic symptoms resembled those of stimulant psychosis. Stimulant psychosis is typically a paranoid psychosis with ideas of reference, delusions of persecution, and auditory and visual hallucinations, in a setting of clear consciousness, although atypical symptoms (such as clouding of consciousness) may occur. For example, Alciati et al. described three cases of delirium in ecstasy users concurrently using ecstasy and cocaine that resolved within five days (Alciati et al. 1999). These could be regarded as cases of atypical stimulant psychosis.

Many cases with psychotic symptoms were not typical of stimulant psychosis. Persisting symptoms after drug discontinuation are not expected in stimulant psychosis. Full recovery was only reported in 34.5% of ecstasy users with psychotic symptoms. McGuire et al. (1994) compared 8 ecstasy users with psychosis to 40 substance naïve psychotic patients. While ecstasy users reported less depression than other patients, this difference was no longer significant after correction for multiple comparisons. In other reports, patients had atypical symptoms. One research group has reported an association between chocolate craving and psychotic symptoms in ecstasy users. In a series of 50 ecstasy users presenting at an addiction treatment unit, chocolate craving was found in 7 of 16 patients with psychopathology (Schifano and Magni 1994). All 7 of these patients, who had psychotic symptoms, reportedly developed chocolate craving after beginning ecstasy use.

In 2 ecstasy users (cases 3 and 11 from McGuire et al., 1994), symptoms more closely

resembled post-hallucinogen persisting perceptual disorder than atypical psychosis. In these cases, patients had full preservation of insight and reported persisting (rather than episodic) hallucinations and illusions. For example, an 18-year-old female who was reportedly a regular ecstasy user experienced persisting visual illusions and hallucinations (McGuire et al. 1994). Brain MRI was normal, and no neurological or opthalmological signs were noted. While chlorpromazine and dothiepin were ineffective, counseling resulted in some improvement.

Affective symptoms were reported in 54.5% (24/44) of psychiatric case reports. The most common affective symptoms were anxiety disorders, which occurred in 40.9% (18/44) of these cases. While anxiety – usually acute panic response or chronic panic disorder – was the sole diagnosis in 38.9% (7/18) of cases, it sometimes occurred in cases with psychotic symptoms (38.9%, 7/18) or depression (16.7 %, 3/18). In some cases, an acute panic attack during ecstasy intoxication rapidly resolved (Whitaker-Azmitia and Aronson 1989). For example, a 25-year-old male with 6 previous ecstasy exposures had a panic attack approximately 30 minutes after ecstasy ingestion while riding on a subway. He experienced "unnatural fear", spatial disorientation, need to escape, tachycardia, sweaty palms, tenseness, hypervigilance, ideas of reference, and difficulty speaking. After recovery, he reportedly used ecstasy without further problems. Persisting anxiety or panic attacks after ecstasy intoxication occurred in several cases (McCann and Ricaurte 1992). For example, a 21-year-old male had panic attacks for 1 mo after consuming 6 ecstasy tablets. He was successfully treated with paroxetine and counseling (Windhaber et al. 1998). Outcome is generally good in cases of pure anxiety disorders in ecstasy users. Full recovery was reported in 6 of 7 cases, and the outcome was not reported in the remaining case.

Depression was diagnosed in 18.2% (8/44) cases with psychiatric symptoms, and a larger number of cases had symptoms of depression but were not diagnosed with it. For example, a 17-year-old male became acutely depressed, agitated, and confused during what was thought to be his first ecstasy exposure, and committed suicide two days later (Cohen 1996). Because this individual was not examined by a clinician, diagnosis cannot be made. Two ecstasy users with depression had psychotic symptoms (case 5 in McGuire et al., 1994, and case 5 in Schifano and Magni, 1994) and 3 had anxiety disorders (case 1 in McCann and Ricaurte, 1991, and cases 2 and 7 in Schifano and Magni, 1994). Full recovery was reported in 2 cases, and partial recovery in 3 cases. Outcome was not available in 2 cases. The case with no improvement was complicated by atypical psychosis in addition to depression (Schifano and Magni 1994).

Several reports have found a relationship between greater ecstasy exposure and likelihood of psychopathology. However, the direction of causality cannot be determined and psychiatric symptoms may have led to increased ecstasy use rather than the other way around. In a comparison of 150 polydrug-using ecstasy users in treatment for substance abuse, ecstasy users with psychiatric problems had significantly earlier age of first ecstasy use (t test, $p < 0.001$), higher lifetime total ecstasy dose (Mann-Whitney test, $p < 0.001$), greater frequency (Mann-Whitney test, $p < 0.001$) and duration of use (Mann-Whitney test, $p < 0.001$), and higher largest single dose (Mann-Whitney test, $p < 0.001$)

than ecstasy users without psychiatric problems (Schifano 2000). In a Spanish-language review of case reports of ecstasy-related psychiatric complications published from 1985-1997, patients with psychotic symptoms were compared to those with affective symptoms (Bango et al. 1998). Patients with psychotic symptoms had significantly higher incidence of family history of psychiatric problems than patients with other symptoms (9/11 vs. 10/25, $X^2 = 3.8$, $p = 0.05$). Patients with psychotic symptoms also tended to have greater ecstasy exposures than those with other symptoms, but this difference was not statistically significant.

The mechanisms by which MDMA could produce or even trigger psychopathology are largely unknown. Stimulant psychosis can be produced by drugs that are not neurotoxic, such as cocaine and *l*-amphetamine. Similarly, psychiatric symptoms in ecstasy users may not necessarily be produced by serotonergic neurotoxicity, although neurotoxicity may contribute to problems. It is also not known if serotonergic neurotoxicity contributes to affective symptoms seen in ecstasy users. Because serotonergic drugs are useful in affective disorders and serotonergic abnormalities can be seen in many patients with affective disorders, some have speculated that serotonergic neurotoxicity may increase risk of affective disorder. This makes sense based on our limited understanding of serotonin, but it has not been demonstrated. Animal studies show that neurotoxicity begins to occur several hours after MDMA administration. Therefore, adverse reactions occurring earlier are likely due to an interaction of the pharmacological effects of MDMA and the individual's susceptibility. McCann and Ricaurte (1992) suggest that panic disorder occurring in a 23-year-old male ecstasy user was likely triggered by the pharmacological effects of MDMA rather than serotonergic neurotoxicity.

Hepatotoxicity in Ecstasy Users

16.1% (32/199) of case reports involved ecstasy-related hepatotoxicity (liver damage). Ecstasy has been reported to be the second most frequent cause of hepatotoxicity in Spanish individuals younger than age 25 (Andreu et al. 1998). It has been further suggested that many cases of subclinical hepatotoxicity occur in ecstasy users and escape detection (Jones and Simpson 1999). There is more than one pattern of ecstasy-related hepatotoxicity. Acute liver failure or hepatitis has occurred after reported ingestion of a single ecstasy tablet (Dykhuizen et al. 1995; Ellis et al. 1996; Henry et al. 1992). In other cases, hepatotoxicity has occurred after regular ecstasy use for months (Andreu et al. 1998). Common symptoms of hepatotoxicity in ecstasy users include jaundice, anorexia, nausea, vomiting, lethargy, dark urine, and pale stools. The delay between ecstasy exposure and onset of hepatic injury varies. Acute liver failure may occur shortly after ecstasy ingestion, while hepatitis may develop as long as four weeks after drug exposure (Dykhuizen et al. 1995; Gorard et al. 1992). There is no clear relationship between the extent of liver damage and duration of ecstasy use or estimated cumulative dose. Although MDMA has been specifically identified in very few of these cases (5.7%, 3/53), it is clear that MDMA or some common ingredient in illicit ecstasy pills is causing hepatotoxicity. Several ecstasy users who have been treated for hepatotoxicity develop new liver damage when they returned to using ecstasy (Khakoo et al. 1995; Shearman et al. 1992). Although evidence of liver damage was not seen in dogs and rats following

28-days of daily dosing with MDMA in one study (Frith et al. 1987), three *in vitro* studies demonstrate that MDMA can impair liver cell viability and that hyperthermia potentiates this impairment.

