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Safety pharmacology of acute MDMA administration in healthy subjects

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Patrick Vizeli and Matthias E Liechti

Abstract

3,4-Methylenedioxymethamphetamine (MDMA; ecstasy) is being investigated in MDMA-assisted psychotherapy. The present study characterized the safety pharmacology of single-dose administrations of MDMA (75 or 125 mg) using data from nine double-blind, placebo-controlled, crossover studies performed in the same laboratory in a total of 166 healthy subjects. The duration of the subjective effects was 4.2 ± 1.3 h (range: 1.4–8.2 h). The 125 mg dose of MDMA produced greater 'good drug effect' ratings than 75 mg. MDMA produced moderate and transient 'bad drug effect' ratings, which were greater in women than in men. MDMA increased systolic blood pressure to >160 mmHg, heart rate >100 beats/min, and body temperature >38°C in 33%, 29% and 19% of the subjects, respectively. These proportions of subjects with hypertension (>160 mmHg), tachycardia, and body temperature >38°C were all significantly greater after 125 mg MDMA compared with the 75 mg dose. Acute and subacute adverse effects of MDMA as assessed by the List of Complaints were dose-dependent and more frequent in females. MDMA did not affect liver or kidney function at EOS 29 ± 22 days after use. No serious adverse events occurred. In conclusion, MDMA produced predominantly acute positive subjective drug effects. Bad subjective drug effects and other adverse effects were significantly more common in women. MDMA administration was overall safe in physically and psychiatrically healthy subjects and in a medical setting. However, the risks of MDMA are likely higher in patients with cardiovascular disease and remain to be investigated in patients with psychiatric disorders.

Keywords

3,4-methylenedioxymethamphetamine, safety, adverse effect, Phase I, human

Introduction

3,4-Methylenedioxymethamphetamine (MDMA; ecstasy) is used recreationally and investigated clinically as a medication in MDMA-assisted psychotherapy in patients with post-traumatic stress disorder (PTSD) (Amoroso and Workman, 2016; Kupferschmidt, 2014; Mithoefer et al., 2010, 2016; Oehen et al., 2013; Sessa and Nutt, 2015). The future use of MDMA in psychiatric practice will depend on its efficacy in specific disorders and its safety of use. The benefits and harms associated with MDMA have been previously discussed (Doblin et al., 2014; Parrott, 2013a, 2014). Currently, however, sufficient data from clinical Phase I–III studies have not been published in peer-reviewed journals. Phase III studies are currently being planned (MAPS, 2016), and more information on the clinical safety of MDMA is needed (Mithoefer et al., 2016). Therefore, the present study sought to provide data on the safety pharmacology of single-dose administrations of MDMA. We primarily addressed the acute effects during the MDMA response (0–6 h) and the subacute adverse effects up to 24 h after the administration of MDMA. We also included data on any adverse events that occurred during the entire clinical studies including blood laboratory values obtained at the end of study (EOS) visit. These data were collected from a series of Phase I clinical studies that were conducted in our laboratory and used the same standardized data recording methods. These studies used one or two single-dose administrations of MDMA at doses equal or similar to those used in MDMA-assisted psychotherapy (Mithoefer et al., 2010; Oehen et al., 2013) and in subjects with no or minimal prior ecstasy use, which is also likely the case when MDMA is used in patients. The aims of the study were to describe subjective effects (self-rated good and bad drug effects), the duration of the acute MDMA response, cardiovascular and hyperthermic effects, and acute and subacute adverse effects, and lasting effects on laboratory indices of liver and kidney function. We also tested the moderating effects of dose (de la Torre et al., 2000; Kolbrich et al., 2008a; Schmid et al., 2014) and sex (Liechti et al., 2001; Pardo-Lozano et al., 2012; Reneman et al., 2001; Simmler et al., 2011; Verheyden et al., 2002) on these acute responses to MDMA.

