Psychopharm

Journal of Psychopharmacology
19(1) (2005) 75–87

ISSN 0269-8811
SAGE Publications Ltd, London, Thousand Oaks, CA and New Delhi
10.1177/0269881105048900

Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy

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Abstract

This review of chronic tolerance to MDMA (3,4-methylenedioxymetamphetamine) covers the empirical data on dosage escalation, reduced subjective efficacy and bingeing in recreational Ecstasy users. Novice users generally take a single Ecstasy tablet, regular users typically take 2–3 tablets, whereas the most experienced users may take 10–25 tablets in a single session. Reduced subjective efficacy following repeated usage is typically described, with many users subjectively reporting the development of tolerance. Intensive self-administration or bingeing is often noted by experienced users. This can comprise 'stacking' on several tablets together, and 'boosting' on successive doses over an extended period. Some experienced users snort Ecstasy powder nasally, whereas a small minority inject MDMA. Chronic tolerance and bingeing are statistically linked to higher rates of drug-related psychobiological problems. In terms of underlying mechanisms, neuroadaptive processes are certainly involved, but there is a paucity of evidence on hepatic and behavioural mechanisms. Further studies specifically designed to investigate chronic tolerance, involving low intermittent dose regimens, are required. Most animal research has involved intensive MDMA dosing regimens designed to engender serotonergic neurotoxicity, and this may comprise another underlying mechanism. If distal serotonin axon terminal loss was also developing in recreational users, it may help to explain why reducing subjective efficacy, dosage escalation and increasing psychobiological problems often develop in parallel. In conclusion, there is extensive evidence for chronic pharmacodynamic tolerance to recreational Ecstasy/MDMA, but the underlying mechanisms are currently unclear. Several traditional processes are probably involved, but one of the possible causes is a novel mechanism largely unique to the ring substituted amphetamine derivatives, namely serotonergic neurotoxicity.

Keywords

Ecstasy, MDMA, neurotoxicity, pharmacodynamic, pharmacokinetic, serotonin, tolerance

Tolerance

'Drug tolerance may be described as a state of progressively decreasing responsiveness to a drug. A person who develops tolerance requires a larger dose of the drug to achieve the effect originally obtained by a smaller dose' (Julien, 1995). The first published reports of human MDMA usage, noted that the positive drug effects started to decline within the first few occasions (Greer and Tolbert, 1986; Peroutka *et al*., 1988; Peroutka, 1989; Shulgin, 1986). For example, Solowij *et al*. (1992) found that the majority of light-occasional users reported some kind of tolerance to Ecstasy. It was also briefly noted by Merrill (1996) and Saunders (1995), whereas Steele *et al*. (1994) commented that some individuals felt that they needed increasing amounts of MDMA to achieve the same reinforcing psychoactive effects. Many latter reviews of MDMA have not mentioned the topic chronic tolerance (Green *et al*., 1995; McCann *et al*., 1996; Hegadoren *et al*., 1998; Morgan, 2000; Parrott, 2000; Schifano, 2000; Cole and Sumnall, 2003a;b). Kalant (2001) noted that it often took years for problems such as tolerance or dependence on new drugs to be acknowledged, and prudence suggests that it is best to reserve judgment. In a recent review, I briefly examined some of the empirical evidence for chronic tolerance (Parrott, 2001). The current review provides a more comprehensive review on chronic tolerance to recreational MDMA in humans, and an introductory debate about possible underlying mechanisms.

MDMA (3,4-methylenedioxymetamphetamine) or 'Ecstasy'

MDMA was described as 'neurochemically messy' by McDowell and Kleber (1994), and subsequent investigations have revealed many further complexities to its actions. MDMA displays high affinity for the serotonin transporter, which allows it to promote carrier-mediated neurotransmitter release and reuptake inhibition

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(Berger *et al*., 1992). These actions are thought to be crucial for generating the marked increase in extracellular serotonin that follows an acute dose of MDMA, although direct vesicle depletion is also important (Mlinar and Corradetti, 2003). An acute dose of MDMA can release large amounts of serotonin in the synaptic cleft, with a 80% loss of brain serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) within 4 h of an MDMA injection (Green *et al*., 1995). Postsynaptic receptors and somatodendritic autoreceptors can each be affected. For example, MDMA inhibits neuronal firing in the medial and dorsal raphe nuclei, by stimulating somatodendritic 5-HT_{1A} autoreceptors (Sprouse *et al*., 1989). In terms of neurotransmitter synthesis and breakdown, an acute dose of MDMA inhibits tryptophan hydroxylase, the rate limiting enzyme for 5-HT synthesis, and this leads to an acute and sub-acute reduction in serotonin availability (Schmidt and Taylor, 1987). However, in line with many other amphetamine analogues, MDMA inhibits monoamine oxidase activity (both MAO_A and MAO_B), and the consequent reduction in metabolic breakdown contributes to the increased levels of synaptic serotonin (and also dopamine and noradrenaline).

MDMA affects not only serotonin, but also other neurotransmitters including dopamine, noradrenaline, acetylcholine and histamine (Berger *et al*., 1992; McDowell and Kleber, 1994; Green *et al*., 1995; Fischer *et al*., 2000; Ricaurte *et al*., 2000; Green *et al*., 2003). The marked increase in extracellular dopamine following an acute dose of MDMA, is probably due to reversal of the dopamine transporter, which stimulates neurotransmitter release and inhibits reuptake (Cole and Sumnall, 2003b; Green *et al*., 2003). Noradrenaline, histamine, GABA, and acetylcholine systems are also affected by MDMA, either through affinity to the transporter (noradrenaline), or binding to receptors (a-noradrenergic, H_1-histaminergic, M_1-muscarinic, and also 5-HT_2, 5-HT_1 and others). The acute effects of MDMA on serotonin, dopamine and other neurotransmitters are related to dosage and time, and can vary across brain regions (Gartside *et al*., 1996). They also show many aspects of inter-dependency (Bankson and Cunningham, 2001), and are modulated by environmental factors such as ambient temperature, hydration and overcrowding; these numerous influences are described more fully elsewhere (Green *et al*., 1995; Hegadoren *et al*., 1998; Cole and Sumnall, 2003b; Green *et al*., 2003).