Acute liver failure has developed in individuals experiencing ecstasy-related hyperthermia. Liver damage is known to occur in heat stroke as well. It appears that the liver damage in these cases is partially due to hyperthermia but that ecstasy plays an additional role. An *in vitro* study using mice hepatocytes showed that MDMA increases the lipid peroxidation and loss of cell viability produced by hyperthermic conditions (Carvalho et al. 2001). 1.6 mM MDMA slightly but significantly decreased cell viability but did not affect lipid peroxidation over 60 to 180 min under normothermic (37º C) conditions. When temperature was raised to 41º C, the hepatotoxicity of MDMA was dramatically increased. At this temperature, 1.6 mM MDMA approximately doubled lipid peroxidation after 180 min and decreased cell viability after as little as 60 minutes. A lower concentration, 0.8 mM MDMA, also decreased cell viability after 180 min at 41º C. Amphetamines, and perhaps ecstasy, may make liver cells vulnerable to heat damage by impairing expression of heat shock protein, which normally helps cells survive heating (Lu and Das 1993). Thus, both hyperthermia and MDMA appear able to contribute to hepatotoxicity.

Not all ecstasy-related hepatotoxicity can be explained by heat stroke. Ecstasy-related acute liver failure has also occurred in individuals without evidence of hyperthermia (Ellis et al. 1996; Henry et al. 1992). In these cases, there are at least two main possibilities. First, a concentration-dependant toxic effect of MDMA may have occurred. Second, an idiosyncratic reaction, with a possible immunological mechanism, may have occurred. These two possibilities will now be discussed.

Two further *in vitro* studies have confirmed that high concentration or extended-duration exposure to MDMA may be directly toxic to liver cells. In one study, MDMA caused increases in ALT, AST, and LDH activities in rat hepatocytes (Beitia et al. 2000). These increases were statistically significant with high concentrations of MDMA (1 mM for six hours) or lower concentrations for prolonged exposures (0.1 mM for 24 hours). Further evidence of MDMA-induced toxicity to hepatocytes came from moderate decreases in ATP (after three, but not one, hour incubation with 0.1 mM MDMA). Beitia et al. suggest that this impairment in liver cell viability may be due to MDMA effects on intracellular calcium ions (Ca^{2+}). In the same publication, the researchers reported that MDMA dose-dependently increased intracellular Ca^{2+}, which is well known as a cause of cell damage. Maximum increase in cytosolic free Ca^{2+} occurred after 3 mM MDMA. The researchers suggest that MDMA may increase Ca^{2+} influx as well as cause release of Ca^{2+} from intracellular stores.

A third *in vitro* study examined the possible pro-fibrogenic effects of MDMA on the liver by measuring expression of procollagen mRNA in a cell line of hepatic stellate cells (Varela-Rey et al. 1999). These cells produce the collagen characteristics of a fibrotic liver. Expression of α1(I) procollagen mRNA was significantly increased by 0.5, but not 0.1, mM MDMA for 24 hr. This effect required sustained exposures, as 1 mM MDMA

for 8 hr did not increase mRNA expression. This pro-fibrogenic effect of MDMA may have been mediated by oxidative stress. Pretreatment with the antioxidants glutathione monoethyl ester or deferoxamine prevented the pro-fibrogenic effect.

All three *in vitro* studies have found that MDMA depletes intracellular glutathione. Glutathione is an important antioxidant produced mainly by the liver. Beitia et al. found that glutathione was depleted after one hour of 0.3 mM MDMA. This depletion was not due to oxidation of glutathione as the potentiation of MDMA-induced glutathione depletion by hyperthermia did not lead to increases in the product of glutathione oxidation, GSSG (Varela-Rey et al. 1999). One possibility is that metabolites of MDMA bind to glutathione, forming conjugates.

The drug exposures in these studies are unlikely to occur in a clinical setting but may occur in illicit settings, especially during 'binges' when repeated doses are taken. The lowest concentration used in the study by Beitia et al. (0.1mM or ~19.3 mg/l MDMA) decreased ATP after 3 but not 1 hour and affected indices of cell viability after 24 hr, but not 6 hr. This same concentration had no significant pro-fibrogenic effect after 24 hr in the other study. This concentration is approximately 40 times higher than the highest plasma level reported in a clinical study, 486.9 µg/l MDMA after 150 mg (de la Torre et al. 2000a), and has only been approached in adverse case reports involving very high doses (see **Tables 6.5** and **6.6**). Liver exposure to drugs is often higher than blood levels. In an autopsy of a deceased ecstasy user, liver MDMA concentration was 7.2 times higher than femoral blood MDMA concentration (Rohrig and Prouty 1992). Thus, the peak liver exposure to MDMA in a clinical setting may be one-fifth the concentration shown to impair cell viability in these studies. Therefore it is unlikely that MDMA exposures in clinical studies will approach those demonstrated in these studies to impair rat liver cell viability or induce procollegen mRNA. On the other hand, it is possible that illicit users achieve hepatotoxic MDMA exposures.

These *in vitro* studies suggest that ecstasy-related hepatotoxicity should be exposure dependant. This has not been consistently observed in case reports. In at least 5 cases, hepatotoxicity has occurred after reported ingestion of a single ecstasy pill (Behan et al. 2000; Brauer et al. 1997; Ellis et al. 1996; Henry et al. 1992; Schirren et al. 1999). However, it must be noted that the presence of MDMA was not confirmed in any of these cases. One of these cases was reported to have symptoms of NMS, but temperature was not reported (Behan et al. 2000). One possible explanation for the apparent lack of exposure-dependence is that repeated ecstasy exposure produces asymptomatic hepatotoxicity that can become symptomatic after a modest dose. Only 9.4% (3/32) of cases of hepatotoxicity were known to have occurred in novice users, while at least 56.3% (18/32) occurred in "regular" or experienced users.

Alternatively, an idiosyncratic toxic reaction to MDMA (or a contaminant) may have occurred. Genetic deficiency in CYP2D6 activity has been hypothesized to influence susceptibility to ecstasy-related hepatotoxicity. However, Schwab et al. (1999) phenotyped three individuals presenting with ecstasy-related hepatitis and determined that all had extensive CYP2D6 activity. Furthermore, the importance of CYP2D6 in

MDMA metabolism may be less than previously thought, since MDMA inhibits CYP2D6 activity (Brady et al. 1986; Delaforge et al. 1999; Wu et al. 1997).

Immunological mechanisms may play a role in ecstasy hepatotoxicity (Jones and Simpson 1999). This suggestion is based on reports that re-exposure to ecstasy produces further liver damage in some patients with a history of ecstasy-related hepatotoxicity (Khakoo et al. 1995; Shearman et al. 1992). Also, liver biopsy in at least one patient showed features (such as eosinophils) of an autoimmune hepatitis-like injury which resolved spontaneously when ecstasy use stopped (Fidler et al. 1996).

Jones and Simpson (1999) discuss treatment of ecstasy-related hepatotoxicity. As always, it is important to eliminate other possible causes of hepatotoxicity such as viruses or alcohol abuse. Treatment of acute hepatic failure is often complicated by other symptoms such as hyperthermia. Theoretically, N-acetyl-cysteine may be useful in acute hepatic failure if *in vitro* studies are correct in suggesting a role for glutathione depletion and oxidative stress. Jones and Simpson state that high dose steroid therapy, such as prednisolone, should be considered in cases thought to have an immunological mechanism. While some cases of ecstasy-related hepatotoxicity have spontaneously resolved, auxiliary or complete liver transplant has been necessary in some cases. Survival rate for cases requiring liver transplant is very poor.

Hyponatremia in Ecstasy Users

Hyponatremia is a term for abnormally low plasma sodium concentration and can lead to serious neurological symptoms and death. Beginning in 1993 (Maxwell et al. 1993), at least 19 individuals with ecstasy-related hyponatremia have been described in medical case reports. The presence of MDMA was confirmed in 63.2% (12/19) of these case reports. Many more cases of this syndrome have occurred in ecstasy users but not been fully described in medical reports. For example, between August 1994 and December 1995, 15 cases of ecstasy-related hyponatremia were identified by the London National Poison Information Service (Henry 2000). This adverse event does not appear to be dose-related and has been documented after reported ingestion of one half of an MDMA-containing tablet by an experienced user who had been dancing (Nuvials et al. 1997). Blood levels of MDMA in hyponatremic ecstasy users are often modest. Most of these individuals appear to have been drinking large amounts of water. However, excessive fluids cannot be entirely blamed for cases of ecstasy-related hyponatremia as MDMA specifically increases risk of hyponatremia by inducing antidiuretic hormone release.

