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Pill content, dose and resulting plasma concentrations of 3,4-methylendioxymethamphetamine (MDMA) in recreational 'ecstasy' users

Kate M. Morefield[1], Michael Keane[1], Peter Felgate[2], Jason M. White[1,3] & Rodney J. Irvine[1]

Discipline of Pharmacology, University of Adelaide, Adelaide, SA, Australia,[1] Forensic Science South Australia, Adelaide, SA, Australia[2] and School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia[3]

ABSTRACT

Aims To improve our understanding of the pharmacology of 'ecstasy' in recreational environments; in particular, to describe the composition of ecstasy pills, patterns of ecstasy use and the relationship between dose of 3,4-methylendioxymethamphetamine (MDMA) and resulting plasma concentrations. **Design, setting and participants** A naturalistic observational study of 56 experienced 'ecstasy' users in recreational settings in Australia. **Measurements** Drug use patterns (number of pills consumed, other drugs consumed). drug content of pills and resultant plasma concentrations of MDMA and related drugs were assessed by gas chromatography/mass spectrometry (GC/MS). **Findings** Ecstasy pills generally contained MDMA, but this was often combined with other drugs such as 3,4-methylendioxyethylamphetamine (MDEA) and methamphetamine. The dose of MDMA per pill ranged from 0 to 245 mg and users consumed from one-half to five pills, with the total dose consumed ranging up to 280 mg. Plasma concentrations of MDMA increased with number of pills consumed and cumulative MDMA dose. Use of larger numbers of pills was associated with extended exposure to the drug. **Conclusions** MDMA is the major active drug in ecstasy pills, but there is a high degree of variation in doses. Use of multiple pills over the course of one session is common and results in a sustained increase in MDMA plasma concentrations over a number of hours. This is likely to lead to a much greater exposure of the brain to MDMA than would be predicted from controlled single-dose pharmacokinetic studies.

Keywords 3,4-methylenedioxymethamphetamine, drug concentrations, drug dose, ecstasy, MDMA, pill content.

Correspondence to: Rodney J. Irvine, Discipline of Pharmacology, Level 5 Medical School North, Frome Road, University of Adelaide, Adelaide, SA 5005, Australia. E-mail: rod.irvine@adelaide.edu.au
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INTRODUCTION

Ecstasy is the common name applied to a recreational drug that gained popularity in the 1980s and 1990s among attendees of raves [1,2] and dance clubs [3]. Since then, use has burgeoned into additional settings such as house parties and other private gatherings [4,5]. The drug (usually found in tablet form but also as capsules; the term 'pill' will be used to refer to both) is taken for its pleasurable effects, including euphoria, heightened sensory awareness and enhanced 'closeness' to others [6]. The active drug is most commonly 3,4-methylenedioxymethamphetamine (MDMA) [7]. The chemically and pharmacologically similar drugs methylenedioxyethylamphetamine (MDEA) and methylenedioxyamphetamine (MDA) are also detected in pills sold as ecstasy [8,9], whether in combination with MDMA or alone. Other drugs, such as methamphetamine, ketamine and caffeine, have also been found in ecstasy tablets [10]. Ecstasy use has been associated with a number of acute adverse effects including nausea, teeth grinding, tremor, panic, hyperthermia, convulsions and even death. However, relative to the prevalence of the drug's consumption, the incidence of the more serious negative effects is low [11,12] and such events occur frequently when the drug is combined with other substances [8,13]. The evidence for long-lasting damage to serotonin (5HT) neurones in the brains of a number of

animal species, including non-human primates, is convincing [10,14]. Although the validity of dose scaling between animals and humans remains controversial [11,12], brain imaging and cognitive testing has indicated that these effects may extend to human users [15,16]. There is also evidence for a link between ecstasy use and depression [17,18], which is consistent with the impact of the drug on serotonergic systems [19,20]. Debate continues in the literature regarding the duration and nature of the drug's post-acute effects [21,22].

