



THE PUBLIC HEALTH SIGNIFICANCE OF MDMA

BECKLEY FOUNDATION SUBMISSION TO THE
ADVISORY COUNCIL ON THE MISUSE OF DRUGS
ON THE CLASSIFICATION OF MDMA
UNDER THE MISUSE OF DRUGS ACT, 1971

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EXECUTIVE SUMMARY

In this submission we comment on the review of the classification of MDMA under the 1971 Misuse of Drugs Act. We examine the evidential basis for reclassifying MDMA from Class A to Class B (along with amphetamines and barbiturates) or Class C (along with anabolic steroids, benzodiazepines and growth hormones) based on the harms of MDMA relative to other drugs in the classification system.

We focus on evidence for the risk of serious medical complications including: fatality following MDMA consumption; neurotoxic effects of MDMA; long term behavioural effects; the relative harms of crystalline MDMA vs. Ecstasy tablets; the risk of developing dependence to MDMA. We also consider the use of MDMA in a therapeutic context and possible harm minimisation strategies to reduce the adverse consequences of MDMA consumption.

We conclude that, whilst there is evidence for long-term behavioural effects following heavy MDMA and other drug consumption, the harms of MDMA relative to other drugs do not warrant its current classification as a Class A drug. There appears to be a disjunct in the experimental literature on the harms of MDMA between animal studies and human studies. Moreover, approval from the Food and Drugs Administration of the US Government for the use of MDMA in carefully controlled therapeutic settings indicates a consensus that there is no significant risk from a few exposures to moderate doses of MDMA.

We think that this evidence make a strong case for better public education about the risks of repeated, heavy ecstasy consumption and the consumption of MDMA together with other drugs. We also believe there should be greater capacity for ecstasy users to determine the content of their ecstasy tablets through the further development of adulterant testing kits and onsite pill-testing programmes at raves, nightclubs and other public events.

DRUG FORMULATION

3,4-methylenedioxyamphetamine (MDMA) is a phenylisopropylamine derived from safrole, an aromatic oil found in sassafras, nutmeg, and other plants (Shulgin 1986). MDMA has been categorised by many researchers as an entactogen (Nichols 1986; Vollenweider et al. 1998a). Entactogen literally means "touching within" and MDMA is considered both the first identified and also a prototypical member of this class of drugs. Entactogens are reported to produce changes in mood, social interactions or feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens (Cami et al. 2000; Gouzoulis-Mayfrank et al. 1999; Liechti et al. 2001b; Tancer and Johanson 2003), but it also appears to possess qualities it shares in common with a small number of related compounds, such as methylenedioxyethylamphetamine (MDE) (Gouzoulis-Mayfrank et al. 1999).

PHARMACOLOGICAL AND TOXICOLOGICAL EFFECTS

MDMA possesses a complex pharmacological profile, but it is dominated by its effects on monoamine release and reuptake. MDMA's chief effect is on the release of monoamines, particularly serotonin but also releases norepinephrine and dopamine (Cole and Sumnall 2003b), and prevents uptake of all three monoamines. Recent *in vitro* studies suggest that MDMA inhibits norepinephrine uptake more strongly than dopamine uptake (Mlinar and Corradetti 2003; Verrico et al. 2007) and that MDMA does not have as strong an affinity for the dopamine transporter as methamphetamine (Han and Gu 2006). MDMA appears to alter the configuration of the serotonin transporter so that it works in reverse of its usual mode, transporting serotonin outside of neurons rather than shuttling extracellular serotonin into these neurons (Cole and Sumnall 2003b; Johnson et al. 1986; see also Rudnick and Wall 1992). While MDMA has some affinity for a range of receptors, it appears that the effects of MDMA at all receptors investigated to date is considerably lower than its

activity at any of the monoamine transporters, suggesting that any receptor-mediated effects reported in humans or nonhuman animals arise indirectly from monoamine release or inhibition of reuptake (Battaglia et al. 1988; Jones et al. 2004). Indirect effects of monoamine are likely involved in producing therapeutic effects, such as facilitated recall and changed meaning of perceptions and events, increased positive mood and increased interpersonal closeness, empathy or compassion for the self and others.

Intravenous MDMA has an LD50 of 97 mg/kg in mice and 49 mg/kg in rats, 14 to 18 mg/kg in dogs and 22 mg/kg in monkeys (Frith et al. 1987; Hardman et al. 1973). Estimating from this data, LD50 in humans is liable to fall between 10 and 20 mg/kg (Shulgin 1986).

Physiological Effects

A large body of research has examined the neurotoxic potential of MDMA, with the general consensus being that MDMA may be neurotoxic to the axons of serotonergic cells at high or repeated doses (Baumann et al. 2007; Cole and Sumnall 2003b). Studies in rodents and nonhuman primates have found that high and repeated doses of MDMA reduce brain serotonin levels and may damage the axons of serotonergic neurons (Cole and Sumnall 2003b). However, lower doses do not appear to do this (Mechan et al. 2006; Wang et al. 2005), and it is not likely that the dosages and regimens used in a therapeutic context produce these effects. The likelihood of MDMA neurotoxicity following recreational use is discussed in greater detail below.

