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Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity

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Abstract *Aims:* Not every tablet sold as “ecstasy” contains MDMA (3,4-methylenedioxyamphetamine). The historical origins and evolution of this mismatch will be reviewed, in order to estimate the proportions of ecstasy tablets containing MDMA at different periods over the past 30 years. *Methods:* Surveys into the pharmacological constituents of ecstasy tablets, dosage levels, and empirical reports of their perceived purity, provide the main data for this review. *Results:* During the 1980s and early 1990s there were few problems with the purity of ecstasy tablets, and the biochemical evidence shows that they nearly always contained MDMA. During the mid-1990s, the majority of ecstasy tablets continued to contain MDMA, while many others comprised MDA (3,4-methylenedioxyamphetamine), MDEA (3,4-methylenedioxyethylamphetamine), or amphetamine drug mixtures. However, a small proportion (4–20% according to survey, time and place), comprised non-amphetamine drugs such as caffeine, ephedrine, ketamine, paracetamol, or placebo. During the late 1990s, the proportion of ecstasy tablets containing MDMA increased to around 80–90%. The latest reports suggest that non-MDMA tablets are now very infrequent, with purity levels between 90% and 100%. Dosage levels of tablets are also highly variable, with low dose tablet often encountered during the mid-1990s, and high dose tablets now seen more frequently. The theoretical and practical implications of these findings will be debated. *Conclusions:* The ecstasy purity problem was predominantly a phenomenon of the mid to late 1990s, when many tablets contained substances other than MDMA. Before and since then, the proportion of ecstasy tablets containing MDMA has been very high.

Keywords MDMA · Ecstasy · Amphetamine · Stimulant · Serotonin · MDMA tablet purity · MDMA tablet analysis

Psychopharmacology and recreational use of MDMA

The ring-substituted amphetamine derivative 3,4-methylenedioxyamphetamine (MDMA) is an indirect monoaminergic agonist and reuptake inhibitor (Berger et al. 1992), boosting serotonin, dopamine, noradrenaline, acetylcholine and histamine (McDowell and Kleber 1994; Green et al. 1995; Fischer et al. 2000). Its neurochemical actions are similar to those of the related ring-substituted amphetamine derivatives 3,4-methylenedioxyamphetamine (MDA), and 3,4-methylenedioxyethylamphetamine (MDEA or MDE). Hegadoren et al. (1999) thus noted: “MDA, MDMA, and MDE have all been reported to produce very similar central and peripheral effects in humans. However, there are differences in potency, time of onset and duration of action”. Their acute psychophysiological effects include sympathomimetic arousal, sensual enhancement, feelings of euphoria, and emotional closeness to others, but also brief initial nausea, then jaw clenching (trismus) and tooth grinding, which is why many users chew gum (Steele et al. 1994; Cohen 1998; Hegadoren et al. 1999; Topp et al. 1999; Parrott 2001).

The recreational use of ecstasy/MDMA has been described in numerous articles (Renfroe 1986; Peroutka et al. 1988; Solowij et al. 1992; Cuomo et al. 1994; Saunders 1995; Cohen 1998; Handy et al. 1998; Wijngaart et al. 1999; Schifano 2000; Parrott et al. 2001; Spruit 2001; Winstock et al. 2001). In historical terms, the use of MDMA was preceded by MDA, with Jackson and Reed (1970) noting that MDA was referred to as the “love pill” by recreational users in Wisconsin. Renfroe (1986) biochemically analysed 610 MDA and MDMA pills submitted anonymously to their laboratory between 1972 and 1985. Every sample sent prior to 1975 was MDA, the first MDMA was noted in 1975, the second in 1976, and over the next few years the number of MDMA capsules grad-

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ually increased, so that by the early 1980s the proportion of MDMA samples exceeded those of MDA (Fig. 3 in Renfroe 1986). Shulgin and Nichols (1978) were the first to describe the human psychopharmacology of MDMA, a compound with an: “Occasional and erratic appearance in the illicit Street drug market”. Amongst the first publications to use the term “ecstasy” was the West Coast publication “MDA/MDM: the chemical pursuit of ecstasy” (Dye 1982a), while the similar street name “XTC” also emerged around then (Dye 1982). In 1985–1986 MDMA was scheduled as an illicit drug by the USA Drug Enforcement Agency, and similar enactments were made by many other governments (Beck 1990; Dowling 1990; Wijngaart et al. 1999; Parrott et al. 2001). Despite this, its recreational use has increased steadily, so that it is now second in popularity to cannabis as an illicit drug (Pope et al. 2001).