Although the drug's long-term effects are likely to be affected by users intentional polydrug use [7], many of the acute adverse outcomes linked to ecstasy have been the consequence of unintended ingestions resulting from variable tablet constituents [23]. In addition to the actual drugs present, the quantities of the drug consumed are important. In animal studies, acute and chronic toxicity have been linked closely to the dose administered and/or the concentration, and it would be expected that the same would be true for humans [24]. In humans, dose–response relationships have been detected for the drug's acute cardiovascular and subjective effects [25], and more intense use is associated with greater neuropsychobiological problems [25]. In an earlier study we showed a range of MDMA concentrations in the blood of recreational ecstasy users, with some reaching concentrations shown to be neurotoxic in primates [26].

In order for doses used in recreational settings to be estimated it is necessary to determine both the number of pills consumed and their composition. In the present study, the patterns of pill consumption in recreational users were recorded and the MDMA doses in the pills they consumed were measured. In addition, blood samples were collected to determine how plasma concentrations change following MDMA administration and how this relates to patterns of 'ecstasy' pill consumption. These data add to the information available from studies in which MDMA is administered to volunteers in a controlled clinical setting. Such studies have revealed useful information on the pharmacodynamics and pharmacokinetics of the drug [27–29], but do not reveal what occurs in typical recreational contexts where there is likely to be greater variability in the doses consumed., In the present study the recreational use of 'ecstasy' was examined in order to: (i) determine the composition of 'ecstasy' pills in terms of both the drugs present and their doses; (ii) describe the different patterns of 'ecstasy' consumption as both numbers of pills consumed and doses; and (iii) determine the relationship between the dose of MDMA ingested and the blood concentrations achieved in a recreational setting. These data are fundamental to understanding the pharmacology of recreationally used 'ecstasy' in humans and the development of evidence-based risk assessment.

MATERIALS AND METHODS

This study was approved by the Royal Adelaide Hospital Human Research Ethics Committee. Participants were recruited via word of mouth and the 'snowball' technique [30]. Each provided informed consent and confirmed that they had consumed ecstasy on a minimum of five previous occasions. Good general physical and psychiatric health based on the clinical judgement of medical staff were required for inclusion. Normal liver biochemistry was also required for inclusion. Pregnancy, breastfeeding, consumption of monoamine oxidase inhibitor medication and having recently donated blood were exclusion criteria. It was emphasized that consumption of ecstasy or other drugs was not a condition of participation in the study, and that participation did not imply that the use of illicit drugs on this or any occasion was safe. Participants donated a scraping of each kind of ecstasy pill consumed for chemical analysis and the weight of the pill was also measured to enable estimation of doses consumed. After a brief medical examination by the medical officer (M.K.), participants were cannulated and a blood sample was drawn prior to ecstasy use and hourly for 5 hours thereafter for determination of drugs in plasma as well as plasma MDMA concentrations. At the end of the study session they were compensated $200 for inconvenience caused by their participation in the study.

Plasma and drug samples were analysed by Forensic Science South Australia using validated methods developed for the courts. Initial drug screens, using commercially available enzyme-linked immunosorbent assay kits (ELISA), were performed on plasma samples, after which positive samples were analysed further by gas chromatography/mass spectrometry (GC/MS) for the quantification of MDMA and other amphetamines using techniques described in detail elsewhere [26]. The initial amphetamine screens (International Diagnostic Systems, St Joseph, MI, USA) had a sensitivity of 0.1 mg/l. Samples were also screened for opioids, benzodiazepines and cannabinoids (Diagnostix Ltd, Ontario, Canada) with sensitivities of 0.02 mg/l for opioids, 0.05 mg/l for benzodiazepines and 0.005 mg/l for cannabinoids. Positive samples were analysed further by GC/MS. The drug samples were extracted into methanol and 1 μl of the extract analysed by Agilent Technologies 6890 N gas chromatograph fitted with a 5973 mass selective detector equipped with a HP-5 capillary column (15 m × 0.25 mm × 0.25 μm) with a helium carrier gas at 6 psi. The flow of the split valve was 50 ml/minute; injector temperature 300°C; oven temperature 90°C for 3 minutes with a 45°C/minute ramp to 300°C with a hold of 1 minute. The concentration of drug in the samples was determined by comparison to a calibration curve of

known drug concentration analysed concurrently. The analysis was capable of detecting amphetamine, methamphetamine, phenteramine, mephentermine, p-methoxyamphetamine (PMA), MDMA, MDEA, MDA, ephedrine and pseudoephedrine. The limit of detection was 0.01 mg/l for all of these substances.