The pharmacology of MDMA has been relatively well-studied. MDMA mainly induces the release of presynaptic serotonin (5-hydroxytryptamine (5-HT)) and to a lesser extent norepinephrine and dopamine through interactions with the corresponding monoamine transporters (Hysek et al., 2012d; Rothman et al., 2001; Simmler et al., 2013). MDMA is generally classified as an 'entactogen' or 'empathogen' because its socio-emotional effects differ from those of prototypic stimulants (Bershad et al., 2016;

Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland

Corresponding author:
Matthias E Liechti, Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Schanzen strasse 55, Basel, CH-4056, Switzerland.
Email: matthias.liechti@usb.ch

Hysek et al., 2014b; Schmid et al., 2014) and it produces fewer perceptual alterations than hallucinogens (Schmid et al., 2015a). Specifically, MDMA increases feelings of closeness to others, trust and openness and enhances emotional empathy for positive situations (Hysek et al., 2014a; Schmid et al., 2014). Such effects are not observed with stimulants that predominantly act on the dopamine system (Schmid et al., 2014). MDMA (Baggott et al., 2016) but not D-amphetamine (Childs et al., 2016) decreased social anxiety. MDMA selectively impaired the recognition of negative emotions (Bedi et al., 2010; Hysek et al., 2014a; Schmid et al., 2014; Wardle et al., 2014), whereas such stimulants as amphetamine and methylphenidate nonselectively enhanced the recognition of emotions (Hysek et al., 2014b; Schmid et al., 2014; Wardle et al., 2012). These findings indicate that MDMA produces unique effects on emotion processing in healthy subjects that are likely linked to its predominant effects on the 5-HT system (Bershad et al., 2016; Hysek et al., 2012b, 2012d) and may be useful in MDMA-assisted psychotherapy (Sessa, 2016).

Earlier studies that described the acute effects of MDMA in healthy volunteers have previously been reviewed (Dumont and Verkes, 2006), but many more have been performed since then (Carhart-Harris et al., 2014; de Sousa Fernandes Perna et al., 2014; Dumont et al., 2008, 2009; Farre et al., 2007, 2015; Hasler et al., 2009; Hysek et al., 2011; 2012a, 2012c, 2012d, 2013, 2014b; Kirkpatrick et al., 2012, 2014a, 2014b; Kolbrich et al., 2008a; Kuypers et al., 2014; Pardo-Lozano et al., 2012; Parrott et al., 2011; Peiro et al., 2013; Schmid et al., 2014, 2015b; van Wel et al., 2012). However, all of these individual studies were relatively small (n = 6–30) in particular to characterize adverse events that are not very common (<10%), and safety aspects were not the primary endpoint or were not described. Additionally, we are unaware of any larger data analyses (n > 100) that focused on the clinical safety profile of acute MDMA administration. The present analyses used a relatively large sample size including data from 166 subjects (equal numbers of males and females) and 166 administrations of MDMA alone and 112 administrations of MDMA with another substance. In contrast to compilations of data from different laboratories, the present data set used the same doses and formulations of MDMA and the same standardized outcome measures across all the individual studies including measures of plasma levels of MDMA. We hypothesized that MDMA would produce predominantly positive mood effects (Baggott et al., 2016; Hysek et al., 2014a; Kolbrich et al., 2008a) and cardiostimulant (Schmid et al., 2016) and thermogenic (Liechti, 2014) responses. Renal failure and hepatotoxicity are potential consequences of uncontrolled ecstasy use (Ben-Abraham et al., 2003; Liechti et al., 2005), but we did not expect to see changes in liver enzymes or creatinine levels after single doses of MDMA in a controlled setting.

Methods

Study design

This was a pooled analysis of nine Phase I double-blind, placebo-controlled, crossover studies in healthy subjects (Hysek and Liechti, 2012; Hysek et al., 2011, 2012a, 2012c, 2012d, 2014b; Schmid et al., 2014, 2015b). These studies were all conducted at the University Hospital Basel and included a total of 166 subjects who were all psychiatrically screened and healthy. The aim of the pooled analysis was to assess the safety pharmacology of one or two single doses of MDMA in healthy subjects with no regular MDMA use and no or minimal previous use. Seven studies each included 16 subjects (total of 112 subjects) who received 125 mg MDMA twice, once alone and once after pretreatment with a medication (Hysek and Liechti, 2012; Hysek et al., 2011, 2012a, 2012c, 2012d; 2014b; Schmid et al., 2015b). An additional unpublished study included 24 subjects who received 125 mg MDMA once without pretreatment (ClinTrials.gov ID: NCT01951508). Lastly, one study included 30 subjects who received a single dose of 75 mg MDMA without pretreatment (Schmid et al., 2014). The focus of this analysis is on the acute effects of MDMA alone. Effects of MDMA with pretreatments are shown in the Supplementary Material online. In all of the studies, the washout periods between the MDMA single-dose administrations were at least seven days to exclude carry-over effects. The studies were all registered at ClinicalTrials.gov (NCT00886886, NCT00990067, NCT01136278, NCT01270672, NCT01386177, NCT01465685, NCT01771874, NCT01951508 and NCT01616407). All of the studies were approved by the local ethics committee and Swiss Agency for Therapeutic Products (Swissmedic). The studies were conducted in accordance with the Declaration of Helsinki. MDMA administration in healthy subjects was authorized by the Swiss Federal Office for Public Health (BAG), Bern, Switzerland. Informed consent was obtained from all of the participants who were included in the studies. All of the subjects were paid for their participation.