Although hyponatremia may occur without symptoms, symptoms are more likely when hyponatremia develops quickly, as occurs in ecstasy users. In acute hyponatremia, symptoms occur when serum sodium falls below approximately 120 mEq/L. The development of symptoms indicates a medical emergency and leads to death in over 15% of hyponatremia cases (Ayus and Arieff 1996). Clinical signs and symptoms of hyponatremia are summarized in **Table 6.4**. In ecstasy-related hyponatremia, individuals frequently show bizarre behavior and vomiting followed by drowsiness and agitation, with epileptiform convulsions in some cases. Death occurred in 15.8% of cases of

ecstasy-related hyponatremia.

Symptoms of hyponatremia are due to the effects of low plasma sodium on the brain. When plasma sodium (and thus osmolality) starts to fall, osmotic pressure immediately causes water to move into cells. In the brain, a number of mechanisms decrease intracellular solutes in an attempt to prevent cell swelling. One important mechanism is the Na^{+}-K^{-} ATPase pump. This pump system can release sodium into the subarachnoid space, causing water to diffuse from the brain into the cerebral spinal fluid. If this and other mechanisms are unable to compensate for hyponatremia, there will be increased intracranial pressure, cerebral edema, brainstem herniation, compression of the midbrain, and possibly death.

Premenopausal women have a greater risk of dying or developing permanent brain damage from hyponatremia than men, probably due to the effects of sex hormones on brain Na^{+}-K^{-} ATPase (Ayus and Arieff 1996). Indeed 84% of the published ecstasy-related hyponatremia cases have been female, even though most cases identified in the literature are male. Thus, while men make up a much greater proportion of the ecstasy case reports, women are significantly more likely to be diagnosed with hyponatremia (chi-square, $x=227$, $p < 0.001$).

Risk of hyponatremia is due to the pharmacological effects of MDMA. MDMA has been shown to induce antidiuretic hormone release in volunteers after doses as low as 40 mg (Henry et al. 1998). This is consistent with a rat study that found MDMA increased basal aldosterone levels (Burns et al. 1996). One case report of ecstasy-related hyponatremia measured antidiuretic hormone, and confirmed it was elevated (Holden and Jackson 1996). In some case reports, laboratory findings and history are more consistent with a syndrome of inappropriate antidiuretic hormone secretion rather than excessive water consumption (Ajaelo et al. 1998; Gomez-Balaguer et al. 2000; Sharma and Nelson 2000). Overall, it appears that MDMA may lead to syndrome of inappropriate antidiuretic hormone and thus, hyponatremia, in the absence of either excessive sweating or extensive fluid intake.

However, factors other than the effects of MDMA contribute to risk of ecstasy-related hyponatremia. Sustained dancing may increase risk of hyponatremia. Exercise without drug use can lead to hyponatremia when solute-free water is ingested. In a recent prospective study, 18% of 605 marathon runners developed hyponatremia (Speedy et al. 1999). Biochemical analyses in some ecstasy-related cases (Matthai et al. 1996) have suggested to some that hyponatremia was triggered by excessive consumption of water and failure to replace lost sodium (Wilkins 1996). In some case reports, witnesses reported that the individual consumed large amounts of water (Box et al. 1997; Holmes et al. 1999; Lehmann et al. 1995; O'Connor et al. 1999; Parr et al. 1997). Thus, ecstasy-related hyponatremia may be partially due to user beliefs that water consumption reduces ecstasy toxicity.

Table 6.4: Clinical Manifestations of Hyponatremic Encephalopathy

Early*	Anorexia Headache Nausea Emesis Muscular cramps Weakness
Advanced*	Impaired response to verbal stimuli Impaired response to painful stimuli Bizarre (inappropriate) behavior Hallucinations (auditory or visual) Asterixis Obtundation Incontinence (urinary or fecal) Respiratory insufficiency
Far Advanced*	Decorticate and/or decerebrate posturing Bradycardia Hyper- or hypotension Altered temperature regulation (hypo- or hyperthermia) Dilated pupils Seizure activity (usually grand mal) Respiratory arrest Coma Polyuria (secondary to central diabetes insipidus)

*Any manifestation may be observed at any stage, and some patients will have only minimal symptoms.
Table reproduced from (Fraser and Arieff 1997)

Health care workers now caution ecstasy users that water is not a panacea for ecstasy toxicity, given the apparently increased risk of hyponatremia in ecstasy users (Finch et al. 1996). In addition, it has been emphasized that it can be dangerous to let semi-conscious ecstasy users "sleep it off" since impaired consciousness may indicate hyponatremia (Matthai et al. 1996).

It may be possible to develop guidelines for ecstasy users based on the American College of Sports Medicine position stand on Exercise and Fluid Replacement (Convertino et al. 1996). One suggestion from this document is that athletes (read as “ecstasy users”) drink about 500 mL (about 17 oz) about 2 hr before exercise (“dosing”) to promote adequate hydration while allowing time for excretion of excess fluids. In other words, individuals should assure that they are adequately hydrated before exercise or ecstasy exposure. Further fluid consumption should be directed towards replacing water lost through sweat (or vomiting). Because solute-free water may increase risk of hyponatremia, ecstasy users are often advised to consume sports drinks or salty foods along with fluids. When

exercise lasts more than 1 hr, the position stand on fluid replacement recommends drinking 600-1200 mL/hr (20-40 oz/hr) of cool fluids containing 4% to 8% carbohydrates and 0.5-0.7 g sodium/L water. This fluid replacement recommendation was developed for athletes engaging in sustained sweat-inducing exercise and suggests volumes that are likely excessive for ecstasy users who are not exercising or losing fluids through sweat or vomit.

Management of patients with hyponatremia is discussed in the ecstasy literature (Zenenberg and Goldfarb 2000) and elsewhere (Fraser and Arieff 1997). Treatment of hyponatremia depends on the severity of symptoms. In symptomatic patients, therapy with hypertonic saline solution is often indicated after a secure airway has been obtained. Because inappropriate treatment of hyponatremia can lead to brain damage and patients require constant monitoring, only trained medical personnel should attempt treatment.

Cardiovascular-Related Complications

At the doses used in published clinical reports, MDMA typically produces robust but clinically insignificant increases in heart rate and blood pressure as well as vasoconstriction. In illicit users, a number of serious adverse events have been due to these cardiovascular effects, including hypertensive emergencies and dysrhythmias.

Drug-induced hypertension may lead to damage in numerous organs, usually when diastolic blood pressure exceeds 130 mmHg. Ecstasy-induced hypertension has been linked to several of these organ dysfunctions, including acute renal failure (Woodrow et al. 1995), aortic dissection (Duflou and Mark 2000), gastric artery perforation (Williams et al. 1998a), retinal hemorrhage (Jacks and Hykin 1998), myocardial infarction (Dowling et al. 1987; Milroy et al. 1996), and cerebral hemorrhage (Gledhill et al. 1993; Henry et al. 1992; Manchanda and Connolly 1993; Selmi et al. 1995). Although the presence of MDMA was rarely confirmed in these cases, these types of events are all well established complications of hypertension and can occur after use of other amphetamines.

While the cardiovascular effects of MDMA have largely resolved in clinical studies by post 6 hrs, dysrhythmias have occurred the day after illicit ecstasy use in two case reports. One individual presented with hyperthermia, 200/110 mmHg BP, sinus tachycardia, agitation, and dehydration, 5 hrs after taking an ecstasy tablet (MDMA was not confirmed). ECG monitoring revealed QT prolongation lasting at least 30 hrs after drug ingestion (Drake and Broadhurst 1996). QT prolongation after ecstasy use has been reported in one other case report (Maxwell et al. 1993). Prolonged QT indicates the cardiac action potential has been prolonged, an event that is associated with *torsades de pointes*, a polymorphous ventricular arrhythmia that may cause syncope and degenerate into ventricular fibrillation.

Ventricular fibrillation leading to death has been documented in at least two ecstasy users. One case involved a previously healthy 18-year-old female who collapsed 60-90 minutes after consuming 1.5 ecstasy tablets with ethanol (Dowling et al. 1987). Postmortem analysis of blood revealed relatively high concentrations of MDMA (1.0

mg/L). In a second case, an individual with Wolff-Parkinson-White Syndrome (a cardiac disorder increasing risk of dysrhythmia) used ecstasy one morning, complained of palpitations that evening, and experienced ventricular fibrillation early the next morning (Suarez and Riemersma 1988). MDMA was confirmed in blood.