Onset of MDMA effects occurs 30 to 60 minutes after administration (Cami et al. 2000; Mas et al. 1999), peak effects appear 75 to 120 minutes post-drug (Liechti et al. 2001b; Tancer and Johanson 2003), and duration of effects lasts from three to six hours (Harris et al. 2002; Liechti et al. 2001a; Vollenweider et al. 1998a), with most effects returning to baseline or near-baseline levels six hours after drug administration. MDMA produces sympathomimetic effects that include elevation in

blood pressure and heart rate, first recorded by Downing (Downing 1986) and replicated by other research teams in the US and Europe (Lester et al. 2000; Liechti et al. 2001a; Mas et al. 1999; Tancer and Johanson 2001). Elevation in blood pressure met diagnosis for hypertension in approximately 5% of research participants receiving at least 100 mg MDMA in research studies (Mas et al. 1999; Vollenweider et al. 1998a), but none of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned. Nevertheless the possibility of MDMA use provoking cardiac disorders in those with a pre-existing condition poses some concern, although most people do not experience elevations that are greater than seen after moderate exercise. Men given the same mg/kg dose of MDMA as women exhibited a significantly greater elevation in blood pressure, and they also exhibited a greater elevation in heart rate than women, as reported in a study summarizing and pooling data from a series of human MDMA studies (Liechti et al. 2001a). These studies did not report any discomfort or increased stress accompanying cardiovascular effects.

As previously noted, MDMA produces only a slight elevation in body temperature (Liechti et al. 2001a) and in humans, this elevation does not appear to be affected by ambient temperature (Freedman et al. 2005). Doses between 1.5 and 2 mg/kg MDMA (approximately 100-150 mg) fail to produce any clinically significant elevation in body temperature (Freedman et al. 2005; Liechti et al. 2001b). Men seem to exhibit a greater elevation in body temperature than women when given the same dose of MDMA in milligrams per kilogram (Liechti et al. 2001a). However, it is notable that participants in controlled studies have not engaged in vigorous exercise and either remained sitting or lying down throughout most drug effects. It may be the case that ambient temperature and vigorous exercise contribute to the occurrence of hyperthermia in people ingesting ecstasy in uncontrolled settings, particularly the confined and crowded settings of nightclubs. One of two naturalistic studies reported that ecstasy users had a slight but not statistically significant increase in body temperature, while the other failed to find any significant differences in ecstasy-user and non-user body temperature at a club (Cole et al. 2005; Irvine et al.

2006). Given evidence that neurotoxic effects in rodents have been found to be more significant at higher ambient temperatures, there are reasonable grounds for concern over potentially increased harms of MDMA when used in hot environments as often found in nightclubs. To understand this better more research is required.

Behavioural and psychological effects

MDMA alters mood, perception and cognition. These effects peak 90 to 120 minutes after oral administration and they are near to or at pre-drug levels three to six hours later (Lamers et al. 2003; Tancer and Johanson 2001; Vollenweider et al. 1998a). Sub-acute effects may occur one to three days after drug administration, but are no longer apparent seven to 14 days later (Harris et al. 2002; see also Huxster et al. 2006). Most of the therapeutic effects of MDMA result from changes in affect, cognition and social interaction.

People receiving active doses of MDMA experience euphoria, positive mood, vigor and positively experienced derealization, consonant with early retrospective reports, and they also experienced anxiety, tension and dysphoria, as concern over losing control over the self (Cami et al. 2000; Harris et al. 2002; Liechti and Vollenweider 2001; Tancer and Johanson 2003). It is uncertain whether the increases in positive and negative mood occur simultaneously or occur at different times throughout the duration of MDMA effects, though there is some suggestion in reports from two different teams that peaks in negative mood may precede peaks for positive mood (Liechti and Vollenweider 2000a; Tancer and Johanson 2003).

MDMA produces modest acute changes in attention and cognition, with previous reports indicating impaired performance on some tasks, e.g. digit-symbol substitution, and not others, e.g. the Stroop task (Cami et al. 2000; Gamma et al. 2000; Vollenweider et al. 1998b). Of particular public health significance has been a recent series of studies conducted in the Netherlands that examined the effects of MDMA on skills needed for driving cars. They reported transient and selective changes in

verbal and visual attention and memory after 75 or 100 mg MDMA (Kuypers and Ramaekers 2005; 2007; Ramaekers and Kuypers 2006). Changes included difficulty learning or remembering lists of words and difficulty recalling object position within an array of objects, but without any impairment in spotting scene changes, although it did provoke excessively cautious response to the actions of another car in an assessment of actual driving. MDMA acutely improved performance on one measure of impulsivity while failing to improve or impair performance on other impulsivity measures (Ramaekers and Kuypers 2006). The cause or causes behind these changes are unclear but may relate to changes in attention, salience of visual objects and altered time perception. Changes in visuospatial recall and driving skills are likely associated with serotonin release or indirect action on serotonin receptors, as the noradrenergic and dopaminergic drug methylphenidate (Ritalin) did not produce similar changes. These changes in cognitive function and psychomotor skills occurred during peak drug effects but were not detectable 24 hours later.