In the 1980s, there were few questions over the purity of ecstasy/MDMA supplies (Renfroe 1986; Peroutka et al. 1988; Solowij et al. 1992). During the early 1990s, the first reports emerged of substantial numbers of ecstasy tablets not comprising MDMA, and this problem continued throughout the mid-1990s (Handy et al. 1998; Wijngaart et al. 1999; Spruit 2001). Then in the late 1990s and early 2000s, the proportion of ecstasy tablets containing MDMA reverted to high levels again (Schifano 2000; Winstock et al. 2001; Cole et al. 2002; Ramsey 2003). Thus there are three broad historical phases in the ecstasy-MDMA relationship: from the 1970s to the early 1990s; during the mid-1990s; then the late 1990s to the present time. In this review of the evolution of the ecstasy/MDMA relationship, three types of study will be debated: firstly, biochemical analyses of the chemical constituents of ecstasy tablets (Renfroe 1986; Schifano 2000; Spruit 2001; Cole et al. 2002); secondly, toxicological analyses of ecstasy-attributed fatalities (Dowling 1990; Henry et al. 1992; Milroy et al. 1996; Schifano et al. 2003); and thirdly, subjective perceptions of purity, as described in the empirical literature on recreational ecstasy/MDMA (Peroutka et al. 1988; Solowij et al. 1992; Handy et al. 1998; Winstock et al. 2001). It should be emphasized that this area is fraught with methodological problems, which may limit the reliability of the findings. Thus, none of the biochemical surveys has used a true randomized sampling procedure, few studies have covered more than a single time point, and the majority have been fairly small. Comparatively few reports have covered dosage levels. Nevertheless, despite these problems, a consistent pattern of findings has emerged. These methodological issues will be debated more fully later, when the practical and theoretical implications of the ecstasy MDMA mismatch will also be discussed.

MDMA and ecstasy from the 1970s to the early 1990s

Renfroe (1986) summarized the analysis of 20,721 street drug samples sent to a Californian laboratory between

1972 and 1985. They were assessed using thin layer chromatography, followed by confirmatory gas chromatography. Of the 610 MDA/MDMA samples, 12% were submitted as MDMA, MDM, Adam, XTC, or ecstasy. The large majority of these 89 samples contained either MDMA or MDMA/MDA mixtures, with only two not containing either MDMA or MDA. One was a capsule from Honolulu containing an amphetamine compound, the other a (largely empty) plastic syringe from Miami labeled as “ecstasy/speed”, but with no identifiable contents (Renfroe 1986, Fig. 3). In comparison with other street drugs, Renfroe (1986) concluded that MDMA supplies were of a high quality: “MDMA, when adulterated, only contained its close relative MDA. Amphetamine and methamphetamine samples, on the other hand, were often impure combinations, including a variety of CNS stimulants and sometimes barbiturates, antihistamines, analgesics and/or synthetic opiates”.

During the late 1980s and early 1990s, there were few complaints from ecstasy users about their MDMA supplies. A survey of 100 American college users reported no concerns over their purity (Peroutka et al. 1988; Peroutka 1989). Similarly in Australia, Solowij et al. (1992) noted that there were “high levels of purity in Sydney”, although it was recognized that a small minority could contain MDA. In many scientific articles from this period, the terms ecstasy and MDMA were used interchangeably, as in “MDMA more commonly known as ecstasy” (Dowling 1990), and: “ecstasy is the common name for 3,4-methylenedioxymethamphetamine” (Solowij et al. 1992; also Peroutka 1989). This perception of a direct equivalence between ecstasy and MDMA continued into the early 1990s. Hammersley et al. (1999) surveyed 209 ecstasy users in Scotland between 1993 and 1995, and no concerns over quality were described. Again, the terms ecstasy and MDMA were used interchangeably, as in “the current legal status of ecstasy as a class A controlled drug”. Davison and Parrott (1997) described an English study from 1993 to 1994, where again recreational users did not describe concerns over purity. In the USA, Dowling (1990) confirmed the presence of MDMA, MDEA or MDA, in a series of acute toxic reactions and fatalities. In the UK, Henry et al. (1992) confirmed MDMA in a similar series of ecstasy-attributed fatalities (Table 1).