The relationships between the number of pills taken and the time at which the peak plasma MDMA concentration (C_{max}) occurred, between C_{max} and the total dose of MDMA that had been consumed prior to C_{max}, and between the dose of MDMA in the pills and the number consumed were explored using Spearman's rho (data did not meet assumptions for parametric analysis). Data were analysed using GraphPad Prism for Windows, version 5.01.

RESULTS

Data were collected from 56 participants with an average age of 25.6 years; 57% were male. Most were employed, with 57% employed full-time and 36% on a part-time or casual basis. Thirty per cent of the sample had a university degree or were studying for such a degree, while 18% had a trade or technical qualification or were studying to achieve the qualification. The average age of first ecstasy use was 19.2 years, indicating that most had had a number of years of experience of ecstasy use.

In addition to ecstasy, a number of other drugs were used by the participants. In Table 1, drugs ever used and those consumed in the 5 hours prior to or 5 hours after the first consumption of ecstasy are shown. Very high rates of co-use of both alcohol and tobacco were recorded. More than 40% of people used methamphetamine and cannabis, while rates of use of other drugs were much lower. In particular, use of the other major stimulant, cocaine, was very low, at 4% of the sample.

Table 1 Drugs ever used and those co-consumed with ecstasy (during party or the preceding 5 hours).

Drug	*Ever used % (n)*	*Co-consumed with ecstasy % (n)*
Alcohol	100 (56)	91 (51)
Tobacco	100 (56)	82 (46)
Methamphetamine	100 (56)	46 (26)
Cannabis	100 (56)	41 (23)
Ketamine	70 (39)	16 (9)
Nitrous	96 (54)	14 (8)
LSD	95 (53)	5 (3)
Cocaine	77 (43)	4 (2)
Benzodiazepines	95 (53)	4 (2)
GHB	61 (34)	2 (1)

GHB: gamma-hydroxybutyric acid; LSD: lysergic acid diethylamide.

Fewer than one in five participants reported ever having tried heroin or ever having injected any drug (data not shown).

The 56 participants consumed ecstasy from 28 different batches (a sample was taken from each batch for analysis) of which 25 were found as tablets and three as capsules. The drugs detected and the percentages of the various drugs present are shown in Table 2. A total of 111 tablets and six capsules were consumed. Nearly half the participants consumed pills that contained only MDMA. One type of pill, a capsule containing MDA, did not contain any MDMA. The drugs most commonly present other than MDMA were MDEA and MDA, and in most instances the concentrations of these drugs were lower than the concentrations of MDMA. The doses of MDMA in each of the 28 types of pills were calculated based on pill weight and the composition of the sample; the distribution of these doses is shown in Fig. 1. It can be seen that most pills (80%) contained less than 100 mg of MDMA, but there was an approximate 10-fold spread in the doses of MDMA present, with one (a capsule) containing an extremely high dose. Each MDMA capsule comprised 80% MDMA and no other active agents were detected.

MDMA was not detected in plasma of seven participants. These individuals consumed one of three types of pill (one type being a capsule) that contained less than 5% MDMA. These seven individuals were excluded from the descriptions and analyses to follow, which are restricted to the 49 participants in whose plasma MDMA was detected. The consumption patterns of these participants and the calculated doses consumed are shown in Fig. 2. The first panel shows the distribution of the number of pills consumed. This number and the MDMA doses in each of those pills enabled the calculation of the total estimated MDMA dose for each participant. This distribution is shown in the second panel of Fig. 2. Most participants consumed more than 100 mg of MDMA on the night, and the maximum dose was 280 mg. Pills were largely consumed orally, although eight participants also crushed and snorted a small proportion (in most cases half a pill) of the total number of pills they consumed. Where multiple pills were taken, these ingestions tended to be spaced out across the duration of the party. Five participants consumed multiple pills at a time, one of whom consumed three pills at the beginning of the party and later another two pills (also consumed simultaneously). No relationship was found between the dose of MDMA in the pills and the number participants chose to consume (Spearman's rho = –0.164, $P = 0.434$).