Retrospective surveys of people who had used MDMA or ecstasy offered similar accounts of MDMA effects to those observed and reported in controlled studies. These studies surveyed or interviewed members of several populations, including college students, psychotherapists, and individuals recruited via word of mouth or in public spaces. Study respondents reported experiencing stimulant-like effects, as greater energy or talkativeness, and hallucinogen-like effects, as perceptual changes or poor concentration. They also reported that MDMA/ecstasy increased feelings of closeness, compassion or empathy toward the self or others (Cohen 1995; Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992). The disparity in detection of entactogenic findings in retrospective versus controlled studies is largely due to failure to measure these effects, but might also relate to aspects of setting in controlled studies that do not permit enough unstructured interpersonal contact to produce or facilitate feelings of interpersonal closeness.

Therapeutic applications

Previous to its scheduling and subsequent prohibition in the mid-1980's, MDMA was used by psychotherapists in the United States in a clinical setting. Small, controlled doses of MDMA can help a patient to access deep-rooted problems and resolve conflicts, both faster and more effectively than traditional psychotherapy. MDMA promotes feelings of intimacy, relaxation, and trust, increases a sense of contemplation (Vollenweider *et al.*1998), and “inhibit(s) the subjective fear response to an emotional threat” (Greer & Tolbert, 1998). The only published study of MDMA-assisted therapy, an uncontrolled study conducted in 29 individuals with mild to moderate psychiatric problems (Greer and Tolbert 1986) found that, when combined with psychotherapy in a supportive setting, MDMA offered benefits to people experiencing various forms of anxiety disorder, including PTSD and anxiety in association with a life threatening illness. Narrative accounts report that individuals experienced less anxiety and sometimes reported feelings of reconciliation with the self or others or greater positive attitudes after MDMA-assisted psychotherapy (Greer and Tolbert 1998; Metzner and Adamson 2001). A majority of the participants in the uncontrolled study of MDMA-assisted psychotherapy followed two months to two years later reported experiencing increased positive mood and more positive attitude changes since undergoing MDMA-assisted therapy (Greer and Tolbert 1986).

To date, there are four investigations underway studying the safety and efficacy of MDMA-related psychotherapy in people with PTSD and in people with anxiety arising from diagnosis with advanced-stage cancer (Halpern 2006).

HARMS ARISING FROM MDMA

MDMA was administered to perhaps thousands of people prior to scheduling, and as of late 2007, it has been administered to approximately 300 people in uncontrolled and controlled studies. People continue to use ecstasy around the world in various nonmedical settings (Beck and Rosenbaum 1994; Carlson *et al.* 2005; Cole and

Sumnall 2003a; Solowij et al. 1992; Sumnall et al. 2006), including dance events, large gatherings, concerts and small parties. While a number of serious adverse events, including fatalities, have been reported after ecstasy use in unsupervised and uncontrolled settings, these events are relatively rare given the prevalence of ecstasy use (Baggott 2002; Gore 1999). Drug-related serious adverse events have not occurred in any of the human MDMA research studies so far. In 2005, the number of MDMA/ecstasy related emergency room visits logged into the US' Drug Abuse Warning Network (DAWN) was 10,752 of approximately 1,449,154 ED visits related to any form of drug, approximately 0.007% or calculated to be 3.6 per population of 100,000 (Substance Abuse and Mental Health Services Administration 2007). Operating on national survey data on drug use and emergency department admissions in the US and a study of Australian polydrug users, Baggott and colleagues estimated that between 2.9 and 11 emergency department visits might arise from 10,000 uses of ecstasy (Baggott et al. 2001, pp. 148-150).

Fatalities

Fatalities have occurred after the use of MDMA or related drugs in non-medical settings (Baggott et al. 2001; Henry and Rella 2001). Ecstasy-related fatalities are rare (Baggott 2002; Gore 1999). Most are related to hyperthermia and complications arising from hyperthermia. Other causes of death include hyponatremia and cardiac events (as arrhythmias or heart attack). Some ecstasy-related fatalities may be due to reckless behavior, such as driving under the influence of ecstasy. Baggott and colleagues found that men outnumbered women in most ecstasy-related fatalities except in the case of hyponatremia, where women outnumbered men (Baggott et al. 2001). The association between MDMA/ecstasy and fatalities is generally dose-dependent, except in the case of hyponatremia-related fatalities (see for example Greene et al. 2003). At least half the ecstasy-related fatalities listed seem to involve use of other drugs (Gilhooly and Daly 2002; Raikos et al. 2002; Schifano et al. 2003).

Common Adverse Effects and Side Effects

Common adverse and side effects of MDMA include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001b; Mas et al. 1999). Some reports indicated decreased rather than increased alertness (Cami et al. 2000). Other common side effects reported in controlled studies include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or facilitated recall (Vollenweider et al. 1998), and unusual thoughts or ideas (Harris et al. 2002). Sub-acute effects appearing 24 to 48 days after MDMA include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability (Baggott et al. 2001; see also Liechti et al. 2001a), with sub-acute effects waning by or within 72 hours of MDMA administration. While ecstasy users in naturalistic studies reported increased feelings of depression or aggressiveness four days after taking ecstasy (Hoshi et al. 2007a; Verheyden et al. 2003), far fewer participants in controlled studies report mood-related sub-acute effects. Naturalistic studies examining the time course of sub-acute effects of ecstasy use have reported a similar trajectory to side effects, with sub-acute effects most apparent three to four days later and no longer apparent seven days later (Hoshi et al. 2004; Huxster et al. 2006). The possibility of long-term effects is discussed in more detail below.