MDMA and ecstasy during the mid-1990s

In 1992, the Netherlands Government established the Drug Information Monitoring System (DIMS), in response to public concern over the increasing use of dance drugs. The aims were to measure the pharmacological constituents of ecstasy tablets, monitor patterns of drug use, and assess their effects on health and well-being (Spruit 2001). The data collection procedures were not systematic, with most of the samples being brought in by individual users with a request for information about their chemical make-up. Each pill and tablet was quick-tested

Table 1 Summary of ecstasy/MDMA study findings from the mid-1970s to the early 1990s

Reference, country, and date of study	Study details	Findings
Renfroe (1986) USA 1975–1985	Biochemical analysis of 89 ecstasy, MDMA, ADAM, and XTC tablets	97% (<i>n</i> =87) contained MDMA or MDA
Dowling (1990) USA 1977–1988	Toxicological analyses of 22 deaths and acute toxic reactions attributed to MDMA and/or MDEA	MDMA and/or MDEA confirmed in each case, often with other drugs
Peroutka et al. (1988) USA 1987	Survey of 100 recreational ecstasy/MDMA users	No subjective reports of purity problems
Solowij et al. (1992) Australia 1990	Survey of 100 recreational ecstasy/MDMA users	High level of purity described
Henry et al. (1992) UK 1990–1991	Toxicological analyses of 7 deaths attributed to MDMA or ecstasy	MDMA confirmed in every case, with one also containing MDA and amphetamine
Davidson and Parrott (1997) UK 1993–1994	Survey of 20 recreational ecstasy/MDMA users	No subjective reports of purity problems
Hammersley et al. (1999) UK 1993–1995	Survey of 209 recreational ecstasy/MDMA users	No subjective reports of purity problems

Table 2 Summary of ecstasy/MDMA study findings from the mid to late 1990s

Reference, country, and years of data collection	Study details	Findings
Spruit (2001), Netherlands 1993–1997	Biochemical analysis of several thousand ecstasy tablets	44–60% MDMA only, 9–25% MDEA or MDA only, 16–25% MDMA/MDA/MDE and/or amphetamine mixtures, 6–18% others
Milroy et al. (1996), UK 1993–1995	Toxicological analysis of 7 ecstasy attributed deaths	MDMA, MDEA, or MDA confirmed in each case, often with other drugs
Milroy et al. (1996), UK 1993–1995	Biochemical analysis of 13 ecstasy tablets*	Majority (77%) contained MDEA, MDMA, MDA, or mixtures, often in low doses. Various others
Sherlock et al. (1999), UK 1994	Biochemical analysis of 25 ecstasy tablets*	Majority (64%) contained MDEA or MDMA, sometimes in low doses. Various others
Saunders (1995), UK 1994	Biochemical analysis of 30 ecstasy tablets*	Majority (87%) contained MDMA, MDEA, or MDA, but at variable dosage levels. Few others
King (2000), UK 1994–1998	Overview of police seizures of ecstasy tablets	Preponderance of MDMA and MDEA. Various others
Handy et al. (1998), UK 1996–1997	Questionnaire survey of 389 ecstasy users	Frequent concerns over the chemical constituents of tablets
Spruit (2001), Netherlands 1998	Biochemical analysis of large number of ecstasy tablets	75% MDMA only, 25% all other drugs and combinations
Baggott et al. (2000), USA 1999	Private (\$100 per test) biochemical analysis of 107 pills**	Majority (63%) MDMA, MDA, MDEA. Various others, including dextromethorphan