In a series of autopsies of 7 ecstasy users, Milroy et al. (1996) found focal or contraction band cardiac necrosis in 4 of 5 cases with confirmed MDMA involvement, including a hyperthermic individual (case 1) in whom cardiac arrest was the cause of death, and a normothermic individual (case 6) in whom sudden death occurred. These cardiac changes resembled those seen in catecholamine-induced injury.

Management of ecstasy-related cardiovascular complications is discussed by Ghuran and Nolan (2000). Given the lack of specific information on treating cardiovascular complications of MDMA, it may be useful to note that the alpha-antagonist, phentolamine, has been recommended for treatment of toxicity from the MDMA-analogue, MDA (Simpson and Rumack 1981).

Cerebrovascular Problems in Ecstasy Users

Ecstasy use has preceded cerebral hemorrhage or infarction in at least five cases. Such cerebrovascular accidents are well-established adverse effects of sympathomimetic psychostimulants (Hughes et al. 1993; Kaku and Lowenstein 1990; Perez et al. 1999). Cerebral hemorrhage after psychostimulant use is likely due to drug-induced hypertension (causing rupture of blood vessels in the brain), with possible contributions from vasculitis in chronic drug users. Cerebral infarction may be due to vasospasm or vasoconstriction-induced ischemia or clot formation (possibly related to dehydration or drug-induced coagulopathy). One case of cerebral venous sinus thrombosis has been reported in a 22-year-old female who became dehydrated after dancing for 8 hr without drinking fluids (Rothwell and Grant 1993).

Three cases of ecstasy-related cerebral hemorrhage have been identified in the medical literature. Hemorrhage locations were subarachnoid (Gledhill et al. 1993; Henry et al. 1992), left frontal cerebral (Selmi et al. 1995), and left frontal parietal cerebral (Manchanda and Connolly 1993). In two of these cases (Gledhill et al. 1993; Selmi et al. 1995) a previously existing underlying arteriovenous malformation appeared to play a role in the event. Both individuals had reportedly used ecstasy on previous occasions without apparent adverse event. In one case, symptoms appear approximately 1 hr after ecstasy ingestion (Gledhill et al. 1993; Henry et al. 1992), as would be expected from a hypertension-related event. In another case, however, onset was over 36 hr after ecstasy ingestion, while the patient was smoking cannabis (Manchanda and Connolly 1993).

Other Neurological Problems in Ecstasy Users

Possible neurological effects of ecstasy exposure have been examined in several studies and case reports. The studies suggest that brain atrophy or ischemic lesions are not common in ecstasy users. However, illicit ecstasy use appears to frequently have

detectable effects on parietal white matter and global brain volume. These studies are summarized below. Other studies have specifically looked for evidence of serotonergic changes that could be the result of selective serotonergic neurotoxicity. These studies, which are discussed in detail in the previous chapter, have generally found that illicit ecstasy use is associated with long-term serotonergic alterations.

In a study comparing 22 ecstasy users and 37 nonusers, MRI found no evidence of brain atrophy or white matter lesions (Chang et al. 1999). Proton magnetic resonance spectroscopy (^{1}H MRS) measures of cerebral metabolites in the same individuals generally supported this conclusion, finding unaltered lactate and N-acetyl-aspartate levels. However, myo-inositol was elevated in parietal white matter, suggesting glial activation, possibly due to damage or pharmacological effects of MDMA. Myo-inositol in parietal white matter ($r = 0.48$, $P = 0.04$) and occipital gray matter ($r = 0.68$, $P = 0.002$) was correlated with the logarithm of cumulative lifetime MDMA dose.

In a study of cerebral blood flow using many of the same volunteers, 21 ecstasy users were compared to 21 nonusers using single photon emission computed tomography (SPECT) and MRI. Although no significant differences were found between ecstasy users and nonusers, duration of ecstasy use negatively correlated with global brain volume, even when co-varied with age ($r = -0.57$, $P = 0.02$). In this same report, regional and global cerebral blood flow was measured in 10 ecstasy users before and after administration of MDMA in a clinical study. The results of this prospective study, which are discussed in the section on human neurotoxicity, indicate that MDMA exposure can alter cerebral blood flow for at least several weeks.

Two reports have identified bilateral lesions in the globus pallidus of ecstasy users. In one case, these lesions were identified during autopsy (Squier et al. 1995). In another case they were identified during magnetic resonance imaging (MRI) of a 26-year-old female who lost consciousness and developed lasting and severe impairment of episodic memory three days after ingesting half an ecstasy tablet (Spatt et al. 1997). Squier et al. (1995) speculate that local release of serotonin led to prolonged vasospasm and necrosis of the globus pallidus. The authors of the second report suggest that lesioning of the globus pallidus was “clinically silent” and not the cause of the patient’s amnesic syndrome, which they hypothesize may have been due to hippocampal toxicity not detected with MRI.

Parkinsonism has been reported in one ecstasy user (Mintzer et al. 1999). Onset of symptoms was three months after last ecstasy use. After excluding other possible causes, the authors hypothesized that delayed MDMA-induced dopaminergic neurotoxicity had occurred, although several letter writers disputed this theory (Baggott et al. 1999; Sewell and Cozzi 1999), including the patient (Borg 1999). Among other points, it was argued that MDMA is not a selective dopaminergic neurotoxin in primates and that the time course of symptoms was not consistent with drug-induced neurotoxicity. Subsequent analysis of the brain of a deceased chronic ecstasy user found no evidence of dopaminergic neurotoxicity (Kish et al. 2000), suggesting that any link between ecstasy use and parkinsonism is not due to dose-dependent dopaminergic neurotoxicity.

Two cases of white matter lesions with different symptoms and outcomes have been reported in ecstasy users (Bertram et al. 1999; Bitsch et al. 1996). In the first case, a 22-year-old male developed fever and gradual loss of vigilance and orientation beginning the day after using a larger dose of ecstasy than was typical for him (Bitsch et al. 1996). After 5 days of worsening symptoms, a generalized seizure occurred, upon which he was taken for medical assistance. Laboratory tests revealed signs of inflammation in blood and CSF. T_2-weighted MRI showed hyperintense white matter lesions throughout the brain. The patient recovered after 7 days of treatment and a MRI at 14 days after onset revealed a reduction in lesions. The authors note that cerebral vasculitis has been reported as a rare complication of amphetamine use.

In a second case, a 19-year-old male with a history of opiate and benzodiazepine abuse lost consciousness the morning after reportedly using ecstasy for the first time (Bertram et al. 1999). On examination, the patient was comatose with respiratory insufficiency and evidence of liver and renal failure, rhabdomyolysis, and pneumomediastinum. Benzodiazepines and unspecified amphetamines were identified in biofluids. Although initial computed tomography was normal, repeated measures at 2, 3, and 4 weeks after admission revealed bilateral hypodense lesions of white matter, which were also detected with MRI. The patient was in a persistent vegetative state and had not recovered when the case report was written. The authors suggest that selective damage to myelinated tracts may have been due to accumulation of lipophilic drug and localized oxidative stress. However, it is not clear why the patient was vulnerable to this severe idiosyncratic complication.

In one case report, a reportedly first-time ecstasy user developed lasting neurological and psychiatric symptoms and was subsequently diagnosed as having suicidal depression and possibly temporal lobe epilepsy *(*Cohen and Cocores 1997). Because the patient had no previous symptoms, personal or family psychiatric history, or other drug use, and symptoms developed with ecstasy exposure, the authors suggest ecstasy may have caused or triggered the onset of this condition.

Hematological Problems in Ecstasy Users

Most hematological problems in ecstasy users have been coagulation disorders occurring in the context of hyperthermia. Disseminated intravascular coagulation (DIC) has already been discussed in the section on hyperthermia. DIC occurred in 25 case reports, 60.0% (15/25) of which were fatal. In addition to these cases, 3 cases of aplastic anemia and 1 case of thrombotic thrombocytopenic purpura have been reported in ecstasy users.