The acute boost in serotonin and dopamine activity can generate profound physiological and psychological changes: increased heart rate, psychomotor stimulation, impaired temperature regulation and a range of intense and generally positive mood states (Cohen, 1998: Liechti and Vollenweider, 2001). The psychological and physiological effects of MDMA are reviewed in more detail elsewhere (Steele *et al*., 1994; Green *et al*., 1995; McCann *et al*., 1996; Hegadoren *et al*., 1998; McCann *et al*., 2000; Morgan, 2000; Parrott, 2000; Kalant, 2001; Parrott, 2001; Cole and Sumnall, 2003a;b; Green *et al*., 2003). Although MDMA is relatively easy to manufacture in illicit laboratories, not every tablet sold as 'Ecstasy' comprises MDMA. When Ecstasy was first used recreationally in the 1980s, and up until the early 1990s, purity was not seen as an issue, and the biochemical evidence shows that the tablets nearly always contained MDMA, or its close relative, and metabolite MDA (methylenedioxyamphetamine; Peroutka *et al*., 1988; Renfroe, 1986; see also Table 1 in Parrott, 2004a). During the mid-1990s, the majority of Ecstasy tablets continued to comprise MDMA, while many of the others contained MDA or MDEA (methylenedioxyethylamphetamine), which are neurochemically very similar to MDMA (Berger *et al*., 1992). Others contained amphetamine drug mixtures, while a small proportion (4–20% according to time and place) contained non-amphetamine drugs such as caffeine, paracetamol, ephedrine, ketamine, or placebo (Schifano *et al*., 1998; King, 2000; Spruit, 2001; see also Table 2 in Parrott, 2004a). The third phase was from the late, 1990s to the present, when the proportion of Ecstasy tablets containing MDMA has increased to values around 80–100% (Cole *et al*., 2002; Hansen *et al*., 2001; Palenicek *et al*., 2002; see also Table 3 in Parrott, 2004a).

Given that not every Ecstasy tablet comprises MDMA, how does this affect the use of recreational user data (especially from studies undertaken during the mid-1990s), to debate chronic tolerance to MDMA? The consumption of Ecstasy tablets that do not contain MDMA will generally contribute to the error variance, and therefore reduce any tendency towards the development of tolerance. This will occur when the tablets comprised weak or inactive compounds, such as starch or caffeine. However, when they contained pharmacologically related substances, such as MDA or MDE, they might contribute towards cross-tolerance due to their similar neurochemical actions (with MDMA being metabolized to MDA; Steele *et al*., 1994). The consumption of other psychoactive substances such as amphetamine, cocaine or ketamine, would influence tolerance in complex and uncertain ways, depending on neurochemical profiles, strength and purity. A comprehensive description of the numerous ways in which all these different compounds might affect tolerance will not be attempted here. However, as a general principle, those that were pharmacologically similar to MDMA would be predicted to contribute towards cross-tolerance, whereas those which were unrelated would add to the error variance.

A related problem is the issue of dosage because any decrease in the strength of tablets could explain a corresponding increase in tablet usage. In a review of Ecstasy tablet constituents (Parrott, 2004a), only three published studies were found to cover several time points. Cole *et al*. (2002) described the average yearly MDMA contents of Ecstasy batches analysed by the Forensic Science Service in the UK. Consecutive values for each year from 1991 to 1996 were: 102 mg, 90 mg, 103 mg, 99 mg, 100 mg and 88 mg. Subsequently, from 1997 to 2001 the yearly values were: 75 mg, 77 mg, 82 mg, 74 mg and 73 mg. There was a noticeable reduction in tablet concentration of approximately 20% during the mid-1990s, whereas before and after that transitional period, the average yearly content levels remained broadly consistent. The two other surveys were from Italy during 1995–2000 (Schifano, 2000) and the Czech republic between 1998 and 2001 (Palenicek *et al*., 2002). Both reported variation in concentration levels, but neither survey suggested that there had been any systematic change over time. The above studies therefore suggest that any increase in tablet consumption cannot generally be explained in terms of reduced tablet strength, although it may be a contributory factor in studies undertaken around the mid-1990s.

The pharmacodynamic effects of single doses of MDMA have been investigated in a number of placebo-controlled studies using human volunteers (Vollenweider *et al*., 1998; Liechti and Vollenweider, 2001). However, these laboratory studies have been criticized because of the potential dangers of serotonergic neurotoxicity: 'It cannot be excluded and even seems likely that administration of a single dose of MDMA to humans causes damage to serotonergic neurones' (Gijsman *et al*., 1999). This means that there are no laboratory studies involving a series of MDMA administrations to humans because they would raise serious ethical concerns. It is therefore not possible to empirically investigate chronic tolerance to MDMA in humans under double-blind, placebo-controlled conditions.

The only empirical information on human tolerance therefore comes from studies of recreational Ecstasy/MDMA users, although surprisingly few have explicitly debated the topic of chronic tolerance (Green *et al*., 1995; Steele *et al*., 1995; McCann *et al*., 1996; Hegadoren *et al*., 1998; McCann *et al*., 2000; Morgan, 2000; Parrott, 2000; Schifano, 2000; Kalant, 2001; Parrott, 2001; Cole and Sumnall, 2003a; Green *et al*., 2003; see earlier comments). Although many studies have involved just a single Ecstasy user group, several have compared two or more groups stratified according to their past usage. They provide systematic data on how drug usage patterns can differ between novice and more experienced users (Scholey *et al*., 2004; Parrott and Lasky, 1998; Schifano *et al*., 1998; Parrott *et al*., 2000; Fox *et al*., 2001a,b; Parrott *et al*., 2001; Verkes *et al*., 2001). Furthermore a number of reports have investigated how subjective reactions and patterns of drug use change over time, whereas others have covered subjective feelings of tolerance (Greer and Tolbert, 1986; Shulgin, 1986; Peroutka *et al*., 1988; Peroutka, 1989; Solowij *et al*., 1992; Topp *et al*., 1999; Cottler *et al*., 2001; Hansen *et al*., 2001; Carlson *et al*., 2002; Verheyden *et al*., 2003a,b).

Subjective reports of tolerance and diminishing responsiveness to MDMA

In one of first articles to describe human reactions to MDMA, the experiential psychopharmacologist Alexander Shulgin (1986; p. 300) commented that: 'MDMA does not lend itself to overuse because its most desirable effects diminish with frequency of use'. This conclusion was supported by the reports of psychotherapists who were using MDMA for personal enlightenment or to facilitate psychotherapy. Greer and Tolbert (1986; p. 326) administered controlled doses of MDMA in quiet surroundings, and concluded that MDMA's diminished pleasurable effects and markedly increased side-effects when taken in either large doses or with greater frequency, distinguish it from most drugs of abuse. In the first study of American college recreational users, Peroutka *et al*. (1988) reported that 67% of those who had taken it on six or more occasions, stated that its positive effects decreased and negative effects increased with successive doses. Solowij *et al*. (1992; p. 1166) undertook an equivalent survey of one hundred Australian Ecstasy uses, of whom 55% had taken it on less than 10 occasions, and 12% had used it more than 30 times. The authors reported that: 'Many respondents alluded to the first time being the strongest, and each successive experience being in some way inferior'. Merrill (1996) similarly commented that a universal findings of descriptive studies of users of Ecstasy was that the first tablet was always the best, and with subsequent use the desired effects declined and side-effects increased.