The range of doses consumed produced both variations in the plasma concentrations achieved and the patterns of concentration change over time. Figure 3 shows the change in MDMA concentration, with participants grouped according to the number of tablets consumed. It

Table 2 The content of the 28 types of ecstasy pill consumed during the parties. Data are expressed as mean percentage [standard deviation (SD)] and range (min–max).

Pill content	*No. of pill types*	*MDMA % mean (SD)*	*MDA % mean (SD)*	*MDEA % mean (SD)*	*Other drug % mean (SD)*	*No. pills consumed of this content*
MDMA only	13	28.8 (21.4) (range 6.3–80.0)	–	–	–	60
MDMA + MDEA	5	18.5 (4.8) (range 13.8–23.6)	–	6.6 (2.7) (range 3.3–10.4)	–	25
MDMA + MDEA + ketamine	1	5.9	–	6.9	Ketamine 3.7	8
MDMA + methamphetamine	4	28.0 (6.8) (range 19.5–35.1)	–	–	Methamphetamine 2.1 (1.7) (range 0.5–3.9)	10
MDMA + methamphetamine + caffeine	1	44.0	–	–	Methamphetamine 1.0 Caffeine NQ	1
MDMA + caffeine	1	11.8	–	–	Caffeine NQ	3.5
MDMA + MDA	1	4.9	17.4	–	–	3.5
MDMA + MDA + pseudoephedrine	1	0.3	3.7	–	Pseudoephedrine NQ	3
MDA only	1	–	1.0	–	–	3

NQ: not quantified; MDMA: 3,4-methylendioxymethamphetamine; MDEA: 3,4-methylendioxyethylamphetamine; MDA: methylenedioxyamphetamine.

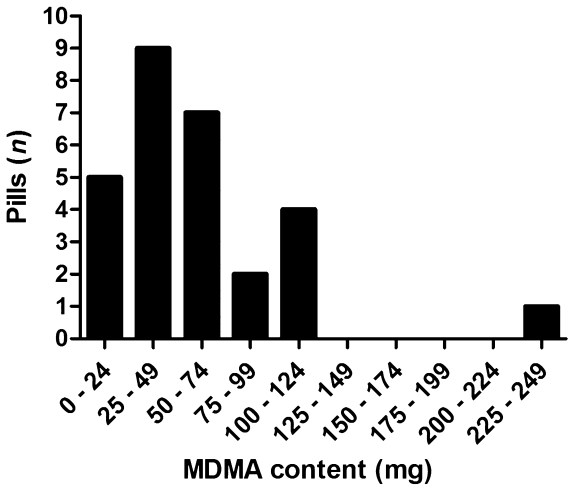

Figure 1 Total 3,4-methylendioxymethamphetamine (MDMA) content (mg) of ecstasy pills consumed by participants, determined from sample composition and pill weights ($n = 28$ types of pill)

can be seen that among consumers of one tablet or less, concentrations tended to reach a plateau within a few hours of administration, whereas those consuming a larger number of tablets showed an escalating pattern of concentration change that had not reached a peak within the 5 hours of the study period. The number of pills that had been consumed was associated positively with the hour at which the maximum measured MDMA plasma concentrations occurred (Spearman's rho = 0.60, $P < 0.0001$).

The peak plasma concentration reached within the 5-hour period was related to dose (Spearman's rho = 0.62, $P < 0.0001$) (Fig. 4). Figure 4 also shows that very high concentrations were reached by a small number of participants. More than one-quarter of participants (13 of 49) were found to have peak MDMA concentrations described as toxic to lethal by forensic laboratory guidelines [31,32], and the suggested neurotoxic level found in primates (approximately 700 mg/l) was reached by three participants, with a further three achieving concentrations very close to that level.