Three cases of aplastic anemia have been reported in ecstasy users (Clark and Butt 1997; Marsh et al. 1994). Aplastic anemia is a rare disorder in which blood cell production is suppressed. It can be caused by viruses or drug exposure, although the cause goes unrecognized in most cases. In cases involving ecstasy users, the link between ecstasy use and the disorder was made by excluding other possible causes. The period from last ecstasy exposure to symptoms was 1 to several weeks. In two cases the condition

resolved spontaneously 7 to 9 weeks after presentation (Marsh et al. 1994), while the third case required bone marrow transplant (Clark and Butt 1997).

Thrombotic thrombocytopenic purpura was diagnosed in a 20-year-old male recovering from ecstasy-related acute liver failure (Schirren et al. 1999). Thrombotic thrombocytopenic purpura is a blood disorder characterized by low platelets and red blood cell fragmentation (caused by premature breakdown of the cells). Platelet clumping leads to transient ischemia of organ systems. In the CNS this can produce behavioral disturbances, headache, or even coma. Bleeding beneath the skin produces characteristic red rashes or bruises.

Ecstasy-Related Pneumomediastinum and Subcutaneous Emphysema

Six cases of pneumomediastinum and one case of cervical emphysema have been reported in ecstasy users. Pneumomediastinum is a condition in which air is present in the mediastinum, the space in the chest between the lungs. Symptoms include chest pain, crackling sounds in the chest and throat, and altered voice. Most cases of non-traumatic mediastinal and cervical emphysema are thought to be due to rupture of the alveolus after a sudden increase in pressure such as during the valsalva maneuver or vomiting. In published cases, emphysema may have been caused by vomiting or retching (Levine et al. 1993; Rezvani et al. 1996), repeatedly blowing a whistle (Pittman and Pounsford 1997), and possibly severe exercise (Quin et al. 1999; Rezvani et al. 1996), although the cause has not always been clear (Bertram et al. 1999; Onwudike 1996; Quin et al. 1999; Rezvani et al. 1996). In most cases, pneumomediastinum has been the sole complaint, although it occurred in one case in conjunction with liver and renal failure, rhabdomyolysis, and neurological symptoms (Bertram et al. 1999). Patients presenting solely with emphysema have recovered with conservative management in these published cases.

Ophthalmic Problems in Ecstasy Users

A 17-year-old male developed double vision due to bilateral sixth nerve palsy approximately 24 hr after taking 2 ecstasy tablets. The patient recovered within 5 days (Schroeder and Brieden 2000). Two cases of corneal epitheliopathy have also been reported in ecstasy users, with corneal exposure thought to be the likely cause (O'Neill and Dart 1993).

Dermatitis in Ecstasy Users

Two cases of dermatitis have been reported in ecstasy users (Wollina et al. 1998). In one case, evidence of altered liver function was seen. Dermatitis has been previously reported as a rare complication of amphetamines (Kauvar et al. 1943).

Dental Problems in Ecstasy Users

A case report (Murray and Wilson 1998), a survey (Topp et al. 1999)**,** and a study (Milosevic et al. 1999; Redfearn et al. 1998) suggest that ecstasy use may lead to dental problems. One review has discussed this issue (Duxbury 1993). In a study of 30 ecstasy users and 28 nonusers, ecstasy was associated with significantly increased wear of the occlusal surfaces (molars and premolars) due to bruxism (jaw clenching) (Milosevic et al. 1999; Redfearn et al. 1998). This erosion of the biting surfaces of the back teeth contrasts to the usual pattern of tooth wear affecting the front teeth. The researchers suggest that ingestion of carbonated and acidic beverages during ecstasy use may contribute to this problem. In a survey of 329 polydrug-using ecstasy users recruited by snowball sampling, 14.6% reported teeth problems that were considered to be only related to ecstasy use (Topp et al. 1999). It is not clear what proportion of this number is due to lasting dental problems because it also includes acute bruxism and mouth ulcers from excessive chewing.

Ecstasy Use During Pregnancy

Ecstasy use during pregnancy may increase risk of birth defect. While alcohol is universally recognized as impairing fetal development, amphetamine has also been associated with adverse outcomes such as clefting, cardiac anomalies, and fetal growth rate deficits (Plessinger 1998). The pharmacological and structural similarities between amphetamines and MDMA raise the possibility that ecstasy might produce similar malformations. This issue has been addressed in two studies of ecstasy users. These studies have not been large enough to draw conclusions, but serve to raise concerns about possible problems. Three animal studies reported only few effects of prenatal or newborn MDMA exposure, while a recent study of newborn rats found that repeated MDMA exposure dose-dependently impaired learning and memory.

The U.K. National Teratology Information Service conducted a prospective follow-up study on 78 infants whose mothers had used ecstasy during pregnancy (McElhatton et al. 1999). There was a significantly higher rate of congenital anomalies (15.4% in these women) than expected in the general population (2-3%). The authors concluded that this small case sample had insufficient statistical power to confirm a causal relation with any particular disorder. This study did not control for effects of inadequate prenatal care such as poor nutrition and use of tobacco. For example, one case of neonatal death involved a mother who had been taking ecstasy, heroin, and methadone throughout pregnancy. Although an earlier Dutch study (available in English only in abstract form) failed to find an effect of ecstasy use on fetal development (van Tonningen-van Driel et al. 1999), this earlier study was smaller and also lacked statistical power to detect rare events. The earlier study examined 36 live births from women who had taken ecstasy (and often other drugs) during pregnancy. In any case, caution dictates that pregnant women should not use ecstasy.

While earlier animal studies found few effects of prenatal MDMA exposure, a recent study of newborn rats found that repeated MDMA exposure dose-dependently impaired

sequential learning and spatial learning and memory (Broening et al. 2001). MDMA was administered twice daily for ten days, with individual doses of 5 to 20 mg/kg. Because of interspecies differences, newborn rats are thought to be the developmental equivalent of a 3rd trimester human fetus. Thus, the newborn rats were exposed to MDMA during the equivalent of the third-trimester in humans. Some rats were administered MDMA during the equivalent of the early part of the third trimester, while others were exposed during the late part of this period. MDMA decreased body weight for both groups. In behavioral tests beginning at least 1 mo after MDMA exposure, rats exposed in the late (but not early) third trimester had significantly impaired learning and memory. These impairments were not correlated to the serotonergic neurotoxicity seen in both groups, which was measured as a 20% or less depletion of hippocampal serotonin.

Pervious studies found more subtle effects of MDMA exposure. A rat study found that a repeated administration of 10 mg/kg MDMA, once or twice daily, for 4 days, decreased the extent to which young rats cried when separated from their mother (Winslow and Insel 1990). This effect was only seen in rats exposed to MDMA shortly after birth (the human equivalent of early trimester) and not earlier. This effect was only monitored for 2 wks after drug exposure. Concurrent measures of locomotion, geotaxis, and weight gain were not altered. Another animal study found only subtle behavioral alterations in offspring after pregnant rats were treated with 2.5 or 10 mg/kg MDMA (St Omer et al. 1991). MDMA treatment increased olfactory discrimination in male and female offspring, and female pups displayed negative geotaxis. No evidence for a "substantive effect" of prenatal MDMA exposure upon offspring was reportedly found. In another study, the administration of MDMA (8, 16, or 32 mg/kg egg wt) or amphetamine to chicken embryos had no significant adverse effect on hatchability or hatch weight (Bronson et al. 1994). Overall, it appears that the effects of prenatal MDMA exposure may depend on the developmental stage of the fetus.