Winstock *et al*. (2001) undertook a questionnaire survey of 1151 readers of *Mixmag*, a publication for ravers and clubbers. The sample covered a wide range of Ecstasy usage patterns, from non-users to heavy experienced users. Fifty-eight percent (n = 596) reported tolerance to Ecstasy, but no further information on tolerance was presented, and it was unclear how it related to past usage. Verheyden *et al*. (2003a) assessed a sample of 430 regular users, who had been taking Ecstasy for around 4 years. They noted: 'The most frequently reported long-term effect of MDMA was tolerance to its effects over time', with around 85–95% reporting a decline in subjective efficacy. In a follow-up investigation into reasons for quitting Ecstasy, Verheyden *et al*. (2003b) noted: 'The majority of participants reported that the pleasurable, acute psychological effects of taking MDMA declined with time. This suggest that users may become tolerant to the effects of MDMA'. It should be noted that none of the above studies reported that first time users were being tentative, or using sub-optimal dose levels on their first occasion. If this were a factor, then novice users would describe subsequent experience(s) as being stronger or better, but this has not been reported.

Cottler *et al*. (2001) surveyed 52 adolescents and young adults from Illinois who had used Ecstasy on more than five occasions. Thirty-five percent reported using much more Ecstasy to achieve the effect they wanted or found that the same amount of Ecstasy had much less effect in them that it did once, or 'tolerance'. These figures represented those who reported using much more Ecstasy or who experienced much less effect. The proportion of users who reported moderate increases in drug use, or moderate reductions in subjective efficacy, were not presented. Carlson *et al*. (2002) described a number of case studies of young recreational users including one 18-year-old suburban high school student who had used Ecstasy over 50 times, and had had to increase her drug use to feel its effects. She also described a range of mental health problems related to her drug use, and stated that: 'My tolerance has increased, so most of the time I take 3 or 4 at once. If I can't get that much, then I'll snort one and a half, chop them up and do them both at once, I've eaten up to 8 at once'. This personal illustration of reduced subjective efficacy, leads naturally to the next topic of dosage escalation.

Dosage escalation in recreational Ecstasy users

Most Ecstasy users take either a single tablet or half a tablet on their very first occasion. Hansen *et al*. (2001) noted that females were more conservative in their initial use with most consuming only 'half an E', more of the males took an entire tablet, but nobody took more than one tablet on their very first occasion. Verheyden *et al*. (2003a) did not specifically ask about the very

first occasion, but enquired about consumption patterns when they had first been taking Ecstasy (e.g. days used per month, tablets per occasion), along with current patterns of usage. These regular users reported that they now used an average of 1.8 tablets per session, compared to 1.2 tablets per session when they had been novice users. Several studies have empirically compared user groups with different levels of drug experience (Parrott and Lasky, 1998; Verkes *et al*., 2000; Fox *et al*., 2001a,b, Parrott *et al*., 2002; Scholey *et al*., 2004). Here, the empirical data on average dose per occasion, frequency of dosing, and highest dosage ever taken, provides some objective indices about chronic tolerance. Parrott and Lasky (1998) compared 15 novice users who had taken Ecstasy on less than 10 occasions, with 15 regular users who had take it one more than 10 occasions. The number of Ecstasy tablets taken one Saturday night was prospectively recorded, with the novice users taking less than the more experienced users (1.45 versus 1.80 tablets; Parrott and Lasky, 1998). Fox *et al*. (2001a) assessed three subgroups differing in their lifetime consumption of Ecstasy, and both the normal dose/occasion, and the maximum dose per occasion, both increased in line with greater experience. The most experienced Ecstasy users (+500 tablets/lifetime) took an a mean of 3.7 tablets/occasion, and reported an average maximum of 10.7 tablets/occasion (Table 1).

In a multicentre internet study of 109 novice Ecstasy users (1–9 lifetime occasions), 136 moderate Ecstasy users (10–99 occasions), and 37 heavy Ecstasy users (+ 100 occasions), the normal dosage/occasion and highest number of tablets ever taken in one week, both increased significantly in the more experienced subgroups (Scholey *et al*., 2004). A normal dose of 1–2 tablets/occasion was reported by 100% of the novice users compared to 62% of heavy users because many of these heavy users now generally took either 3–4 tablets/occasion (24%), or +4 tablets/occasion (14%; Scholey *et al*., 2004). With reference to the most tablets ever taken in 1 week, a maximum of 1–2 tablets/week was reported by 91% of novice users, 23% of moderate users and 0% of heavy users; whereas a maximum of +10 tablets/week was reported by 0% of novice users, 9% of moderate users and 35% of heavy users (Table 2). The percentage of users in each group who complained of problems that they attributed to Ecstasy use also increased significantly in line with lifetime usage, with depression, memory problems, anxiety, mood fluctuation, poor concentration, infections, tremors/twitches and weight loss, all significantly associated with the extent of past Ecstasy use (Parrott *et al*., 2002a).

Verkes *et al*. (2001) compared three groups of regular club ravers: 21 moderate Ecstasy users (defined as 12–48 occasions in the past 2 years), 21 heavy Ecstasy users (defined as +48 occasions in the past 2 years), and 20 never-users. The heavy user group reported significantly greater lifetime Ecstasy/MDMA consumption (741 compared to 169 tablets), and took significantly more tablets on each occasion (3.1 compared to 2.0 tablets). This study demonstrated a close correspondence between the frequency and intensity of Ecstasy usage, in two groups who were closely matched on many potentially founding factors. Their duration of Ecstasy use was almost identical (4.4 compared to 4.5 years), they reported nearly identical cannabis and cocaine usage patterns, whereas amphetamine and alcohol usage rates were also similar. Neuroendocrine indices of serotonergic functioning and cognitive memory task performance were impaired in both groups of Ecstasy users compared to controls, but these decrements were comparatively greater in the heavier users: 'This study shows significant association of chronic Ecstasy use with diminished memory performance and serotonergic neuroendocrine function' (Verkes *et al*., 2001). Schifano *et al*. (1998) compared 71 non-problematic and 79 problematic users who reported psychopathological disturbances

Table 2 Normal Ecstasy dose, and maximum weekly Ecstasy usage, reported by novice users (1–9 lifetime occasions), moderate users (10–99 lifetime occasions) and heavy users (± 100 lifetime occasions) (Scholey *et al*., 2004)