*Sample size too small to generate a useful population estimate

**Paid sample probably generating an overrepresentation of atypical drugs

in a three-stage procedure: initial measurement, Marquis/acid test to reveal whether it contained MDMA, MDA, MDEA or (meth)amphetamine, and cross-reference to a visual recognition chart. Those pills that could not be identified by the quick-test procedure were sent for chemical analysis, with on average “more than 100 pills a week analyzed in the laboratory” (Spruit 2001). In each year between 1993 and 1996, around 48–60% of pills contained MDMA alone, 12–20% contained MDEA alone, 2–5% comprised MDA alone, 7–13% contained MDMA mixed with amphetamine or other drugs, 1–4% contained amphetamine alone, and 2–7% comprised amphetamine mixtures excluding MDMA (i.e. with MDEA, MDA, others). Thus every year, over 80% of ecstasy samples contained a ring-substituted amphetamine or amphetamine drug type (Table 2 in Spruit 2001). However, between 6% and 17% of these yearly samples comprised “other drugs” not in the amphetamine class: hallucinogens (LSD, DOB, ketamine, 2C-B), medications (atropine), weak psychoactive drugs (caffeine, paracetamol), or un-

known compounds. In 1997, only 44% comprised MDMA alone, although 14% contained MDMA plus another drug, while 24% contained MDA, MDEA, or amphetamine, often as mixtures. The proportion of other non-amphetamine drugs was 18% (Table 2 in Spruit 2001). The low proportion of MDMA tablets in 1997 coincided with a period of high demand, and difficulties experienced by the illicit drug manufacturers in obtaining supplies of the chemical precursor for MDMA. These problems were resolved towards the end of the year, so that in 1998 the percentage of ecstasy tablets comprising MDMA had increased to 75%, and this rose further to 81% in 1999 (Spruit 2001).

Other studies from the mid-1990s also reported a range of chemical constituents in ecstasy tablets. Although generally too small to provide useful population estimates, they illustrate the variety of tablets then available (Table 2). Thus in a survey from 1994, the contents other than MDMA, MDA or MDEA comprised caffeine, amphetamine or ephedrine mixed with caffeine, caffeine

Table 3 Summary of ecstasy/MDMA study findings from the late 1990s to early 2000s

Reference, country, and date of study	Study details	Findings
Schifano (2000), Italy 1995–2000	Biochemical analysis of 20,000 ecstasy tablets	85–90% MDMA, 8–10% MDA/MDEA, 1% inactive, 1% others
Ramsey et al. (2001), UK 1998–99	Biochemical analysis of amnesty bin drug samples	“High proportion of tablets” contained MDMA. Others included 4-MTA
Spruit (2001), Netherlands 1999	Biochemical analysis of large number of ecstasy tablets	81% MDMA only, 19% all others
Winstock et al. (2001), UK 1999	Questionnaire survey of 1151 regular/heavy ecstasy users	Subjective reports of recent improvements in quality of supplies
Schifano et al. (2003), UK 1997–2000	Toxicological analyses of 75 deaths attributed to ecstasy, XTC, MDMA or MDA	91% MDMA, 9% MDA, Other drugs also in 93% of cases, mainly opiates and sedatives
Palenicek et al. (2002), Czech Republic 1998–2001	Biochemical analysis of 120 ecstasy tablets	+80% MDMA, 4% MDA, <16% others and mixtures
Cole et al. (2002), UK 2001	Biochemical analysis of 136 ecstasy tablets	100% MDMA
Dancesafe.org website, USA 2002	Biochemical analysis of 175 ecstasy tablets	88% MDMA, 4% MDA/MDE, 4% others, 4% no identifiable drug
Ramsey (2003), UK 2001–2002	Biochemical analysis of amnesty bin ecstasy samples	“Almost all” MDMA