Traffic Accidents and Dangerous Behavior in Ecstasy Users

A number of reports have suggested that ecstasy use may impair driving or otherwise lead to motor vehicle accidents. MDMA concentrations associated with impaired motor vehicle operations are summarized in **Table 6.5**. The table excludes cases of MDMA users who were injured as pedestrians or passengers (Henry et al. 1992; Hooft and van de Voorde 1994). Several reports offer insufficient information from which to draw strong conclusions. For example, one letter (Davies et al. 1998) mentioned 16 ecstasy abusers who were injured as a result of "reckless driving", but did not differentiate drivers from passengers, provide blood or urine levels, or comment on the presence of other drugs. Henry et al. (1992) cited 5 cases of road accidents, but only one of these fatalities involved a driver. Dowling reported a case of a driver who died in an accident while under the influence of the related analogue MDE, although this fatality was attributed to atherosclerotic cardiovascular disease rather than the accident itself (Dowling et al. 1987). Similarly, it is not known to what extent MDMA impairment of driving ability may be attributable to seizures or other ecstasy-induced medical conditions, as opposed

Table 6.5. Traffic Accidents Involving Drivers Under the Influence of MDMA

Population	MDMA Level:	Other Substances Confirmed	Reference
9 cases	0.18 ± 0.14 mg/l blood		(Omtzigt cited in Crifasi et al. 1999)
18-yr-old male driver killed in collision	0.1 mg/l plasma postmortem.	None mentioned in text, although Crisfasi (1996) states this case was complicated "by the presence of other drugs".	(Henry et al. 1992) Case 17 of 24.
29-yr-old male driver killed in collision	2.32 mg/L blood postmortem	MDA	(Crifasi and Long 1996)
18 cases of impaired driving in Germany	Median 76 (range: 1-514) ng/mL serum.	Alcohol, Amphetamine, Cannabis, Codeine, and Bromazepam, MDA and/or MDEA were also reported in sample from which these cases are a subset.	(Moeller and Hartung 1997)
136 "drugged drivers" in Norway.	"64% of the MDMA positive samples presented drug concentrations equal to or lower than the blood concentrations obtained after intake of a 'standard dose' of 100 mg MDMA."	"Frequent presence of other drugs in the samples."	(Morland 2000)

to a decrement in such mundane factors as reaction time, spatial/temporal perception, cognitive judgment, or emotional equilibrium.

Dangerous behavior during ecstasy use has resulted in injury. Ecstasy-intoxicated individuals have received serious burns (Cadier and Clarke 1993), been electrocuted and fallen to their death (Dowling et al. 1987), and been killed while attempting to stand on top of a moving vehicle (Hooft and van de Voorde 1994). In these cases, drug intoxication may have impaired judgment and facilitated risky behavior or may have impaired ability to successfully complete risky behaviors.

Is Risk of Ecstasy-Related Toxicity Dose Dependant?

It is commonly said that ecstasy toxicity in humans is not dose-related. Originally this statement was intended to convey that many ecstasy-related emergencies did not occur because the patient consumed an unusually large dose of ecstasy. More recently, harm reduction advocates have additionally suggested that toxicity can be explained by the use of ecstasy in a risky manner (e.g. high ambient temperature, exercise, too little or too much fluid consumption) rather than "overdose". Blood concentration of MDMA in published case reports confirm that survival is not closely related to MDMA concentration (see **Tables 6.6** and **6.7**). A danger of stating that ecstasy toxicity is not dose-related lies in the possibility that the reader will interpret this to mean that ecstasy toxicity is never dose-related.

Perhaps the most accurate statement would be that high dose is a risk factor for some types of ecstasy toxicity, but it is only one of several risk factors. Other probable risk factors include exercise, dehydration, over hydration, and hot or humid settings. More frequent use or greater total lifetime dose may be risk factors for psychological problems. For example, psychiatric disturbances appear more likely in individuals who have used more ecstasy. Still other risk factors remain unknown. While rare, serious ecstasy toxicity cannot be predicted beforehand, and in many specific cases cannot be explained afterwards. Serious adverse reactions or even death can occur after modest amounts of ecstasy in the absence of known risk factors.

Several reports provide evidence that common adverse effects of ecstasy are related to dose. In a survey of 100 ecstasy users, the severity of side effects reported was positively correlated with both the total number of doses consumed ($r = 0.34$, $p < 0.05$) and the frequency of use ($r = 0.50$, $p < 0.01$) (Solowij et al. 1992). Topp et al. (1999) found that those who had binged on ecstasy reported increased physical (nine versus seven; $t_{344} = -5.3$; $p < 0.001$) and psychological side-effects (five versus four; $t_{319} = -3.6$; $p < 0.001$). As described below, Topp et al. found that recent bingeing on ecstasy and the quantity of ecstasy typically used were associated with physical side effects in a regression analysis.

Bingeing was also identified as a risk factor for adverse effects by van de Wijngaart et al. (1999). In a comparison of polydrug-using ecstasy users and drug-free volunteers, Parrott et al. (2000b) found that ecstasy users with an average of 6.8 (range: 1–20) ecstasy exposures differed from non-drug users in self-reported measures of paranoid ideation and psychoticism. Individuals with an average of 371 (range: 30–1000) ecstasy exposures had more self-reported anxiety, paranoid ideation, and appetite than less experienced users. This study is limited because volunteers were only asked to not use ecstasy on the day of testing. Therefore it is not clear whether these differences are due to preexisting differences, acute ecstasy withdrawal, longer lasting ecstasy effects, or the effects of other drugs.

Table 6.6: Blood Concentrations of MDMA in Published Fatalities

Identity	MDMA mg/L	Diagnosis	Reference
19 M	7.15	Hyperthermia; DIC	Fineschi et al., 1999
32 M	4.56	MDMA-Ritonavir interaction	Henry & Hill, 1998
21 M	4.2	Cardiac arrest	Milroy et al., 1996
53 M	3.71	Hyperthermic syndrome	Walubo & Seger, 1999 *
20 M	2.8	Acute poisoning due to insufflation of MDMA, cocaine, and heroin	Moore et al., 1996
20 F	2.3	Hyperthermic syndrome	Mueller & Korey, 1998
17 M	2.3	Gross pulmonary edema, amphetamine abuse	Dar and McBrien, 1996
21 M	2.1	Inhalation of vomit	Milroy et al., 1996; Forrest et al., 1994 *
18 M	1.53	Hyperthermic syndrome	Henry et al., 1992
20 M	1.41	Hyperthermic syndrome	Henry et al., 1992
32 M	1.1	Asthma	Dowling et al., 1987
18 F	1	Acute MDMA intoxication	Dowling et al., 1987
26 F	0.82	hyperthermia; terminal cardiac arrest	Byard, et al., 1998
22M	0.55	Hyperthermic syndrome	Cox & Williams, 1996
16 F	0.516	Hyperthermic syndrome	Henry et al., 1992
16 F	0.424	Hyperthermic syndrome	Chadwick et al., 1991
18 M	0.44	Hyperthermia, Cardiac Arrest	Henry et al., 1992
22 F	0.3	Hyperthermic syndrome	Byard, et al., 1998 *
34 M	0.2	Sudden cardiac death	Suarez & Riemersma, 1988 **
20 M	0.185	Hyperthermic syndrome	Fineschi and Masti, 1996
27 F	0.219	Hyponatremia	O'Connor, et al., 1999
20 M	0.18	Hyperthermic syndrome	Fineschi et al., 1999 *
21 F	0.13	Hyperthermic syndrome	Henry et al., 1992
21 F	0.134	Hyperacute liver failure; Hyperthermic syndrome	Ellis et al., 1996
15 F	0.05	Hyponatraemia	Parr et al., 1997
20 M	0.04	Hyponatraemia	Milroy et al., 1996

* sample taken postmortem ** units unclear (given as “mg%” in paper)
When necessary, plasma/serum concentrations were converted to blood levels using a hematacrit of 0.45 and partitioning data from Garrett et al. (1994)

Abbreviations: DIC – disseminated intravascular coagulation.

Table 6.7 Blood Concentrations of MDMA in Survivors of Adverse Events

Identity	MDMA mg/L	Diagnosis	Reference
33 F	7.9	Toxic psychosis; hyperthermia	Hayner & McKinney, 1986
32 F	6.5	Hyperthermia; multiple severe complications from ingestion of MDMA	Brown & Osterloh, 1987
19 M	5.2	Confusion, central depression	Regenthal et al., 1999
20 M	4.92	Hyperthermia, vomiting, convulsions	Roberts and Wright, 1993
30 M	1.2	Unconsciousness, apnea, convulsions	Ramcharan et al., 1998
19 F	1.2	Hyperthermia, Thrombocytopenia	Henry et al., 1992
21 M	0.91	Hyperthermia; DIC; severe multiple organ failure	Murthy et al., 1997a,b
13 month M	0.9	Agitation, twitching, convulsions	Bedford Russell et al., 1992; Henry et al., 1992
19 M	0.46	Hyperthermia; DIC; acute liver damage	Ellis et al., 1996
20 M	0.29	Hyperthermia; DIC; rhabdomyolysis, ARF	Henry et al., 1992
25 F	0.26	Subarachnoid hemorrhage	Henry et al., 1992; Gledhill et al., 1993
23 M	0.2	Hyperthermia, DIC, ARF, rhabdomyolysis; impaired liver function	Barrett and Taylor, 1993
23 M	0.2	Hyperthermia, DIC, ARF, rhabdomyolysis	Henry et al., 1992
23 M	0.2	Hyperthermia, acute renal failure	Fahal et al., 1992
24 F	0.06	Hyponatraemia	Satchell & Connaughton, 1997
17 F	0.061	Hyponatraemia	Maxwell et al., 1993
36 M	0.016	Hyponatraemia with hyperthermia then delayed severe rhabdomyolysis	Lehmann, et al., 1995

When necessary, plasma/serum concentrations were converted to blood levels using a hematacrit of 0.45 and partitioning data from Garrett et al. (1994)
Abbreviations: DIC – disseminated intravascular coagulation; ARF – acute renal failure.