	Normal dose of Ecstasy on one occasion		
	1–2 tablets	3–4 tablets	+4 tablets
Novice users (n = 109)	100%	0%	0%
Moderate users (n = 136)	84%	13%	3%
Heavy users (n = 37)	62%	24%	14%
[chi-square = 39.40, d.f. = 4, p < 0.001]			
	Highest number of Ecstasy tablets in 1 week		
	1–2 tablets	3–9 tablets	+10 tablets
Novice users (n = 109)	91%	9%	0%
Moderate users (n = 136)	23%	68%	9%
Heavy users (n = 37)	0%	65%	35%
[chi-square = 169.99, d.f. = 4, p < 0.001]			

Table 1 Drug usage characteristics reported by low, medium and high Ecstasy/MDMA users (Fox *et al*., 2001a)

Drug group	Low	Medium	High	ANOVA–gp
Age	25.7 ± 4.5	26.9 ± 4.8	28.0 ± 5.3	–
Gender	5M/9F	9M/5F	6M/5F	–
Ecstasy usage (tablets)				
Lifetime (the defining criterion)	1–99	100–499	500+	
Usual tablets per occasion	1.8 ± 0.9	2.2 ± 1.1	3.7 ± 3.8	p < 0.10
Maximum tablets per occasion	3.6 ± 1.5	5.1 ± 2.0	10.9 ± 8.7	p < 0.01
Two-tailed significance values.				

Data are mean ± SD.

which they attributed to Ecstasy. The non-problematic group reported median lifetime experience of three capsules (interquartile range 1–7) compared to the problematic group's median of 47 capsules (interquartile range 20–125). The non-problematic group reported that the largest dose they had ever taken on one occasion was significantly lower (median 1, interquartile range 1–1 tablets), than the maximum amount reported by the more experienced problematic group (median 3, interquartile range 1.25–5 tablets; Schifano *et al*., 1998). Lifetime usage and dosage per occasion were again closely related.

Fox *et al*. (2001b), compared two groups who differed mainly their overall duration of Ecstasy usage; the short-term group had used it for on average 3.9 years, whereas the long term group had used it for 10.9 years. The short-term group had a significantly lower lifetime consumption (223 tablets) compared to the long term group (811 tablets). Interestingly, the long-term group reported using slightly less tablets (2.1) than the short term group (2.5 tablets; difference non-significant). This study shows a different pattern of interrelationship between duration and intensity of usage, to the other studies described in this section (Schifano *et al*., 1998; Fox *et al*., 2001a; Verkes *et al*., 2001; Scholey *et al*., 2004). It demonstrates that the long-term use of Ecstasy is not invariably linked to dosage escalation. There may even be a link between continuing with 'low' doses and longevity of usage. However, it should be noted that whereas both Ecstasy groups showed significantly poorer memory task performance than the non-user controls, only the long-term group were significantly impaired on executive cognitive processing (Fox *et al*., 2001b). These findings shows that drug usage parameters are complex and multi-faceted, and that the many different aspects may contribute in different ways to neuropsychological functioning; this is debated more fully later.

Bingeing

In one of the earliest studies of recreational users, Peroutka (1989) commented: 'It is extremely rare to find individuals who have taken large quantities of this drug … to my knowledge there are simply no reports of individuals who take frequent and large amounts of MDMA'. Other American reports from this period also described its overuse as rare (Shulgin, 1986). In their Australian survey (details above), Solowij *et al*. (1992) also found no evidence for bingeing. Winstock (1991) noted that bingeing was extremely unusual in Britain at that time. Some of the very first descriptions of bingeing were in a Scottish study from 1993 to 1995 by Hammersley *et al*. (1999). Two types of binges were described: stacking or taking several Ecstasy tablets at once, and boosting or taking repeated tablets over the evening or successive days. During a binge, many users were found to both stack and boost. Furthermore, bingeing was significantly related to heavy and erratic patterns of use, with experienced users reporting significantly more drug binges. Thus, 76% of the heavy users ('more than weekly use') had binged at least once, whereas only 16% of the light users ('less than monthly usage') had binged at all. Hammersley *et al*. (1999) noted that these intensive patterns of Ecstasy use were associated with more drug-related problems. Heavy erratic use and bingeing were both related to more problems, including days-off with illness, appetite loss and depressive experiences.

Winstock *et al*. (2001) surveyed over a thousand ravers/clubbers (mean age 24 years), the overwhelming majority of whom were Ecstasy users. Over half (54%) reported taking a maximum of five or more tablets in a single session; 16% reported a maximum of +10 tablets per session; 5% reported a maximum of +15 tablets per session, while 2% ($n = 18$) reported a maximum of +20 tablets per session. Unfortunately the cross-tabulation data with lifetime usage were not presented, and the relationship between lifetime usage and maximum tablets per session could not be gauged. Topp *et al*. (1999) assessed 329 regular users, with a mean age of 23 years and, as with many Ecstasy/MDMA studies, the proportion of males and females was similar. They had been taking Ecstasy for a mean of 3.6 years. Bingeing was defined as using the drug on a continuous basis without sleep for 48 h or more and, by this strict criterion, approximately one-third had binged during the previous 6 months. There were no demographic differences between the bingers and non-bingers, but the bingers had used Ecstasy on significantly more days in the past 6 months, and complained of significantly more physical and psychological side-effects. Topp *et al*. (1999) also assessed occupational, social, financial and legal problems, which the users attributed to Ecstasy/MDMA. Multiple regression revealed that the overall 'problem index' was significantly related to: more recent Ecstasy bingeing, self-reported tolerance to Ecstasy, greater frequency of recent Ecstasy use, and being younger. It was also noted that a small subsample felt dependent on Ecstasy and wanted to reduce their usage, but no further findings on tolerance or dependence were presented. Approximately 16% of users had injected MDMA, while 30% had snorted it (Topp *et al*., 1999). There is very little data on these other administration routes, but they are consistent with the notion of increased intensity of use in experienced users.