DISCUSSION

The demographic characteristics of our participants were consistent with other studies examining cohorts of ecstasy users [31]; in particular, there was a high level of participation in employment and education. Nearly all participants consumed alcohol in combination with ecstasy, most co-consumed tobacco and many also consumed methamphetamine and cannabis, findings again consistent with other studies which have reported polydrug use (and especially co-consumption of these drugs) as the norm for ecstasy users [5,31,33]. It was of interest that 82% of our participants used tobacco on the night when the percentage of daily smokers in this demographic is normally around 20% in Australia [33]. Similar rates of tobacco co-consumption have been noted in other studies of ecstasy users. The low rate of cocaine use compared to that described for in this sample is reflec-

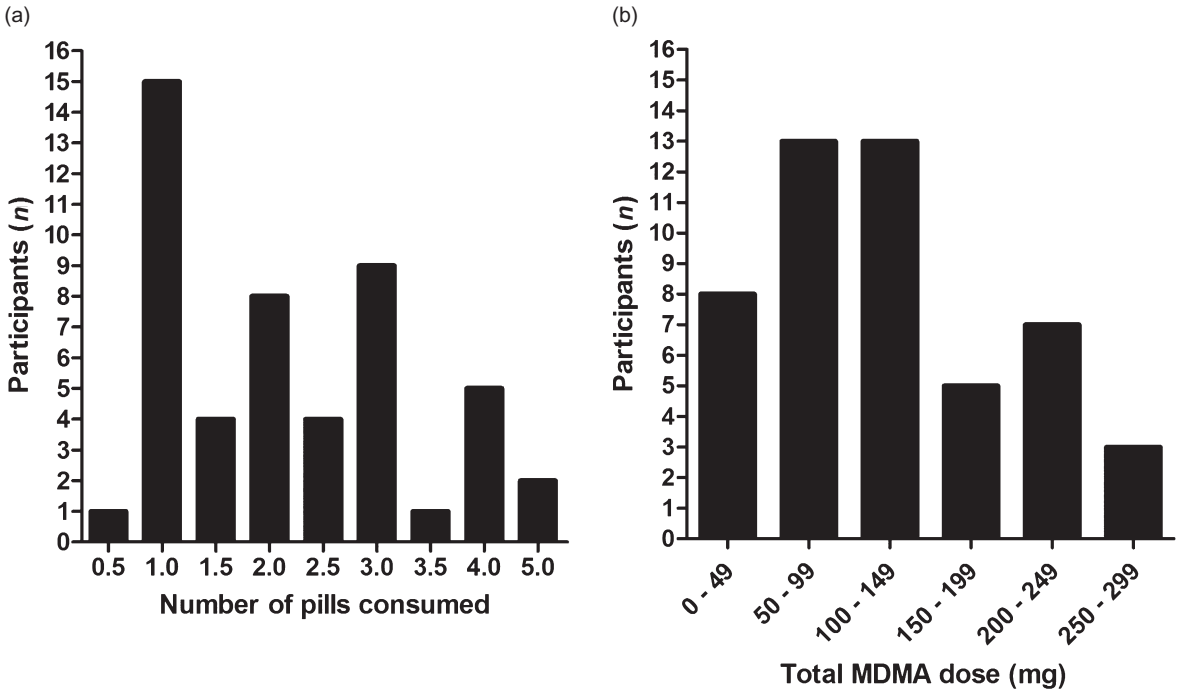

Figure 2 The number of ecstasy pills taken (a) and the resultant total dose of 3,4-methylendioxymethamphetamine (MDMA) (mg) consumed (b) during parties. Doses for individuals were calculated from MDMA content of pill types consumed and total pills of each type taken ($n = 49$ participants where MDMA detectable in plasma)