The adverse effects of described in the previous paragraph are self-reported. Such self-reported common adverse effects cannot necessarily be equated with more serious adverse events requiring medical intervention. Evidence that serious adverse events are related to ecstasy dose or exposures is limited to the report by Schifano et al. (1998, 2000) that found that polydrug-using inpatient ecstasy users with psychiatric problems had used significantly more ecstasy than those without problems. In this sample, those who had used more than 11 tablets were 17.4 times more likely to have experienced psychiatric problems than those who had taken it once or twice. As stated before, causality cannot be demonstrated this study and it is possible that individuals with psychiatric problems tend to use ecstasy more than others.

There are a number of considerations that help us understand why ecstasy toxicity does not appear to be dose dependant. These considerations, which are discussed below, include tolerance to the effects of MDMA, the influence of environment on amphetamine lethality, and the triphasic dose-lethality curves of some amphetamines.

Tolerance to the Effects of MDMA. Extensive anecdotal evidence suggests that ecstasy users develop tolerance to the euphoric effects of ecstasy. Animal studies confirm that high dose regimens of MDMA decrease the ability of the animal to distinguish between a lower dose of MDMA and placebo. An ascending dose regimen produced long-term tolerance to the effects of MDMA on performance of various behavioral tasks by nonhuman primates (Frederick et al. 1995). Ecstasy users may also develop tolerance to the physiological effects of ecstasy, allowing them to self-administer doses that would be toxic to novice users.

The Influence of Environment on Amphetamine Lethality. A large literature has established that many amphetamines, including MDMA, have increased lethality when test animals are housed in groups rather than individually. In individually housed male albino mice, the 24 hr LD50 for IP MDMA is 97.6 (95% CI: 82.8 – 115.0) mg/kg, while in group-housed mice the LD50 is lowered to 19.9 (11.9 – 33.2) mg/kg (Davis and Borne 1984). Thus the lethality of MDMA is increased almost five-fold when mice are group-housed. This increase may be partially due to the stress of the novel physical and social environment, since acclimation reduces the effect of group housing on *d*-amphetamine lethality (Vargas-Rivera et al. 1990).

Triphasic Dose-Lethality Curves of Some Amphetamines. Several studies have found certain amphetamines to have complex, triphasic dose-response curves for lethality. The percent of animals killed within 24 hr of a dose does not increase smoothly as dose is increased. Instead, lethality may decrease at some doses, producing valleys in the dose-lethality curve. While MDMA does not appear to have been examined in this regard, researchers have investigated the lethality of MDA and MMDA (3-methoxy-4, 5-methylendioxyamphetamine which is structurally 5-methoxy-MDA, although its functional groups are conventionally numbered differently) (Davis et al. 1977). The researchers found evidence of a triphasic lethality pattern for MMDA in both individually and group-housed mice and for MDA in individually housed mice only. MMDA was

also noteworthy for the steepness of its dose-lethality curve, with doses spaced by 0.05 log units. If MDMA were to have a similar steep and triphasic dose-toxicity curve, toxicity would likely appear dose-independent under the varied conditions of illicit ecstasy use.

Factors in addition to ecstasy exposure have been linked to risk of adverse effects in ecstasy users. In the survey of 329 Australian polydrug-using ecstasy users (Topp et al. 1999), adverse psychological effects were predicted by being female ($\beta = 0.91$; $p < 0.001$), recent bingeing on stimulants ($\beta = 0.58$; $p < 0.05$), number of drugs typically used when recovering from ecstasy ($\beta = 0.41$; $p < 0.001$), and more extensive recent polydrug use ($\beta = 0.15$; $p < 0.05$). This model accounted for a relatively small proportion of variance (16%) and does not indicate the direction of causality. In the same report, adverse physical effects were predicted by being female ($\beta = 1.6$; $p < 0.001$), being younger ($\beta = -0.20$; $p < 0.001$), number of drugs typically used when recovering from ecstasy ($\beta = 0.88$; $p < 0.001$), recent bingeing on ecstasy ($\beta = 1.4$; $p < 0.005$), quantity of ecstasy typically used ($\beta = 0.52$; $p < 0.01$) and unemployment ($\beta = -1.2$; $p < 0.05$) were independently associated with more physical side-effects. This model accounted for 29% of the variance. Another study interviewed individuals before and after a series of dance events (1121 participants before, of whom 768 returned afterward) (van de Wijngaart et al. 1999). 81% of participants had used ecstasy, 64% on the night of the study. Results of regression analysis (not actually described in the publication) were used to create "risk profiles" of dance events attendees. In these profiles, risk factors for having adverse events at parties included: having less experience with drug use; lacking a social safety net; being female; bingeing; and regularly buying "fake" ecstasy pills. Observations and objective measurements of temperature, humidity, and other variables were also made. The researchers reported that a regression analysis found that ambient conditions, such as temperature and humidity, played "virtually no role" in the incidence of self-reported complaints and illness. This finding is limited by the fact that adverse events were self-reported and that users experiencing serious adverse events were unlikely to be available for after-events interviews. This possible bias appears serious when one considers that 353 participants were interviewed before but not after the dance events.

When one considers the risk factors identified in these two studies, it seems likely that not all of these risk factors actually cause adverse events. For example, the number of drugs typically used when recovering from ecstasy is likely higher in individuals who suffer more severe adverse effects. Thus the use of drugs to recover from ecstasy is likely an effect of toxicity, not a cause. Controlled clinical trials suggest that females may experience more anxiety and dysphoric reactions and physical side effects than men (Liechti et al. 2001a). This increased sensitivity may be further amplified by the fact that females tend to weigh less than men and thus may often receive a larger dose (in mg/kg) from an equivalent number of pills. It is not clearer if regularly buying fake ecstasy pills is a risk factor merely because users ascribe adverse effects to fake ecstasy or if fake ecstasy actually causes more toxicity than MDMA.

It is possible that some drug combinations increase risk of ecstasy toxicity. In addition to MDMA, 78% of ecstasy-related emergency department cases in 1999 involved other

drugs, most commonly ethanol. In the series of cases reported by Williams et al. (1998), two-thirds (32/48) involved a substance in addition to ecstasy. Unfortunately, there are insufficient data to conclude that some combinations involving ecstasy and other illicit substances are more dangerous than others.

Drugs that are known to have potential for adverse interactions with sympathomimetic amphetamines may adversely interact with MDMA. For example, case reports describe apparent adverse interactions between ecstasy and MAO inhibitors (Kaskey 1992; Smilkstein et al. 1987). It can also be speculated that there might be pharmacological interactions between MDMA and other drugs that are also substrates for cytochrome P-450 isozymes 2D6, 1A2, 3A4, or 2B6 (Kreth et al. 2000; Maurer et al. 2000). Such a pharmacological interaction may have occurred with the protease inhibitor, ritonavir (Henry and Hill 1998).

Contents of Ecstasy Pills

Published data suggest that most illicit ecstasy pills contain MDMA. For example, Schifano (2000) reports that about 85-90% of the over 20,000 ecstasy pills seized in northeast Italy over a 5 year period contained MDMA. In an analysis of the first 107 ecstasy pills submitted to the DanceSafe testing program in the United States, Baggott et al. (2000) reported that 63% contained some MDMA or an analogue (MDA or MDE). However, there are also many pills containing other substances (see **Table 6.9**). Analysis of biofluids of individuals who had reportedly taken ecstasy has revealed other compounds such as amphetamine (Cox and Williams 1996; Hughes et al. 1993; Smit et al. 1996) and PMA (Byard et al. 1998; White et al. 1997). In an attempt to capitalize on the popularity of MDMA, other intoxicants such as gammahydroxybutyrate (GHB) and *Ephedra* extracts have been marketed using names like “Liquid Ecstacy” [sic] and “Herbal Ecstacy” [sic].