There are several case studies of individuals who have consumed 10–25 tablets in single sessions, and complained of severe problems which they attribute to Ecstasy (McGuire and Fahy, 1991; Schifano and Magni, 1994; Milani, 1997; Soar *et al*., 2002). Jansen (1999) outlined three case histories of extremely heavy users with severe problems. Case A was a 19-year-old male who had first used MDMA when aged 17 years: 'taking one or two pills in the weekend at parties'. Over the next 2 years, his use intensified because he had ready access to large amounts of drug. After 1 year: 'The usual pattern was to commence consumption Thursday night and continue in a binge pattern until the early hours of Monday … described as an 80-h weekend … the rest of the week was usually spent recovering. He exhibited signs if weight loss and often felt very weak'. He was currently taking 20–40 tablets of MDMA and large amounts of amphetamine and cocaine every weekend, but had just suffered a seizure which is why he was being seen at the clinic. Case B was a 30-year-old male who had originally used one or two pills on occasional weekends, although over the next 8 years he occasionally took up to 10 pills in a weekend. He then gained access to a large supply of pure MDMA powder and, for 6 months, he had been injecting 250 mg of MDMA intravenously, up to four times daily. He became highly tolerant, and reported that 250 mg

taken orally had almost no effect. The highest quantity taken in 24 h was 4 g. The powder was tested and was found to be of a very high purity with no adulterants. Despite severe depression, he was unable to stop using MDMA, although he believed this was a cause. Case C was a 25-year-old male who showed a similar pattern of dosage escalation and was now taking 25–30 tablets each weekend: 'His mother confirmed that he had sold everything he owned so he could buy MDMA, alcohol and go clubbing. He sold his television, video and clothes. He would go without sleep for days at a time, and would not eat' (Jansen, 1999).

Animal data on putative underlying mechanisms

Three underlying mechanisms for chronic tolerance to psychoactive drugs are traditionally described: hepatic/metabolic, neurochemical, and behavioural (Leonard, 1997; Julien, 1998). In terms of hepatic breakdown, MDMA/Ecstasy is metabolized mainly by CYP2D6, with several other liver enzymes including CYP2B6 and CYP1A2 also involved (Tucker *et al*., 1994; Lin *et al*., 1997; De la Torre *et al*., 2000; Heydari *et al*., 2002; Kreth *et al*., 2000;). Following its administration, MDMA forms an intermediate metabolite complex with CYP2D6, leading to the almost complete loss of the enzyme for several days, then gradual recovery over the subsequent 2–3 weeks (Heydari *et al*., 2002). In terms of enzymatic induction, a literature review uncovered no repeated dose investigations. However, Tucker (personal communication, 2002) stated: 'There is no evidence that MDMA could be subject to enzyme induction as a mechanism of tolerance – CYP2D6 is not inducable and the evidence is that even a single dose of Ecstasy will wipe out the enzyme by mechanism-based inhibition. On this basis, Ecstasy users would be recommended to dose no more frequently than 10 days to allow their 2D6 to be resynthesized! Any tolerance must be related to pharmacodynamics rather than pharmacokinetics'. It has been suggested that production of the MDMA/CYP2D6 intermediate metabolite complex may lead to the permanent loss of some enzyme (Wu *et al*., 1997). In hepatic/metabolic terms, repeated or frequent dosing would be predicted to lead to an increased susceptibility to the acute toxic effects of MDMA (Wu *et al*., 1997; Heydari *et al*., 2002). Against this prediction, many experienced users are able to regularly 'binge' (see earlier), whereas consistent with the prediction, it is the intensive users who develop the most drug-related problems (Topp *et al*., 1999).

Another factor which needs to be considered is possible neuroactive metabolites of MDMA (Marsden *et al*., 2004) because their production might be altered following repeated dosing and/or hepatic enzyme changes. Also of potential concern are the 5–9% of Caucasians deficient in CYP2D6, and it has been suggested that they could be particularly susceptible to the adverse effects of MDMA (Tucker *et al*., 1994). However, this prediction has not been empirically confirmed. Gilhooly and Daly (2000) analysed the CYP2D6 genotypes of 14 Ecstasy-attributed deaths, and found that none of them were poor metabolizers, replicating earlier post-mortem findings. To summarize, currently there is no evidence for hepatic enzyme induction as an underlying mechanism for chronic tolerance. However, there is a paucity of studies into effects of repeated MDMA on liver enzymes, and more detailed pharmacokinetic studies are required. It was noted earlier that the rate limiting enzyme for 5-HT synthesis, tryptophan hydroxylase, is inhibited by a single dose of MDMA (Schmidt and Taylor, 1987). This means that effects of successive doses of MDMA could be attenuated, leading to acute tolerance which might last for many days (Schmidt and Taylor, 1987). However, this factor may be partially counter-balanced by its acute inhibitory effects on MAO (see earlier), leading to the effects of successive MDMA doses being potentiated. The topic of acute tolerance is not formally covered in this review, although any changes in the patterns of acute tolerance with repeated MDMA usage, might affect chronic tolerance.

With reference to neurochemical tolerance, Callaway and Geyer (1992) noted that: 'Many neurotransmitter receptors undergo adaptive changes of number or sensitivity in response to prolonged overstimulation. In particular, both 5-HT_1 and 5-HT_2 receptors have been found to down-regulate or desensitize during treatments that increase 5-HT availability'. Because MDMA is a powerful indirect 5-HT agonist, neurochemical tolerance following its repeated administration would be predicted. Callaway and Geyer (1992) confirmed that MDMA pre-treatment led to some reduction in response to a subsequent MDMA challenge, although only at certain time points (e.g. see their Fig. 4). They concluded that their findings were broadly consistent with a functional desensitization of the postsynaptic 5-HT receptors that mediate the behavioural effects of s-MDMA. However, their 21-day data were statistically only borderline, with a significant ANOVA group–time interaction (congruent with tolerance), and a non-significant post-hoc group comparison (suggesting non-tolerance; Callaway and Geyer, 1994). Aguirre *et al*. (1995) found that an intensive repeated dose regimen (30 mg i.p. twice daily over 4 successive days), led to an increase in 5-HT_{1A} receptor density in the frontal cortex, together with a parallel decrease in 5-HT_{1A} receptor density in the dorsal raphe region. The frontal cortex post-synaptic receptor density changes were interpreted as possibly indicating: 'Adaptive changes to compensate for the loss of serotonin nerve terminals' (also in the hippocampus; Aguirre *et al*., 1995). Because MDMA acutely stimulates 5-HT_{1A} autoreceptors in the raphe region, equivalent neuroadaptive mechanisms were proposed to explain the decrease in somatodendritic autoreceptors after repeated dosing. Reneman *et al*. (2002) demonstrated a time-dependent increase in cortical 5-HT_{2A} receptor density, which was strongly correlated with the extent of MDMA induced serotonin loss; again, this was interpreted as compensatory up-regulation.