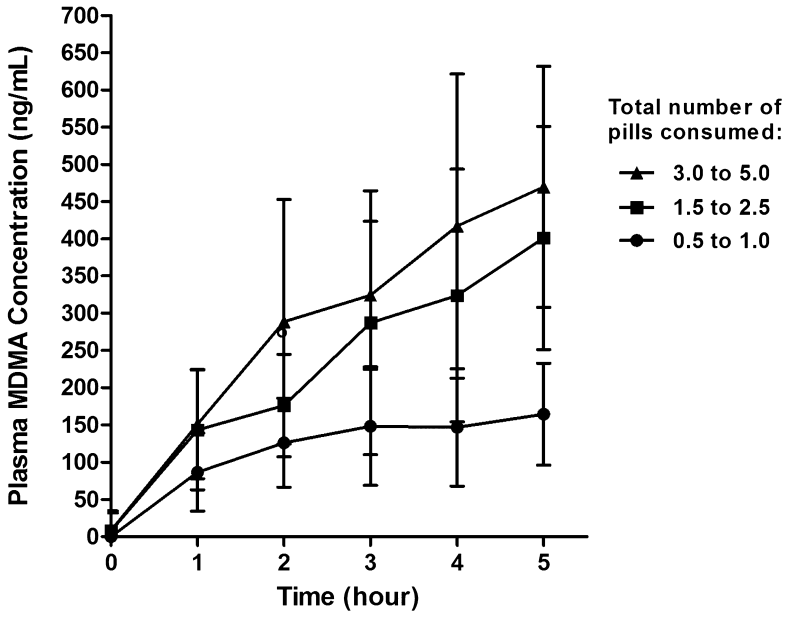

Figure 3 Plasma 3,4-methylendioxymethamphetamine (MDMA) concentrations (ng/ml) measured hourly following initial ecstasy ingestion, grouped by total number of pills consumed. Data are expressed as means (±standard deviation). ($n = 49$ participants where MDMA detectable in plasma)

tive of low rates of use in Australia; in the 20–29-year age group (the group most likely to have used either cocaine or ecstasy), 5.1% reported using cocaine in the past 12 months, compared to 11.2% reporting any ecstasy use in the same period [33].

All the tablets and capsules contained one of the methylenedioxyamphetamines (MDMA, MDA and MDEA), which reportedly produce very similar central and peripheral effects in humans [34]. MDMA was detected in 27 of 28 pill types analysed, the majority of pills consumed (51.3%) contained only MDMA as the active ingredient and MDMA was the major constituent in 85% of pills consumed (24 pill types). These findings are consistent with recent local data and recent findings from the United Kingdom [35,36], although purity rates reported from pills analysed in North America have

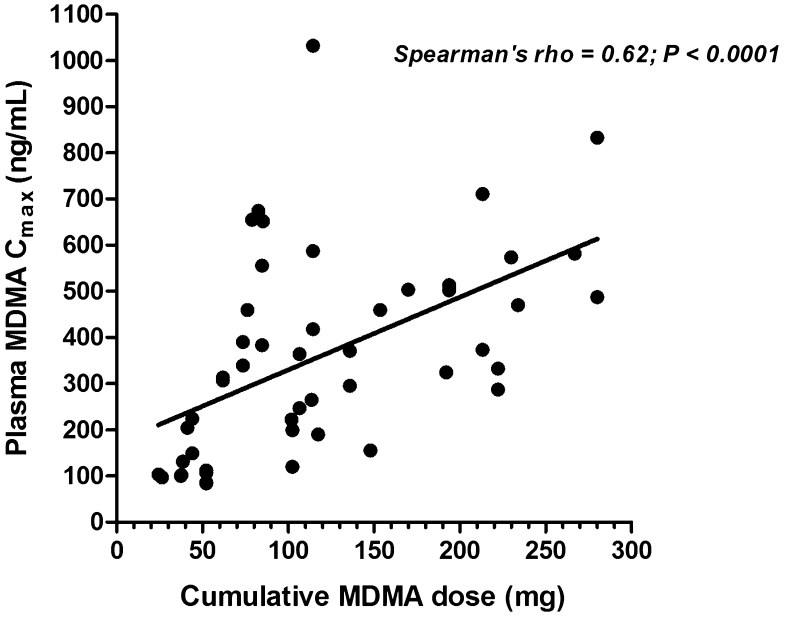

Figure 4 The relationship between maximum plasma 3,4-methylendioxymethamphetamine (MDMA) concentration (C_{max}) and cumulative MDMA dose consumed by the time of maximum plasma concentration ($n = 49$). Correlation coefficient (Spearman's rho), *P*-value and line of best fit are shown ($n = 49$ participants where MDMA detectable in plasma)

tended to be lower [34,37]. Very recent reports suggest a growing number of pills contain other substances based on analogues of cathione [38]. With one exception, containing 225–249 mg, most of the pills contained less than 124 mg of MDMA. The majority of doses were in the range of 25–74 mg per pill, consistent with findings from the United Kingdom in the 2000s [7,23]. There was a 12-fold variation in MDMA content within the 25 types of ecstasy pill containing sufficient quantities of the drug to be detectable in plasma. This highlights a significant public health concern, particularly regarding the existence of pills containing more than 200 mg of MDMA. No serious adverse events occurred in this study; individuals who consumed higher doses were clearly intoxicated, but did not exhibit signs of physical of mental distress.