and paracetamol, or ketamine/ephedrine/caffeine mixtures (Sherlock et al. 1999). In a later USA survey, many samples contained the antitussive dextromethorphan, while others contained caffeine, ephedrine, pseudoephedrine, salicylates, or no identifiable drug (Baggott et al. 2000). In a report from the London Police Forensic Science Laboratory, the large majority contained MDMA or MDEA, but others included phenylbutanamine, 2C-B, 4-methylthioamphetamine, and ketamine/ephedrine. Milroy et al. (1996) analyzed 13 tablets with very different appearances; they comprised a diverse array of drug mixtures, including MDMA, MDEA, MDA, amphetamine, caffeine, and pseudoephedrine, often in very low doses. During this period, there was a widespread recognition of the purity problem. Handy (1998) noted that: “It would appear that the likelihood of one purchasing ecstasy containing only (or any) MDMA has decreased as the drug’s popularity has increased”. However, it should be emphasized that the large majority of tablets still contained either MDMA, or another ring substituted amphetamine derivative. Saunders (1995) found that 26 out of 30 tablets (87%) contained MDMA, MDEA, or MDA. Similarly in Northern Italy, a survey of thousands of tablets revealed that 85–90% contained MDMA, with most of the others comprising MDA (Schifano 2000; see next section). Milroy et al. (1996) toxicologically confirmed the presence of MDA, MDE, or MDMA in a series of ecstasy related deaths (Table 2). The World Health Organization (1996) concluded at an international meeting on dance/rave drugs, that the term ecstasy was “virtually generic” for these ring-substituted amphetamine derivatives, although it was recognized that many other drug types could be encountered.

MDMA and ecstasy from the late 1990s to the early 2000s

In a review of Italian ecstasy/MDMA research, Schifano (2000) noted: “As for the content of ecstasy tablets, sources from local forensic toxicological laboratories, which have examined at least 20,000 ecstasy tablets in the last 5 years, suggest that about 85–90% of ecstasy tablets seized in the north-east of Italy contain MDMA as their active ingredient, in doses of 100–150 mg per tablet, thus confirming other reports. Methylenedioxyamphetamine and methylenedioxyethylamphetamine, drugs with effects similar to those of MDMA, are usually found in the remaining tablets. Phenylbutanamine has occasionally been found, and the rate of dummy tablets has been about 1% of the material examined”. This large survey shows that a very high proportion of ecstasy tablets from Northern Italy during the latter 1990s comprised MDMA. Spruit (2001) described the improved situation in the Netherlands in the late 1990s, following the supply problems of the mid-1990s (Tables 2 and 3); thus in 1999, around 81% of pills contained MDMA. Palenicek et al. (2002) analyzed 120 ecstasy pills and capsules from the Czech Republic between 1998 and 2002. Gas chromatography and IR-spectroscopy revealed that “over 80% of tested assays contained only MDMA”. The other samples contained amphetamine, methamphetamine, MDEA, ketamine, ephedrine, MDA, and various drug combinations, some involving MDMA.

Hansen et al. (2001) noted that Australian users surveyed between 1998 and 2000 estimated that around one tablet in every four or five was a “dud”, a ratio which approximates closely to the more systematic survey data (Schifano 2000; Spruit 2001; Palenicek et al. 2002). Winstock et al. (2001) surveyed 1151 dance clubbers in June 1999, including numerous experienced users from the “harder end” of the drugs/dance music scene. Their questionnaire covered beliefs about ecstasy/MDMA, consumption patterns, and perceptions of quality: “The

majority of respondents believed that ecstasy has become more popular over the last year.... This finding supports other anecdotal reports that the illicit ecstasy market has recovered from the quality and supply problems that were reported in the latter half of the 1990s". The American website www.dancesafe.org listed each ecstasy tablet sent in for a commercial biochemical analysis. During 2002, around 175 tablets were submitted, and 88% contained MDMA (alone or in combination), while 4% contained MDE or MDA (alone or in a non-MDMA combination; Table 3). Ramsey et al. (2001) analysed the contents of an amnesty bin from the entrance of a London dance venue. Items recovered from the bins included prescription medicines, sweets/confectionaries, and a CS gas canister. Analysis of the drug samples revealed that: "A high proportion of the tablets contained MDMA, while the powders were predominantly amphetamine". The amnesty bin analyses have been continuing, and when requested to describe their most recent findings, Ramsey (2003) reported that: "The ecstasy tablets we find in the amnesty bins at the moment are almost all MDMA". Cole et al. (2002) analysed 136 ecstasy tablets submitted to the Forensic Science Service in the north-west of England during 2001. High pressure liquid chromatography indicated the presence of MDMA in every case: "This sample of ecstasy tablets is unique in that they all contain MDMA" (Table 3).