Animal studies have employed a variety behavioural measures. Slikker *et al*. (1989) found a marked decline in the acute serotonin syndrome scores, of rats treated with MDMA over 4 successive days; however, the locomotor activity scores did not change significantly. Zacny *et al*. (1990) reported chronic tolerance, with reduced levels of MDMA-induced suppression of milk-drinking in deprived rats, following a previous series of daily MDMA injections. Two studies have demonstrated reverse tolerance or sensitization. Li *et al*. (1989) administered a brief series of MDMA doses, and found: 'Four weeks later there was an increase in sensitivity to a single administration of MDMA'. Spanos and Yamamoto

(1989) also found an augmented serotonin syndrome response, and greater locomotor changes to an acute MDMA challenge, following an earlier series of MDMA injections. Frederick *et al*. (1995) administered an escalating dose regimen to rhesus monkeys (0.10 mg/kg to 20 mg/kg intramuscularly, twice daily over 14 consecutive days). Performance on the operant test battery (short-term memory, learning, motivation and other tasks), demonstrated tolerance following repeated exposure within each dose level, and with each escalating dose. Twenty-one months later, the animals were sacrificed and showed significantly reduced levels of hippocampal 5-HIAA, 5-HT uptake sites and 5-HT turnover, although 5-HT concentration levels were not significantly affected in any brain region. The authors concluded: 'These data suggest that chronic administration of gradually increasing doses of MDMA results in long-lasting tolerance to the drug's acute effects … It is uncertain, however, if such tolerance is related to the observed decreases in uptake sites and turnover of 5-HT in the hippocampus…' (Frederick *et al*., 1995). Tolerance was confirmed in a subsequent study, when rhesus monkeys showed an attenuated behavioural response to an MDMA challenge, following an earlier (non-incremental) intensive dosing with MDMA. Here, the reduced behavioural responses on the operant test battery, were accompanied by a significant decrease in 5-HT in several brain regions, together with a depletion of 5-HT receptor uptake sites on the frontal cortex (Frederick *et al*., 1998). In conclusion, behavioural performance measures and neurochemical assays have often indicated tolerance, but further studies are required. Callaway and Geyer (1992) suggested that the occurrence of tolerance in some studies, but reverse tolerance in a few others, might be due to different behavioural measures, testing environments or dosing regimens.

However, it may be that none of the above studies have been using a dosing regimen which is optimal for inducing chronic tolerance; more widely spaced doses over a longer time frame might provide a better model. For example, see the design utilized by O'Shea *et al*. (1998; outlined below), or the self-administration paradigm used by Fantegrossi *et al*. (2004). Here, seven rhesus monkeys were initially trained on cocaine self-administration, then three of them were assessed an extended series of MDMA self-administration sessions. The overall group showed a reduction in responding over the 18 months, suggesting that MDMA had become less reinforcing over time. This contrasted with the unaltered levels of cocaine self-administration. However, the three MDMA monkeys showed considerable individual variation in their changing patterns of self-administration over time. Two of the three animals demonstrated a right shift in their dose–response curves. Their responses reduced to the lower doses, but were maintained (one animal), or increased (the other animal), to the higher dose conditions. By contrast, the third monkey demonstrated a reverse pattern (Fantegrossi *et al*., 2004, see their Fig. 3). Neurochemical correlates were investigated, but no significant differences between the MDMA and 'control' monkeys (extensive polydrug users!) emerged. However, the very small sample sizes were acknowledged as a limitation, and it was also noted: 'Although not significant, downward trends in 5-HT content were present in several brain regions following long-term MDMA self-administration; depletions of 40–50% were evident in frontal, parietal, and temporal cortex' [for a more detailed discussion of Fantegrossi *et al*., 2004; see Parrott (2004c)]. These findings lead naturally to the next topic of serotonergic neurotoxicity.

Serotonergic neurotoxicity and chronic tolerance to MDMA

In laboratory animals, single high doses of MDMA, or a series of lower doses, cause the loss of distal 5-HT axon terminals in higher regions, while leaving the midbrain cell bodies intact; this serotonergic neurotoxicity is a well established phenomenon in rats, rhesus monkeys, and baboons (Schmidt, 1987; Sprague *et al*., 1988; Steele *et al*., 1994; Green *et al*., 1995; Huether *et al*., 1998; Ricaurte *et al*., 2000; Green *et al*., 2003). In humans, it is not possible to empirically investigate neurotoxicity directly, but there is an increasing body of evidence for equivalent structural and functional problems. Brain imaging studies of recreational Ecstasy users often indicate serotonergic loss (McCann *et al*., 1998; Obrocki *et al*., 1999, Semple *et al*., 1999; Kish *et al*., 2000; Reneman *et al*., 2001, Kish *et al*., 2002; Reneman *et al*., 2002; but see also Kish, 2002), or a reduced prolactin response to a dexfenfluramine challenge (Gerra *et al*., 2000; Verkes *et al*., 2001). Abstinent recreational users display various functional deficits which have been linked to serotonergic loss: significant memory impairments (Parrott *et al*., 1998; Morgan, 1999; Meyfrank *et al*., 2000; Morgan, 2000; Rodgers, 2000; Fox *et al*., 2001a,b; Rodgers *et al*., 2001; Verkes *et al*., 2001; Zakzanis and Young, 2001; Fox *et al*., 2002; Gouzoulis-Parrott *et al*., 2002; Rodgers *et al*., 2003), higher cognitive processing deficits (Morgan, 2000; Wareing *et al*., 2000; Fox *et al*., 2001b, 2002), disrupted sleep (Allen *et al*., 1994), and elevated psychiatric symptom profiles (Mc Cann *et al*., 1996; Schifano *et al*., 1998; Parrott *et al*., 2000, 2001; Soar *et al*., 2001). These functional deficits may be exacerbated by a range of drug-related factors (Parrott, 2001; Parrott *et al*., 2001).

The extent of neuropsychobiological problems has also been found to be significantly related to the amount of past Ecstasy/MDMA usage. Dafters (1999) reported that reduced EEG coherence, was significantly negatively related to the amount of Ecstasy used in the previous 12 months. McInnes *et al*. (2001) found that the maximum number of Ecstasy tablets taken in 12 h, was significantly related to the severity of current depression in former users. Zakzanis and Young (2001) prospectively demonstrated that Ecstasy usage in a 12-month period, was significantly correlated with the decline in performance on some memory tasks. Bolla *et al*. (1998) noted that lower concentrations of cerebrospinal 5-HIAA were associated with poorer memory performance. Fox *et al*. (2001a) found that the degree of memory impairment was significantly related to past usage. Several other studies have demonstrated a similar association between past Ecstasy/MDMA use and neurocognitive impairments (Parrott and Lasky, 1998; Verkes *et al*., 2001; see also Table 1–3 in Morgan, 2000). Several have also found a significant association between past Ecstasy use, and the extent of psychobiological problems or psychiatric symptoms (Topp *et al*., 1999; Milani *et al*., 2000; Parrott *et al*., 2002).