Medical Emergencies and Adverse Events in Ecstasy Users

An examination of the literature published up through early 2001 located over 205 published case reports or case series concerning adverse events after ecstasy use. The most frequently reported events were hyperthermia (25.1% of 199 case reports), psychological symptoms or psychosis (22.1% of 199), hepatotoxicity, or liver conditions and problems (16.1% of 199 cases), and hyponatremia (9.5%) accounted for the majority of the serious adverse events after ecstasy use (Baggott et al. 2001). A

second examination of the literature in 2004 found that these continued to be the most frequently reported problems reported in literature assessed after the initial examination (Jerome 2004), with only two new conditions reported in the literature, gingivitis from maintaining an ecstasy tablet between the lips and gum (Brazier et al. 2003), and chorioretinopathy, an eye condition sometimes associated with use of sympathomimetic drugs that cleared up after cessation of use (Michael et al. 2003).

Set and setting may play a role in the development of some ecstasy-related adverse events, such as rigorous exercise, lack of attention to somatic cues and too little or too much hydration in the case of hyperthermia and hyponatremia (Henry and Rella 2001). Hall and Henry address medical emergencies related to ecstasy use, describing all events mentioned in Baggott and colleagues (Hall and Henry 2006). While case reports do not provide an appropriate basis for estimating the relative frequency of these events, they can provide information on the possibility of an event occurring. Most ecstasy-related emergency department admissions are the result of people experiencing anxiety or panic reactions after use and involve supportive care only (Cregg and Tracey 1993; Liechti et al. 2005; Williams et al. 1998). It is notable that none of these events has occurred during a human MDMA study, so that even psychological distress has not required pharmacological intervention or hospitalization. Other serious adverse events occurring after ecstasy use include cardiac problems (as arrhythmias), cerebrovascular events, hematological, respiratory events (as pneumothorax), dermatological, ophthalmological and dental events (Baggott et al. 2001). As with the four most common serious adverse events, none of these events have occurred in the context of human MDMA research.

In vitro and in vivo investigations of the effects of MDMA on cardiac, hepatic (liver) and kidney tissues or cells have occurred over the past ten years (Baggott et al. 2001; Jerome 2005) (see for example Beitia et al. 2000; Caballero et al. 2002) (Varela-Rey et al. 1999). Researchers conducting in vitro studies often use large doses (in micromoles) that are unlikely to occur after a typical human dose. At these high or extremely high doses, MDMA damages liver cells, particularly under warm ambient

temperature, possibly mimicking hyperthermia-related hepatotoxicity in humans. In one case series of postmortem heart tissue, Patel and colleagues determined that 58.3% of the hearts from ecstasy-associated deaths were larger than normal versus 18.7% of the hearts from non-ecstasy related deaths (Patel et al. 2005). Since myocardial hypertrophy (an enlarged heart) is associated with stimulant use, and given the large extent of polydrug use in ecstasy users, this study cannot rule out the possibility that the increase they saw was not a result of psychostimulant use. A recent retrospective comparative study using echocardiograms in 29 heavy ecstasy users (reporting use of 3.6 tablets per week) and 29 age and gender matched undergraduate controls detected abnormalities indicative of potential valvular heart disease (VHD) in eight ecstasy users and none in controls, though less pronounced than abnormalities seen in people taking the anti-Parkinson's disease medication pergolide (Droogmans et al. 2007). The average cumulative dose in people with detectable abnormalities was 943 +/- 1162 tablets versus 242 +/-212 tablets in those without abnormalities. The authors hypothesize that the observed cardiac changes in ecstasy users were less prominent than in people taking pergolide because of weekly rather than daily use, and because drug-induced VHD is reversible. These findings suggest that regular use of ecstasy may have some of the same risks as regular use of other 5HT2B agonists, as some migraine medications and the appetite suppressant fenfluramine.

However, in terms of rate of complication, MDMA is responsible for far fewer serious complications than most other commonly used recreational drugs. On a scale of harm developed by Nutt and Blakemore, in which 20 substances of abuse in the UK were ranked based on physical harm, dependence, and social harm, MDMA ranked only higher than Alkyl nitrates and Khat (Nutt *et al.* 2007). It ranked significantly lower than all other Class A drugs, and also alcohol, ketamine, barbiturates, and amphetamines.

Long-Term Effects

Central Serotonin Function, Cognition and Affect: Retrospective Studies

There is a wealth of research examining the effects of repeated doses of MDMA in nonhuman animals (Cole and Sumnall 2003b; Green et al. 2003). Findings included reduction in brain serotonin, signs of impaired transport of serotonin and some behavioral changes, such as increased anxiety (Callahan et al. 2001; Gurtman et al. 2002; Hatzidimitriou et al. 1999). These findings suggested that MDMA could damage serotonin axons, producing a form of neurotoxicity. However, as noted earlier, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses. It now appears that lower doses of MDMA fail to reduce brain serotonin. Monkeys allowed to self-administer MDMA for an 18-month period had no reductions in brain dopamine, slight reductions in brain serotonin and no chemical markers of neuronal injury (Fantegrossi et al. 2004), and rats receiving lower doses of MDMA do not exhibit signs of neurotoxicity, such as changes in serotonin transporter sites or markers of neuronal injury (Wang et al. 2005). While a recent report detected increases in one marker of neuronal injury without detecting any decreases in brain serotonin after administering two human-equivalent doses of MDMA to rhesus monkeys for two days (Meyer et al. 2006). However, studies in very moderate ecstasy users failed to see an increase in this marker (de Win et al. 2007), and only one of three studies of this marker in humans detected it in heavy users (Chang et al. 1999; Cowan et al. 2007; Reneman et al. 2002).