Table 6.8. Potency of MDMA-Containing Ecstasy Pills

Report	0-25 mg	26-75 mg	76-125 mg	126-159 mg	Total
Bean & Pearson 1993 §	6 (50%)	3 (25%)	3 (25%)	0	12
Milroy et al 1996	2 (67%)	1 (33%)	0	0	3
Saunders 1995	1 (5%)	10 (45%)	0	11 (50%)	22
Sherlock 1999	3 (25%)	2 (17%)	5 (42%)	2 (17%)	12
Category totals	12	16	8	13	49

Adapted from (Sherlock et al. 1999). § Bean declined to confirm findings from his unpublished 1993 report, which was cited by Sherlock.

Few reports present quantitative information on the contents of ecstasy pills. The amount of MDMA found in ecstasy pills often seems to be lower than many authors assume. In neurotoxicity studies, it is commonly assumed that each pill contains 100 mg. In contrast, Sherlock et al. reported a 70-fold quantitative range of MDMA in illicit ecstasy pills. In one study of illicit ecstasy pills seized in Ireland, the quantity ranged from "not detectable" to 180 mg per pill (O'Connell and Heffron 2000).

Is Ecstasy Addictive?

Early reports found no evidence of ecstasy dependence. For example, Siegel interviewed 44 ecstasy users and determined that none engaged in compulsive use, although two had periods of intensified use during which they used ecstasy daily, ostensibly for therapeutic reasons (Siegel 1986).

However, increasing reports indicate that a minority of users engages in an out-of-control pattern of ecstasy use that leads to significant problems. Such behavior may fit the standard definition of substance dependence. The criteria for substance dependence in the most widely used psychiatric system in the United States, the Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV), are shown in **Table 6.10**. Individuals meeting three or more of these criteria within a 12-month period are considered dependent. Although the DSM-IV is not uniformly used internationally, criteria for substance dependence are almost identical in other widely used systems.

A few dependent ecstasy users have been described in the medical literature. For example, Jansen (1999) presented three case reports of dependent ecstasy users. In addition, case reports have described ecstasy users who developed ecstasy-related hepatotoxicity and, after treatment, continued to use ecstasy despite evidence of new liver damage (Khakoo et al. 1995; Shearman et al. 1992). While there is not sufficient information to diagnose these individuals as dependent, it seems likely that they would be so diagnosed if sufficient information were available.

Although the incidence of ecstasy dependence cannot be stated with certainty, recent surveys suggest that a substantial minority of ecstasy users may be dependent. In the survey of 329 polydrug-using ecstasy users in Australia, 25% wished to reduce ecstasy consumption (Topp et al. 1999). Their motivations for wanting to reduce usage were financial difficulties (57% of users), physical health problems (45%), psychological health problems (35%), occupational problems (37%), desire to improve quality of life (28%), relationship problems (17%), and feeling dependent on ecstasy (16%). Three of the 329 individuals had attended a detoxification program to reduce ecstasy use and three individuals (possibly the same ones) had attended Narcotics Anonymous for that reason. While these users cannot be conclusively classified as dependent based on this information, it seems likely that many would be considered dependent if sufficient information was available.

Table 6.9. Non-MDMA Contents of Ecstasy Pills

Content	Reference
MDA	(Curran 2000; Milroy et al. 1996; O'Connell and Heffron 2000; Renfroe 1986; Solowij et al. 1992; Sondermann and Kovar 1999; Winstock and King 1996)
MDEA or MDE	(Baggott et al. 2000; Curran 2000; Milroy et al. 1996; O'Connell and Heffron 2000; Saunders and Doblin 1996; Sherlock et al. 1999; Winstock and King 1996; Wolff et al. 1995)
MBDB	(Winstock and King 1996)
Methamphetamine	(Sherlock et al. 1999)
Paramethoxyamphetamine	(Felgate et al. 1998)
Amphetamine	(Curran 2000; Milroy et al. 1996; O'Connell and Heffron 2000; Sherlock et al. 1999; Winstock and King 1996; Wolff et al. 1995)
"Amphetamine compound"	(Renfroe 1986)
Ephedrine	(Baggott et al. 2000; O'Connell and Heffron 2000; Saunders and Doblin 1996; Shewan and Dalgarno 1996)
Pseudoephedrine	(Baggott et al. 2000; Milroy et al. 1996; O'Connell and Heffron 2000)
Procaine	(Shewan and Dalgarno 1996)
Caffeine	(Baggott et al. 2000; Milroy et al. 1996; O'Connell and Heffron 2000; Saunders and Doblin 1996; Sherlock et al. 1999; Sondermann and Kovar 1999; Winstock and King 1996; Wolff et al. 1995)
Ketamine	(Curran 2000; Sherlock et al. 1999; Shewan and Dalgarno 1996; Wolff et al. 1995)
Triprolidine	(Milroy et al. 1996)
N-methyl-1-phenylethylamine	(O'Connell and Heffron 2000)
Phenylpropanolamine	(Saunders and Doblin 1996)
Dextromethorphan	(Baggott et al. 2000; Saunders and Doblin 1996)
Selegiline	(Shewan and Dalgarno 1996)
Glyceryl guaiacolate	(Saunders and Doblin 1996)
1-Phenylethlamine	(Winstock and King 1996)
Methylaine	(Renfroe 1986)
Salicylates	(Baggott et al. 2000; O'Connell and Heffron 2000)
Paracetamol	(O'Connell and Heffron 2000; Sherlock et al. 1999; Wolff et al. 1995)

Additional drugs may have been detected in three reports that we have not yet been able to obtain (Bohn et al. 1993; Frost et al. 1996; Rashed et al. 2000).

Table 6.10. DSM-IV Criteria for Substance Dependence

Substance Dependence: A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12 month period:
1. Tolerance, as defined by either of the following: a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect b. markedly diminished effect with continued use of the same amount of the substance. 2. Withdrawal, as manifested by either of the following: a. the characteristic withdrawal syndrome for the substance b. the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms. 3. The substance is often taken in larger amounts or over a longer period than was intended. 4. There is a persistent desire or unsuccessful efforts to cut down or control substance use. 5. A great deal of time is spent in activities necessary to obtain the substance, or recover from its effects. 6. Important social, occupational, or recreational activities are given up or reduced because of substance use. 7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

The fact that a minority of users appear to develop ecstasy dependence should not be misinterpreted as evidence that MDMA has high abuse liability as the term is commonly understood with regard to drugs such as heroin. In the survey of partygoers in the Netherlands, ecstasy was not among the top three substances that participants found it most difficult to do without (van de Wijngaart et al. 1999). These substances were tobacco, cannabis, and alcohol.

Given the widespread illicit use of ecstasy, it seems almost redundant to mention studies demonstrating that animals will self-administer MDMA or find its effects rewarding. Two primate studies found that animals trained to self-inject cocaine will subsequently take MDMA. In one study, three of four rhesus monkeys self-administered MDMA (Beardsley et al. 1986). In the second primate study, three baboons self-administered MDMA at doses of 0.32 to 3.2 mg/kg per injection (Lamb and Griffiths 1987). Self-administration of cocaine occurred at a higher rate than MDMA in both studies. MDMA also makes rats more likely to electrically stimulate electrodes implanted in the median forebrain bundle or other areas of the brain thought to be involved in pleasure and drug-taking (Hubner et al. 1988; Lin et al. 1993; Lin et al. 1997a; Reid et al. 1995). The dose-dependent rewarding effects of MDMA can be further seen in conditioned place preference experiments. In these studies, animals administered MDMA will subsequently prefer the physical location in which they experienced the drug (Bilsky et

al. 1991; Bilsky et al. 1990; Bilsky et al. 1998; Bilsky and Reid 1991; Bronson et al. 1996; Marona-Lewicka et al. 1996; Schechter 1991).

The increasing evidence of ecstasy dependence in a minority of users follows a pattern seen with the non-medical use of other drugs, such as cocaine and amphetamines. When a drug is first used non-medically, reports of serious toxicity are rare and dependence is seldom recognized. However, as more people use the drug, serious toxicity and dependence syndromes may be reported. This is likely due to the changing user population and patterns of drug use as well as the fact that rare adverse events can only be detected in large samples.