Speculation in the literature that lower-strength pills would be associated with a corresponding increase in tablet usage [7] was not supported by the findings in the present sample. The number of pills taken ranged from 0.5 to five pills during the session, which represents a range similar to those reported in other studies [23,32,38]; the participants can be considered reflective of the low-, medium- and high-range use patterns proposed to categorize users [31,39]. The total dose resulting from these ingestions varied considerably, with most participants using 50–150 mg of MDMA over the study session. It should be noted that 14 participants exposed themselves to doses of MDMA in excess of the 2 mg/kg. This is the maximum dose (chosen for reasons of safety and ethics) used in the controlled clinical studies [40] which have been the substantive basis for our understanding of the pharmacology of MDMA in humans.

Among those consuming in excess of one pill, plasma concentrations of MDMA continued to climb through the study period. These data support the suggestion of de la Torre and colleagues that larger MDMA doses are associated with non-linear accumulation of MDMA in plasma [27,41,42]. This hypothesis has been confirmed in recent human studies [28] and in other species [43,44]. A study which followed the participants for the subsequent 24 hours would be of particular interest here, as a sustained high plasma concentration of MDMA may well have important implications for the development of long-term effects such as neurotoxicity [44]. However, it is also possible that the increasing drug concentrations reflect the use of multiple pills over the period of the study.

The data in the present study are consistent with the development of acute tolerance to the psychotropic effects of MDMA. Most reports indicate that the main desired effects of MDMA begin to diminish after about 2 hours [25,45], whereas our data and reports in the published literature show that blood concentration has not declined at that point [27,28]. Moreover, the prevalence of repeated dosing in this sample (in the absence of a decline in plasma concentration) further supports the likelihood of acute within-session tolerance to the effects of the drug. The finding that more than two-thirds of the participants chose to consume more than one ecstasy pill is also consistent with the descriptions in the literature regarding chronic tolerance to the drug [46]. Chronic tolerance is associated with the more intensive self-administration patterns observed in the present research: 'stacking' or taking several ecstasy tablets at once and 'boosting', taking repeated tablets over the evening [46]. These kinds of use patterns are associated with greater neuropsychobiological problems [24], and may place users at increased risk of toxicity.

The seven participants who consumed MDA pills and who did not show evidence of MDMA consumption (based on plasma concentrations) consumed lower doses of drug than did the MDMA consumers. However, they were not necessarily at less risk of harm, given the greater potency and longer duration of action of MDA [34]. In addition, both substances are reportedly neurotoxic [47]. At present, however, there is insufficient information about MDA to make definitive statements regarding relative harms. Evidence regarding the likely contribution of MDEA (present in one in five of the pills) to acute or chronic toxicity is also mixed [48].

The correlation between maximum plasma concentration achieved and cumulative dose is modest, but does indicate a relationship. There are some deviations from the line of best fit, indicating that some individuals may achieve much higher concentrations compared to others after consumption of a given dose. Consideration of the body mass or gender did not improve the correlations, but this should be re-examined with larger numbers of participants. These very high concentrations achieved by some users may be important in explaining why acute toxicity to MDMA is rare and hard to predict. It also has implications for the concept of pill testing (whether using field kits or laboratory analysis [49,50]), as knowing the composition of the pills that are ingested will not necessarily predict peak biological exposure.

In the present study, the great majority of people using ecstasy in a recreational setting consumed the drug MDMA. However, the quantities consumed were highly variable due to variation in pill dose and in the number of pills consumed. While dose was predictive of plasma concentrations of MDMA, some users reached unexpectedly high concentrations and these may be associated with significant risk of neurotoxicity. A sustained increase in MDMA plasma concentrations was observed among those who consumed multiple pills over the course of the study period. Such an increase in MDMA concentration is likely to lead to a much greater exposure of the brain to MDMA than would be predicted from controlled single-dose pharmacokinetic studies.

Declarations of interest

None.

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