Changes in Serotonin Function and Indicators of Neuronal Injury or Repair

Spurred on by nonhuman animal studies that found that repeated or high doses of MDMA damaged the axons of serotonin neurons, researchers began studying the effects of repeated non-medical or recreational use of ecstasy in humans (see for example Krystal et al. 1992; McCann et al. 1999; McCann et al. 1994; Semple et al. 1999). These studies detected differences in mood and cognition in ecstasy users, and possible changes in brain serotonin uptake sites. Researchers assumed that if MDMA reduced serotonin function, it should produce observable effects, such as reduced

brain serotonin uptake sites or changes in mood or psychological well-being. These early investigations possessed a number of methodological flaws, including retrospective design and poor matching of ecstasy users with appropriate controls (Gouzoulis-Mayfrank and Daumann 2006a; b). Later studies sought to remedy some of these problems by using carefully matched polydrug user or cannabis user controls, or by relying on a sample with relatively low exposure to psychoactives, including alcohol (Buchert et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Thomasius et al. 2003). Some of these investigators also conducted longitudinal studies, comparing ecstasy users, sometimes alongside controls, at two separate time points (Daumann et al. 2004b; Gouzoulis-Mayfrank et al. 2005); (Buchert et al. 2006; Zakzanis and Campbell 2006; Zakzanis and Young 2001). For the most part, these studies suggested that heavy but not moderate ecstasy users had impaired verbal memory and lower numbers of estimated SERT sites, with heavy use often defined as being at or greater than 50 times or tablets.

Estimated SERT sites returned to control levels after sustained abstinence from ecstasy, while cognitive function did not return to control levels (though see Zakzanis and Campbell 2006). These studies failed to find improved cognitive function after abstinence from ecstasy use, and they failed to find further deterioration after continued use. The different pattern of findings for SERT sites and cognitive function suggested that changes in one domain should not be treated as an indicator of changes in another domain.

Impaired Cognitive Function

Two independent meta-analyses of memory in ecstasy users arrived at somewhat contradictory conclusions (Laws and Kokkalis 2007; Zakzanis et al. 2007). While both analyses detected an association between ecstasy use and impaired performance on at least some measures of memory, one analysis, that of Laws and Kokkalis, reported that this association had a medium to large effect size and found no effect of ecstasy dose, while the other, that of Zakzanis and colleagues, reported that the association had a small to medium effect size and found a dose effect. Zakzanis and colleagues

also concluded that use of other drugs independently impaired cognitive function, while Laws and Kokkalis failed to find an association between cannabis use and verbal memory performance, relating it instead to visual memory performance. It is unclear why the two analyses reached somewhat different conclusions. Both examined a similar though not identical set of retrospective studies. It is important to note that minimum cumulative use in both analysis was above ten uses, and that average cumulative use was considerably higher (287 tablets in Zakzanis' analysis and 327 in Laws and Kokkalis' paper).

Previous research has established a link between repeated ecstasy use and impaired executive function, defined here as planning, decision-making, and inhibiting a well-learned response (Baggott et al. 2001; Cole and Sumnall 2003; Jerome 2005). The nature and strength of the association between regular ecstasy use and impaired executive function remains inconclusive, with some reports finding impaired executive function in ecstasy users, particularly heavy users (Halpern et al. 2004; Wareing et al. 2004) while others failed to find differences between ecstasy user and non-user executive function (Thomasius et al. 2003), or found executive function impairments only in male ecstasy users (von Geusau et al. 2004). Current studies continue to support both presence and absence of a relationship between ecstasy use and executive function. It is possible that variations between participants in the use of other drugs might account in part for the variation in these findings (Hoshi et al. 2007b; Medina and Shear 2006). It is also possible that variations in participants' anxiety of confirming others' negative views might have influenced the outcome of these studies. Ecstasy users performing tests of cognitive function may be affected by stereotype threat, the fear of confirming negative beliefs people hold about a specific group membership, such as race or gender. When ecstasy users heard from investigators that ecstasy use had no effects on memory, they scored higher on measures of memory than ecstasy users given information stating that ecstasy use impairs memory, while both groups of ecstasy users scored similarly to non-user controls on measures of executive function (Cole et al. 2006). Hence it may be the

case that findings of impaired cognitive function in ecstasy users are due in part to the disruptive effects of stereotype threat.

Two prevalent flaws in MDMA research between the late 1980's and the early years of this century are lack of control for polydrug use, and the continued confusion of MDMA and 'ecstasy'. Most experimental subjects included in research do not use MDMA exclusively. MDMA studies that have tracked use of other drugs have typically reported that subjects were polydrug users, which in more recent studies has been found to explain many of the psychobiological changes originally attributed to MDMA (Soar *et al.* 2008).