Table 3 Novice, moderate, and heavy recreational Ecstasy/MDMA users. Percentage of each group reporting problems when drug-free, which they attribute to the use of Ecstasy (Parrott *et al.*, 2002; note: same Internet study and participants as Table 2)

Ecstasy/MDMA user group	Novice	Moderate	Heavy	
Ecstasy usage (lifetime occasions)	1–9	10–99	+100	
Sample size (*n*)	109	136	37	
Mood and cognitive problems attributed to Ecstasy use				Chi-square
Depression	33%	54%	65%	16.23***
Mood fluctuation	38%	70%	80%	31.21***
Impulsivity	18%	26%	32%	3.79, NS
Anxiety	32%	40%	60%	9.37**
Poor concentration	32%	62%	70%	29.80***
Memory problems	19%	52%	73%	42.74***
Physiological and medical problems attributed to Ecstasy use				Chi-square
Weight loss	10%	37%	48%	28.99***
Infections	5%	9%	35%	24.94***
Tremors/twitches	14%	20%	38%	9.95**
Poor sleep	37%	41%	52%	2.15, NS
Sexual problems	7%	11%	22%	3.94, NS

Chi-square analyses (2 × 3, d.f. = 2, two-tailed) on the yes/no responses from the three groups. ***$p < 0.001$, **$p < 0.01$. NS, non-significant.

The data from an Internet study of 282 recreational Ecstasy users are summarized in Table 3; they show that Ecstasy-attributed problems increase in line with greater lifetime usage.

Serotonin loss may be an important contributory factor for chronic tolerance. Any reduction in functioning neurotransmitter will reduce subjective efficacy, and cause the need for higher doses. However, these higher doses will be acting on an increasingly impaired system, and will therefore not be able to induce stronger subjective effects. In the early stages, there may be some balance between repeated usage and receptor up-regulation, allowing positive subjective experiences to be largely retained. However, with increasing use, there will be a further loss in efficacy, more serotonergic psychobiological problems will develop, and patterns of usage will intensify – with bingeing, snorting, and/or injecting. This is exactly the pattern found with many Ecstasy/MDMA users (Topp *et al.*, 1999). Hence, on current evidence, one possible contributory factor for chronic tolerance is the gradual loss of functional serotonin. Merrill (1996) was the first to suggest that serotonergic neurotoxicity may be causing tolerance to MDMA in humans: 'A universal finding of descriptive studies of users of Ecstasy is that the first tablet is always the best, and with subsequent use the desired effects decline and side-effects increase. As Ecstasy is pharmacologically active for only a few hours and most users limit their use to weekends, neurotoxicity seems a more likely explanation than tolerance through neuro-adaptation'. Saunders (1995) also suggested that the common complaint of recreational users that Ecstasy tablets were becoming weaker might be a reflection of serotonergic loss. The explanatory model being proposed here is that as more Ecstasy/MDMA is used, then 5-HT axonal terminal loss will increase, and concomitant functional deficits will also develop. Recreational users will need to take higher doses, but these will be acting upon a damaged serotonin system, and will therefore be less effective. Further dosage escalation will lead to yet more neural damage, such that heavy Ecstasy/MDMA users will complain of numerous problems (Table 3). Thus, chronic tolerance, structural damage, and functional problems, will all develop in parallel. It should be emphasized that neural damage should be seen as an additional possible factor, rather than an alternative to the more traditional mechanisms.

Methodological caveats and future research

A number of methodological and theoretical caveats need to be raised. Ecstasy/MDMA users are generally polydrug users, with heavy users in particular taking a wide range of legal and illicit drugs (Pedersen and Skrondal, 1999; Topp *et al.*, 1999; Parrott *et al.*, 2000, 2001; Winstock *et al.*, 2001; Parrott *et al.*, 2002; Scholey *et al.*, 2004). The contribution of polydrug use towards Ecstasy/MDMA tolerance is unclear, but will certainly be complex. The regular use of other central nervous system stimulants may foster cross-tolerance to MDMA, whereas the contribution of other psychoactive drugs would depend upon their neurochemical profiles. The next complicating factor is that MDMA affects a wide range of neurotransmitter systems, not just serotonin, but also dopamine, noradrenaline, acetylcholine, and histamine (Berger *et al.*, 1992; McDowell and Kleber, 1994; Green *et al.*, 1995; Hegadoren *et al.*, 1998; Fischer *et al.*, 2000; Ricaurte *et al.*, 2000; Green *et al.*, 2003). Neuroadaptive changes in all these neurotransmitter systems would be predicted to contribute to tolerance, although in complex ways which may be difficult to untangle. To give one possible scenario, if serotonergic tolerance developed at a faster rate than tolerance to these other neurotransmitters, then the psychoactive profile of MDMA would alter with repeated usage. These ideas and possibilities merely serve to emphasize the limitations of current knowledge.

In terms of future research, a core aim of animal studies should be to clarify the relative roles of neurochemical adaptation, hepatic

enzyme changes, behavioural tolerance and serotonergic neurotoxicity. All these mechanisms probably have contributory roles, but they are likely to display a range of subtle and complicated interrelationships. One crucial aspect may be receptor up-regulation in the higher brain regions, in response to serotonin axon terminal loss, coupled with somatodendritic down-regulation in the raphe nuclei (Aguirre *et al*., 1995; Reneman *et al*., 2002). Another is the possible links between neuroadaptive changes and serotonergic loss (Frederick *et al*., 1995, 1998). This may be further illustrated with reference to Gartside *et al*. (1996), who administered a neurotoxic regimen of MDMA (20 mg/kg subcutaneous, twice daily for 4 days), and found a diverse pattern of neural activity changes 2 weeks later. The extent of 5-HT release from the frontal cortex following electrophysiological stimulation of the dorsal raphe nucleus, was markedly reduced. However, there was no change in 5-HT release from the hippocampus, after stimulation of either the dorsal or median raphe nuclei. In this same study, the neurotoxic regimen resulted in a 50% reduction in 5-HIAA levels in both regions, whereas 5-HT release to low levels of stimulation were unaffected. The authors discussed these (and related) findings in terms of neuroadaptive up-regulation, which provides partial compensation for the distal axon terminal loss. This allows basal functioning to be left intact, with deficits only becoming apparent under particular conditions: 'Our data suggest that, after MDMA, although cortical 5-HT nerve terminals can maintain 5-HT release at low frequency of cell firing, they are unable to do so when the frequency of cell firing increases'. They also noted that their study was only short-term, and that: 'Deficits in 5-HT neuronal function may be more marked in the long term' (Gartside *et al*., 1996).