Discussion

The relationship between ecstasy and MDMA has not been static over time, but instead has changed and evolved. This review has revealed three broad phases: before the early 1990s, throughout the mid-1990s, then from the late 1990s to the present. The first descriptions of MDMA being used recreationally were in the late 1970s, and the street name "ecstasy" first originated around 1981 (Shulgin and Nichols 1978; Dye 1982a, 1982b; Renfroe 1986). Throughout the 1980s, the street supplies of ecstasy/MDMA were of high quality and purity, although it was recognized that a small proportion of tablets might contain MDA. This allowed the scientific papers from this period to use the terms MDMA and ecstasy more-or-less interchangeably (Peroutka et al. 1988; Peroutka 1989; Cuomo et al. 1990; Dowling 1990; Solowij et al. 1992; Hammersley et al. 1999). This situation altered in the early 1990s, when a noticeable proportion of ecstasy tablets were found to contain substances other than MDMA. The problem was most pronounced during the mid-1990s, when numerous articles noted the chemical diversity of ecstasy tablets, although the overall preponderance of MDMA, MDEA, and MDA was still acknowledged (Saunders 1995; Milroy et al. 1996; Handy et al. 1998; Wijngaart et al. 1999; Spruit 2001). The final phase covers the late 1990s to the current time, when the proportion of ecstasy tablets comprising MDMA has reverted to a high level again

(Schifano 2000; Spruit 2001; Winstock et al. 2001; Cole et al. 2002; Ramsey 2003).

The non-equivalence of ecstasy and MDMA has been described in numerous recent articles, although none has described its historical origins, nor how it has evolved over time (Handy et al. 1998; Wijngaart et al. 1999; Curran 2000; McCann et al. 2000; Parrott 2000, 2001, 2002a; Schifano 2000; Spruit 2001). It should be emphasized that MDMA review papers published prior to the mid-1990s, did not mention it as a problem (Solowij 1993; Steele et al. 1994; Green et al. 1995). This was not negligence, but simply a reflection that then it was not then an issue. The current review has also revealed that while non-equivalence was important during the mid-1990s, it has become far less of a problem in recent years; possible reasons for this are discussed later. One of the aims of this article was to state the proportion of ecstasy tablets that contain MDMA, and although this is obviously difficult, some broad estimates will be offered. From the 1980s to the early 1990s, around 90–98% of ecstasy tablets probably comprised MDMA, with the remaining 2–10% generally containing MDA. During the mid to late 1990s, between 50 and 80% of pills sold as ecstasy contained MDMA, with around 5–30% containing MDA or MDEA, and around 4–20% comprising "other" drugs. In the late 1990s, around 80–95% of ecstasy tablets contained MDMA (Spruit 2001; Winstock et al. 2001), and this percentage has become even higher in the early 2000s, with the most recent surveys generating values that approach 100% (Cole et al. 2002; Ramsey 2003).

These estimates can, however, only be seen as very approximate, due to the limited nature of the empirical evidence. Only three reports have involved large samples over an extended time period: the anonymous drug testing service from California (Renfroe 1986), the DIMS project funded by the Netherlands government (Spruit 2001), and the extensive survey from Northern Italy (Schifano 2000). These studies have generated by far the most useful data for the current review, especially for generating the overall purity estimates, but the validity of their conclusions has largely been confirmed by the smaller surveys (Tables 1, 2 and 3). Nevertheless, it should be emphasized that no study has employed a randomized sampling procedure. Most have used samples brought in by recreational drug users, or obtained from amnesty bins (Renfroe 1986; Sherlock et al. 1999; Ramsey et al. 2001; Spruit 2001). Others have been of police seizures, but when these involve large batches of uniform tablets it may lead to an overestimated level of purity (Cole et al. 2002). Most biochemical testing services have been free, although Baggott et al. (2000) charged \$100 for each pill to be analyzed. This was far more than their street value, and probably led to the preponderance of atypical drugs. Thus the authors acknowledged: "Pills associated with unexpected drug effects may be over-represented in this series". These limitations emphasize the need for genuine randomized surveys, covering the full range of recreational drugs over an extended time frame.