A further potential confound in MDMA research is the confusion of MDMA with the recreational drug, 'ecstasy'. A number of studies over the past decade analyzing the substances included in ecstasy pills have found decreasing amounts of MDMA. Instead, pills often included a blend of other drugs (recreational and otherwise), being sold as MDMA.

Ecstasy vs MDMA

When ecstasy tablets first became widely used, they could be expected to contain one ingredient – MDMA. However, in the decades since MDMA came into regular recreational use, ecstasy tablets have come to include a variety of substances, in varying amounts, and as often as not include no MDMA. Ecstasy pills may contain pure MDMA, a drug-cocktail containing MDMA, or a drug-cocktail not including MDMA. In a US study of over 1,200 ecstasy tablets (Tanner-Smith, 2006), 39% of the tablets were pure MDMA, 46% included no MDMA, and the remaining 15% included MDMA and other substances. Some substances commonly sold as ecstasy (whether on their own, or as part of a mixture) were methamphetamine, ketamine, caffeine, barbiturates, hallucinogens, and amphetamines. An earlier UK study (Cole, 2002) found higher levels of purity, with all tablets analysed including some MDMA. However, that study was on a much smaller scale (n= 80), and the tablets were all confiscated in 2001 from a single seizure.

The EMCDDA's 2006 report on the purity of synthetic drugs highlights how the MDMA content in ecstasy pills is declining. This may be interpreted as a decrease in the overall potency of ecstasy pills, or a reduction in the amount of MDMA included in them. Based on the larger US study, we expect the latter to be true. If this is the case, it would mean that recreational users are actually taking unknown drugs in unknown quantities, and also that research studying such drug users is based on flawed data. As shall be reviewed below, there is a growing body of evidence indicating that some of the harms associated with MDMA use are actually more directly attributable to polydrug use. Given the decreasing likelihood of ecstasy tablets containing MDMA alone, this gives rise to the possibility of differential harms between long term use of ecstasy tablets and MDMA obtained as a crystalline solid. In order to clarify this, more research needs to be done into the relative harms of MDMA in these different forms.

Polydrug Users

Research throughout the 1990's associated MDMA with a number of psychopathological problems. However, most studies failed to specify a difference between ecstasy and MDMA, and whether subjects also used other drugs. Epidemiological studies have found that regular MDMA users are very likely to use other recreational drugs (Webb *et al.* 1996, Pedersen & Skrondal 1999, Fox *et al.* 2001, Hopper, *et al.* 2006). Drugs commonly used in addition to MDMA include tobacco, alcohol, cannabis, amphetamine and cocaine (Gouzoulis-Mayfrank & Daumann 2006), as well as other hallucinogenic and stimulant drugs (Scholey *et al.* 2004).

Many of these substances have been associated with adverse psychological changes and health problems (Mass *et al.* 2001), and the degree of psychobiological changes in MDMA users seems to be directly related to the rate of polydrug use in addition to use of MDMA (Parrot *et al.* 2001, Medina & Shear 2007, Daumann *et al.* 2004, Morgan *et al.* 2002). Recent research suggests that psychopathological effects that have been connected to MDMA use, and reported adverse effects, may in fact be associated

more with heavy polydrug use than MDMA. Soar, Parrott & Turner (2008) found that MDMA users most often attributed positive and negative life changes to a combination of used drugs, rather than to one in particular.

As individual drug use varies in terms of regularity, dose, quality, and type of drugs used, it is impossible to say with any certainty whether damage caused was indeed a result of MDMA use. Most recent research into the long-term effects of MDMA takes into account both polydrug use and ecstasy use, which has led to a decrease in the extent of long-term effects attributed to MDMA.

Drawing conclusions from retrospective studies continued to raise questions concerning the strength and causal link between findings, especially when studies in representative samples suggested that people who chose to use ecstasy and other drugs were liable to have psychological problems prior to use (Huizink et al. 2006; Lieb et al. 2002), and given the fact that polysubstance use is so prevalent among ecstasy users (Gouzoulis-Mayfrank and Daumann 2006a). It is notable that some of the most recent studies have either found that polydrug use was equally associated with impaired cognitive function as was ecstasy use (Hoshi et al. 2007b), or that use of cannabis or other drugs make additional and even greater contributions to differences between ecstasy users and controls (Jager et al. 2007a; Montgomery and Fisk 2007).

Prospective Studies

The Netherlands XTC Toxicity team is the first to perform prospective research studies comparing ecstasy users before and after their first few uses, sometimes comparing them with controls who have not yet taken ecstasy (De Win et al. 2005). Average cumulative use in these studies ranged from 1.8 to 6 tablets, and maximum use in two of three studies was 10 tablets. In one study, the researchers imaged the brains of 30 people before and approximately seven weeks after having used ecstasy. They failed to find any chemical markers of neuronal injury in ecstasy users, and they found very few changes in cerebral blood flow, with the exception of decreased