Ambient temperature is important for the development of serotonergic neurotoxicity (Malberg and Seiden, 1998), and tolerance may develop more rapidly in animals administered MDMA under high temperature conditions. Indeed, this paradigm could provide a test for the hypothesized links between developing tolerance, and the neuroadaptive, hepatic, and neurotoxic changes. Differences in metabolic profiles across animal species and strains may also help elucidate the relevant factors; possibly a comparison of Dark Agouti versus Sprague-Dawley rats within the same study? Another important topic is how the different neurotransmitter systems adapt to repeated MDMA administration, both singly and inter-relatedly (Bankson and Cunningham, 2001). A related topic is acute tolerance, or the effects of closely spaced successive doses. There is some limited data on this issue (Pacifici *et al*., 2001), but the topic needs to be further studied in both animals and humans. Another factor is the spacing of doses. O'Shea *et al*. (1998) compared the effects of single doses (low to high), closely spaced multiple low doses (daily or twice daily), and more widely spaced multiple low doses (twice weekly for 8 weeks). Neurotoxicity was apparent in the intensive regimens, but did not develop in the more widely spaced condition. This paradigm could be used to investigate many of the hypotheses being raised here.

There are several important topics for future human research. One crucial question is the role of drug usage patterns. How do intermittent versus frequent usage, low versus high doses, or the combined use of MDMA in polydrug cocktails, influence the development of tolerance? Are some individuals more cautious in their patterns of drug use, and does this help them to minimize the development of tolerance or avoid it completely? This is related to the question of how some Ecstasy users continue using MDMA for many years. Do they have a robust serotonergic system, use MDMA only in cool/quiet conditions (non 'rave' environments), or otherwise follow a health conscious route, and so minimize dosage escalation (Hansen *et al*., 2001; Parrott, 2003, 2004b,d)? Many of these questions might be addressed by prospective brain imaging studies, with changes in neurotransmitter activity, MDMA/Ecstasy usage patterns, and neuropsychobiological integrity, being assessed in parallel over time. This could provide valuable data on how the development of tolerance to MDMA, was related to any structural and functional changes in serotonergic activity. It may be that some mechanisms are more important during the earlier stages of tolerance (behavioural and neuroadaptive?); whereas other mechanisms may become more prominent following repeated usage (neurotoxicity?). A crucial period may be the first few occasions of Ecstasy use. How do the subjective experiences and psychophysiological reactions alter with continued usage, and could they be related to the different patterns of dosage escalation, and the hypothesized alterations in neural integrity? Clearer data on dosage regimens would be useful, behavioural mechanisms for tolerance need to be studied (Julien, 1998), while individual difference and genetic factors may help to explain any variation in rates of development.

Overview

Chronic tolerance to Ecstasy/MDMA in humans is a robust empirical phenomenon. Many recreational users report reducing subjective efficacy with repeated drug use, together with dosage escalation, and bingeing. However, the patterns of tolerance displayed by regular users, and the underlying mechanisms, both appear to be rather unusual. MDMA has been described as unique it is acute entactogenic effects because it displays a mixed stimulant, hallucinogenic and euphoriant profile (Nichols, 1986; Cole and Sumnall, 2003a). MDMA is also unique in some aspects of its chronic tolerance. First, it often develops quite rapidly. Numerous commentators have noted that Ecstasy users describe their first experience as the 'best', and that with repeated use its positive effects subside (Peroutka *et al*., 1988); this is not generally apparent with any other class of psychoactive drug. Fantegrossi *et al*. (2004) noted that the reinforcing effects of self-administered MDMA declined over time in rhesus monkeys, whereas the rewarding effects of cocaine remained undiminished. Shulgin (1986) predicted that MDMA would not become a drug of abuse, specifically because of the early reduction in subjective efficacy. Instead, many recreational users increase their dosage levels. Here again, the effects are rather unusual: 'Taking a double dose of MDMA does not double the supposed good effects of the drug but simply increases the negative effects' (Peroutka, 1989). Dosage escalation appears to help to maintain a positive drug experience in the face of reducing efficacy; but this greater intensity of usage is associated with an increase in drug-related neuropsychobiological problems (Schifano *et al*., 1998; Topp *et al*., 1999; Milani *et al*.,

2000; Parrott *et al*., 2000, 2002; Scholey *et al*., 2004) (Table 3). Regular user therefore need to balance their desire for an optimal on-drug experience, with the need to minimize the post-drug consequences.

This subtle equation may help explain why Ecstasy users can follow such a range of drug taking patterns (Fox *et al*., 2001b; Parrott *et al*., 2002b, Parrott, 2003). Some individuals intensify their usage to maximize the on-drug experience, whereas others use it sparingly to minimize the long-term consequences. These two patterns are illustrated in two Australian studies of Ecstasy/MDMA users (Hansen *et al*., 2001; Topp *et al*., 1999). In both studies the average duration of usage was 3.5 years, but the patterns of drug use were markedly different. The participants in Topp *et al*. (1999) used Ecstasy/MDMA intensively, often at raves and clubs, with some injecting, snorting, or using it continuously for +48-h periods; they also reported numerous psychobiological problems which they directly attributed to Ecstasy. By contrast, the group studied by Hansen *et al*. (2001) used Ecstasy/MDMA intermittently, generally at parties, and none described themselves as ravers. They reported being aware of the dangers of MDMA/Ecstasy, and showed only slight dosage escalation with one participant noting: 'I think the major risk is taking too many'. (Hansen *et al*., 2001). Comparatively few drug related problems were described, but even with this health conscious group: 'It was universal that as users became more experienced, they exhibited a pattern of use that included the consumption of greater amounts of Ecstasy'. Although chronic tolerance generally accompanies regular MDMA usage, its rate of development can be variable, and a number of users may not develop it. The limited evidence suggests that intermittent patterns of usage, in non-hyperthermic environments (Hansen *et al*., 2001; Parrott, 2001, 2002, 2004b) may help to minimize its development.

In terms of underlying mechanisms, hepatic enzyme induction, neuroadaptation and behavioural changes are the traditional routes for chronic tolerance to psychoactive drugs (Leonard, 1997; Julien, 1998). Neuroadaptive changes certainly occur, but current knowledge is insufficient to describe their full complexity, and further studies are certainly needed. Given the paucity of data on other mechanisms, their relative contributions are also unclear, but it would be unusual if they did not also have contributory roles. However, there is extensive empirical data on serotonergic neurotoxicity, and this would comprise a clear (although novel) mechanism for inducing chronic tolerance. Indeed, it is difficult to see how any drug could fail to become less effective, if it is gradually destroying the axon terminals needed for the desired psychological experiences. Thus, the unusual pattern of chronic tolerance with MDMA, may at least partially reflect a unique underlying mechanism – serotonergic neurotoxicity.

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