The non-equivalence of ecstasy and MDMA has practical consequences for recreational ecstasy users, and theoretical implications for MDMA researchers (Curran 2000; McCann et al. 2000; Morgan 2000; Rodgers 2000; Parrott 2001). However, these implications will depend on the exact nature of the tablets. When they contain MDA or MDEA, their similar neurochemical profiles to MDMA mean that users would probably not be aware of any marked differences, except possibly in duration of action, or subtle variations in subjective experience (Hegadoren et al. 1999). They also have similar neurotoxic profiles, so that their neurocognitive and psychobiological consequences in long-term users will be broadly similar. Morgan (2000) noted: "Tablets sold as 'ecstasy' generally contain MDMA, or the related compounds MDEA and MDA, that produce similar neurotoxic effects". Spruit (2001) reported that even in those years when the proportion of MDMA tablets was at its lowest (1994 and 1997), the large majority to tablets still contained MDMA, MDEA, or MDA. Thus, even when the ecstasy supplies were most problematic, recreational users were still generally taking MDMA or another ring substituted amphetamine derivative (Table 2). At all other periods, the congruence between ecstasy and MDMA has been even closer, with values often around 90% (Tables 1, 3). Thus, one of the key findings to emerge from this review is the broad validity of using data from recreational ecstasy users, to estimate the human psychobiological consequences of repeated MDMA.

However, a substantial minority of ecstasy tablets comprise other psychopharmacological compounds (Table 2). Spruit (2001) noted that between 1993 and 1997, between 6% and 18% of ecstasy samples comprised "other drugs" not in the amphetamine class. Rodgers (2000) similarly noted: "Many of the pills available commercially contain, in addition to, or instead of MDMA...lysergic acid diethylamide (LSD), amphetamine sulphate, heroin, ketamine and cocaine". The ingestion of these chemically diverse compounds has a range of practical and theoretical implications. Firstly, the individual may have a very unexpected experience. The effects of the ketamine are so different from MDMA, that it could be extremely distressing when taken unknowingly. Other drugs may be even more problematical. Ramsey et al. (2001) found 4-methylthioamphetamine (4-MTA) or "flatliners" in their amnesty bins: "This drug is known to be highly toxic, having been implicated in four deaths in Britain and one in the Netherlands". A small proportion of ecstasy tablets comprise pharmacologically weak substances such as paracetamol, caffeine, or placebo, while those with stronger psychoactive profiles include atropine, opiates, phenylbutanamine and dextromethorphan (Milroy et al. 1996; Sherlock et al. 1999; Baggott et al. 2000; King 2000; Schifano 2000; Spruit 2001). The acute effects of these drugs could be unexpected and unpleasant. Hansen et al. (2001) noted that novice users were often wary about unknown tablets, whereas with experienced users: "Uncertainty was part of the process". However, it should also be noted that the majority of ecstasy/MDMA users

consciously take a wide range of legal and illicit drugs (Pedersen and Skrondal 1989; Parrott et al. 2000, 2001, 2002b; Fox et al. 2001, 2002; Winstock et al. 2001; Scholey et al. 2004). This deliberate polydrug usage is probably far more important as a potential confound than accidental/unintentional drug ingestion, and almost certainly contributes to the adverse neuropsychobiological profiles of recreational ecstasy/MDMA polydrug users (Curran 2000; Schifano 2000; Fox et al. 2001, 2002; Parrott et al. 2001, 2002; Scholey et al. 2004).