cerebral blood volume in the dorsolateral frontal cortex (De Win 2006). Another study examined working memory in 25 people reporting an average use of 2 tablets with 24 controls. This study failed to find any significant differences either in brain activity as assessed via functional magnetic imagery (fMRI) or on tests of working memory and selective attention (Jager et al. 2007b). A study examining self-reported depression symptoms, failed to find an association between low ecstasy use and symptoms of depression, though they also failed to find a relationship between symptoms of depression and likelihood of taking ecstasy (de Win et al. 2006). Finally, a study comparing 58 people reporting use of 3.2 tablets with 60 controls before and after use (up to 18 months later) found an association between ecstasy use and performance on measures of verbal memory, and not attention or working memory (Schilt et al. 2007). While all participants exhibited scores within the normal range both times they were tested, people who did not use ecstasy showed greater improvement in performance than did people who used it. Analyses in the study assessing cognitive function apparently included one individual reporting higher cumulative ecstasy use, 30 tablets. In contrast, data from a prospective controlled study that was presented at a conference failed to find impaired cognitive function in drug-naïve individuals after two doses of 1.5 to 1.7 mg/kg MDMA (Ludewig S et al. 2003). Taken together, a majority of the prospective studies failed to find indications of structural or functional change after low ecstasy use, while one study found impairment in memory after low to moderate use. While these prospective studies do not and cannot demonstrate either a definite lack or presence of long-term effects from a few exposures to MDMA, they did not find the types of changes seen in heavy ecstasy users.

Conclusions on harms

Many studies in nonhuman animals suggest that frequent or high doses of MDMA can damage serotonin neurons, and some studies in ecstasy using humans suggest that repeated use, especially when heavy, can affect serotonergic function and specific domains of cognitive function. Ecstasy users exhibit impairment in specific areas of cognitive function, particularly verbal memory. However, when apparent,

most long-term effects seem to be more strongly associated with heavy and not moderate use, and particularly heavy polydrug use rather than MDMA use. Evidence from retrospective and prospective studies of ecstasy users suggest that this risk of impaired serotonin function or verbal memory is minimal after a low number of exposures.

Abuse Potential

Studies in humans and nonhuman animals suggest MDMA possesses some abuse potential. However, it also appears that MDMA has fewer or less intensely rewarding effects than psychostimulants, and even heavy ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence MDMA possesses moderate abuse liability that is greater than abuse liability for serotonergic hallucinogens but lesser than for psychostimulants.

Mice, rats and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006), indicating that MDMA has rewarding properties in nonhuman animals. Monkeys chose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans (Fantegrossi et al. 2004), but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine (Lile et al. 2005; Wang and Woolverton 2007). Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence (von Sydow et al. 2002), though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence (Cottler et al. 2001), and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency (Topp et al. 1999).

HARM MINIMISATION STRATEGIES

There is a strong case for educating the public about the adverse health effects of MDMA., particularly the increased risks to neuro and cognitive function of heavy MDMA consumption and combining MDMA use with the use of other drugs. There is also an argument for raising awareness of how the drug content of ecstasy tablets is extremely variable and consequently, so are the risks associated with ecstasy tablet use. In this section we present some possible strategies to reduce the harms associated with ecstasy and MDMA use, and some possible content for advice to be given to the public on the risks of MDMA and ecstasy, and how to minimise these.

1) Avoid combining MDMA use with other drugs: Given the convergence of evidence associating long term harms with polydrug use, it is important to advise users against the simultaneous use of MDMA and other drugs. It is also important to advise users of the likelihood of ecstasy pill use being inherently polydrug use due to the varying drug content of such pills.

In order to develop a better idea of the dangers presented by ecstasy pill use, we would recommend a wider programme of analysing the content of seized ecstasy pills. We would also recommend research into whether there are increased risks associated with consumption of crystalline MDMA, particularly the risk of overdose with the drug in this form. If no increased risks are found, then MDMA users might be advised to choose crystalline MDMA over ecstasy pills.

2) Implementation of on-site pill testing programmes and the development of better adulterant testing kits: Although not currently available in the UK, adulterant screening or "pill testing" is an important harm reduction service for Ecstasy users that has been implemented in various European countries and the US. Although such pill testing programmes have been criticised for encouraging drug use and increasing the likelihood of drug use, this has been refuted by a largescale EMCDDA report on such programmes. Their 2002 Report, 'Evaluation Study: Impact Of Pill

Testing Programmes With Regard To The Consumption Behaviour And Risk Consciousness Among Users Of Synthetic Drugs (ecstasy)' prepared by the Exchange on Drug Demand Reduction Action (EDDRA) analysed the results of pill-testing programmes in Hanover, Amsterdam and Vienna. They found that: 1. Health warnings about dangerous substances are received with greater trust and acceptance when delivered in the context of pill-testing programmes. 2. Pill-testing programmes result in better-informed drug users and increasingly health-conscious behaviour. 3. Pill-testing programmes do not stimulate the use of ecstasy and most likely will not extend the circle of ecstasy users. 4. Pill testing programmes lead potential ecstasy users to postpone or abstain from an initial use of the drug. 5. Pill-testing programmes serve to demystify synthetic drugs. These results are supported by a survey of Australian drug users (Johnston et al., 2006), which found that the results of pill testing might influence drug use if users found that a pill contained substances they did not want to ingest. For more information on the practicalities of pill testing, please see appendix A.

3) Advice to the public to reduce the harms associated with MDMA use: Harms from ecstasy/MDMA appear to be cumulative so reducing consumption per session and lifetime pattern of consumption can reduce harm. As many of the fatalities associated with MDMA use are the result of hyperthermia, many of the harm minimization strategies focus on raising ecstasy users' awareness of the need to be proactive in managing their temperature. The following advice is copied from the DanceSafe website (www.dancesafe.org):

- **Only take one dose on a given day/weekend.** It's a common practice among ravers to take more 'ecstasy' when they start to 'come down' off the first dose. While this may keep the party going, it may also be dangerous; the more pills you take in an evening, the greater the risk is of all sorts of bad things happening, including neurotoxicity.
- **Minimize Use to Minimize Harm.** While it is still uncertain whether MDMA is neurotoxic at recreational doses...it is clear that less frequent use is less likely to cause problems. Frequent use leads to tolerance which requires people to use higher doses

for the same effects. Keeping use to less than once every 4-6 weeks can help reduce both tolerance and chances of long-term negative impact.

- **Don't mix MDMA with other stimulants, such as amphetamines.** Combining other stimulant drugs with MDMA is a bad idea; the combination increases the risk of becoming seriously overheated, which we know is a major risk factor for neurotoxicity (and death and liver damage and many other bad things.)
- **Be aware of overheating risks and avoid hot environments.** It's much easier for your body to keep itself cool if the air temperature is low. In one experiment, rats placed in a cool room suffered no neurotoxicity from a dose of MDMA that extensively damaged the brains of rats in a warm room. If you're going to be out dancing, pick a club that's cool and has good air flow, and regularly take short breaks to cool off and assess how you're doing.

There are no absolute guarantees. While there are things you can do (and avoid doing) to reduce risk (probably by quite a bit), *any drug use poses inherent risks.*

CONCLUSIONS

Whilst the evidence reviewed in this document highlights that MDMA use is not without harms, it also indicates that MDMA itself is not as harmful as other Class A drugs, or indeed other amphetamines (currently Class B). However, the classification of MDMA poses a particular policy challenge as in the form it is most commonly consumed in, ecstasy tablets, it can be found in combination with other drugs, both Class A and Class B. Heavy use of such tablets also carries with it the increased risks of various cognitive deficits associated with heavy polydrug use. There is an argument therefore for different classifications of MDMA as a crystalline solid and ecstasy tablets, as this would highlight the increased risks associated with taking pills of unknown drug content. This said, in terms of risk of serious medical complications, the rate of such incidents following consumption of ecstasy tablets is still very low in comparison to other drugs.

Given what we know about the possible harms caused by MDMA consumption and how such harms arise, there is a strong argument for the implementation of both onsite pill testing programmes and also better public information programmes. This will help users to minimize the harms associated with MDMA and ecstasy use.

Finally, we think that the potential of MDMA as an important aid to certain psychotherapeutic treatments deserves to be further investigated, and we would like to see the development of such research programmes in the UK.

APPENDIX A

Below is some further information on pill testing programmes from the DanceSafe website (www.dancesafe.org)

What is onsite pill testing?

Onsite pill testing is a public safety service that DanceSafe and other harm reduction organizations offer to ecstasy users at raves, nightclubs and other public events where ecstasy is used socially. Users who are unsure of the authenticity of a pill they possess can bring it to a booth where trained harm reduction volunteers will test it, using a reliable, liquid reagent. All pill-testing volunteers are trained to follow strict, harm reduction protocols for responsible pill testing. These protocols have become international standards and are used in many other countries.

A short FAQ for the General Public

1. If someone's pill tests positive for ecstasy, isn't it illegal to hand it back to them?

We always hand the pill back to the user before we perform the test. The test is performed by putting a drop of testing fluid onto a tiny bit of powder we scrape from the pill. Our volunteers are in possession of the tablet only long enough to obtain the scraping and hand it back. Also, the chemical composition of the scraping is thoroughly destroyed upon contact with the testing fluid.

2. Do the police allow you to do this publicly?

Yes. Pill testing is understood as a necessary harm reduction service that saves lives without encouraging or enabling drug use. In every city where DanceSafe has tested pills onsite, we have had the support of the local police. The officers present have granted users amnesty, agreeing not to arrest them for utilizing our testing services. Similar amnesty has been given to needle exchange programs, addiction treatment centres and emergency room staff treating overdose victims. If the police started arresting users who sought out these health services, they would no longer be utilized, and more people would die.

3. Doesn't pill testing promote or enable drug use?

No. Every person who has come to our booth to have a pill tested was going to swallow it anyway. We have never enabled anyone to obtain or ingest a pill they weren't already going to take. But we have successfully prevented thousands of people from ingesting pills they thought contained ecstasy, but actually contained different drugs entirely, many of which are far more dangerous than MDMA.

4. But aren't you giving people the false impression that ecstasy is a safe drug?

We follow strict, harm reduction protocols around pill testing that were carefully designed not to give false safety reassurances to the user. No drug use is entirely safe, including and especially ecstasy, which has many inherent risks. The language we use to communicate a positive test result carefully explains this. We also require them to read a sign which further reinforces the message that a positive test result does not mean their pill is "safe" or "good."

Authored by Jonny Hazell, Researcher at the Beckley Foundation and
Amanda Feilding, Lady Neidpath, Director of the Beckley Foundation.

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