One intriguing question is why the supplies of ecstasy first became problematical. Wijngaart et al. (1999) noted: "It was not until the end of 1988 that this substance (MDMA) was placed on list 1 (drugs with unacceptable risk) of the Dutch Opium Act.... In subsequent years, analogs such as MDEA (1993) were also placed on the list". It was suggested that the 5-year time lag between the categorisation of MDMA as illegal, and the similar categorisation of MDEA, helped to explain why these related drugs became more widely sold during this period. Dowling (1990) described a similar process in the United States, where: "MDEA, also known as 'Eve', has only stated to gain prominence since the placement of MDMA on schedule 1 of the controlled substances act". The mid-1990s saw a rapid increase in demand for dance drugs, and Spruit (2001) noted that it was when MDMA was unavailable, that other psychoactive chemicals or dummy capsules were most often sold as ecstasy. Recreational users were then fully aware of these problems (Handy et al. 1998), although when interviewed, they can readily differentiate between those occasions when they feel they have taken MDMA, and their other experiences. Psychophysiological indices such as jaw clenching (trismus), tooth grinding, and the quality of subjective mood changes, are used to gauge the purity and strength of tablets. Hansen et al. (2001, p. 195) noted that the initial feelings of nausea provided a subjective estimate of MDMA purity: "Renee was the first to come on. She said that it was pretty strong as she was feeling quite vomitous. Adam reported that this was the sign of a good E". Recreational users are also very aware of poor quality supplies. This was illustrated in three studies undertaken at the University of East London over the winter of 1997, when subjective complaints were very frequent. We failed to find any neurocognitive impairments, which led to the suggestion of "poor quality tablets protecting against neurotoxicity" (Parrott 2000). Uncertainty over tablet purity has led many potential users to avoid illicit drugs (Winstock et al. 2001), while regular users often become more wary, only obtaining supplies from friends (Riley et al. 2001). Spruit (2001) suggested that consumer demand was the key factor in resolving the purity problem since "consumers prefer the conventional product".

Dosage is another important topic. Schifano (2000) noted that most samples from Italy ranged between 100 and 150 mg during the years 1995–2000. In the United Kingdom, Cole et al. (2002) noted annual average values of 90–102 mg between 1991 and 1995, which fell to 73–88 mg for the years 1996–2001. Several of the small scale

studies from the UK during the mid-1990s found dosage levels to be variable and often low. For instance, Sherlock et al. (1999) noted that while some tablets contained 100–140 mg MDMA, others contained around 50 mg, while some contained less than 20 mg (also Milroy et al. 1996). Palenicek et al. (2002) described a range of dosage levels in the Czech Republic: “Tablets vary from 30 mg to 100 mg, with borderline values 152 mg and 0 mg (lactose)”. A sample of 80 white dove tablets from a large UK police seizure in 2001 ranged between 73 mg to 89 mg, with an overall mean of 79 mg MDMA (Cole et al. 2002). Spruit (2001) noted that after the supply difficulties of 1996–1997, high dose tablets were occasionally encountered during 1998. Green et al. (2003) similarly noted that an American drug user website listed a number of high dose tablets during 2002; but while www.dancesafe.org listed various high dose examples, many were at far lower levels (or mixtures). Unknown dosage thus remains a key area of uncertainty. High dose MDMA tablets may be particularly dangerous for first time users, since they could induce a severe acute serotonin syndrome reaction (Polkis et al. 1979; Parrott 2002a, see below). In order to avoid tablets of uncertain chemical provenance and dosage, some ecstasy users have turned to powders that are often perceived as less adulterated (Parrott 2002b); however, there are no empirical data to support this notion, and powders are certainly easy to adulterate. Another potential problem is unknown chemical contaminants: ‘It is possible that contaminants of the MDMA preparation played a role in the genesis of med complications’ (Steele et al. 1994). However, King (2000) noted that: “Concern has been raised about toxic contaminants in so-called bad batches of MDMA, but there is no analytic evidence for this”. Schifano (2000) similarly noted in their large survey that “toxic impurities have not been found”.

To summarize, unknown chemical constituents will always be a problem for purchasers of any illicit drug. These practical dangers can be illustrated by a case study from the dawn of the designer drug era, although it involved MDA rather than MDMA. In 1979, a 24-year-old male took 840 mg MDA powders at a party, but died from acute MDA intoxication 4 h later: “The decedent, himself a dealer in the illicit drug market, and all present at the party believed the ingested white powder to be a mixture of morphine, LSD, and amphetamine, hence MDA. They were totally unfamiliar with methylenedioxyamphetamine, MDA.” (Polkis et al. 1979). With the increasingly wide range of illicit drugs currently available, unknown chemical constituents will always remain a serious potential problem. Nevertheless in relation to ecstasy this was mainly a issue during the mid-1990s (Spruit 2001; Table 2). In earlier days, ecstasy/MDMA was seen as a drug of high street purity (Renfroe 1986; Peroutka et al. 1988; Table 1), and in recent years its good reputation has been largely restored (Schifano 2000; Cole et al. 2002; Ramsey 2003; Table 3), with the most recent surveys suggesting MDMA purity rates of around 90–100%.

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