Subjects

A total of 166 healthy European/Caucasian subjects, aged 18–45 years (mean ± SD = 24.5 ± 4 years) were mostly recruited from the University of Basel campus and included in the studies. The mean ± SD body weight was 69 ± 10 kg (range: 46–95 kg). Thirty subjects (15 men, 15 women) received a single 75 mg dose of MDMA. One hundred and thirty-six subjects received a single 125 mg dose of MDMA. In these 136 subjects, MDMA was administered as a single dose in 24 subjects (12 men, 12 women) and as two single doses of 125 mg (once alone and once combined with another drug on two separate occasions at least seven days apart) in 112 subjects (56 men, 56 women), resulting in total exposure of 250 mg MDMA. The time interval between the two MDMA administrations was 26 ± 17 days.

The detailed exclusion criteria were reported elsewhere (Hysek and Liechti, 2012; Hysek et al., 2012a, 2012c, 2012d), including a history of psychiatric disorders, physical illness, a lifetime history of using illicit drugs more than five times (with the exception of past cannabis use), illicit drug use within the last two months, and illicit drug use during the study, determined by urine tests that were conducted before the test sessions. Fifty-nine subjects had prior drug experience (1–5 times), of which 34 subjects had previously used MDMA (1–4 times).

Study drug

(±)MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) was administered orally in a single dose of 75 or 125 mg prepared as gelatin capsules (25 or 100 mg, Bichsel Laboratories, Interlaken, Switzerland). Similar amounts of MDMA are found in ecstasy pills

(Brunt et al., 2012) and have been or are being used in clinical studies in patients (Mithoefer et al., 2010; Oehen et al., 2013). Male and female subjects were treated with the same 125 mg dose irrespective of body weight in the clinical studies in patients (Mithoefer et al., 2010; Oehen et al., 2013). Similarly, in the present study, the doses were not adjusted for body weight or sex. The dose per body weight (mean ± SD) was 1.7 ± 0.4 mg/kg (range: 0.8–2.7 mg/kg). For the 75 mg dose of MDMA, the dose per body weight was 1.0 ± 0.1 mg/kg for men and 1.2 ± 0.1 mg/kg for women. For the 125 mg dose of MDMA, the dose per body weight was 1.7 ± 0.2 mg/kg for men and 2.1 ± 0.3 mg/kg for women.

Pharmacodynamic measures

Visual analogue scales (VASs) were repeatedly used to assess subjective effects over time (Hysek et al., 2014a). The VASs included 'any drug effect', 'good drug effect' and 'bad drug effect'. The VASs were presented as 100-mm horizontal lines (0–100%), marked from 'not at all' on the left to 'extremely' on the right. The VASs were applied before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 h after MDMA or placebo administration. In the study that evaluated 75 mg MDMA, the 0.33 h time point is missing. In one study that evaluated 125 mg MDMA ($n = 24$), the 2 and 2.5 h time points are missing. The onset, offset and duration of the subjective response were determined using the VAS 'any drug effect'-time curve, with 10% of the individual maximal response as the threshold, in Phoenix WinNonlin (version 6.4, Pharsight, Certara L.P., St. Louis, MO, USA). Because subjective effects were assessed only up to 6 h, the offset in two subjects with an effect >10% at 6 h was determined by log-extrapolation. Four subjects were excluded from this analysis because they reported no subjective effects.

Blood pressure, heart rate and body temperature were assessed repeatedly before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 h after MDMA or placebo administration. Systolic and diastolic blood pressure and heart rate were measured using an automatic oscillometric device (OMRON Healthcare Europe NA, Hoofddorp, Netherlands). The measurements were performed in duplicate at an interval of 1 min and after a resting time of at least 10 min. The averages were calculated for analysis. Core (tympanic) temperature was measured using a Genius™ two ear thermometer (Tyco Healthcare Group LP, Watertown, NY, USA). In the study that evaluated 75 mg MDMA, the 0.33 h and 2.5 h time points are missing. In one study that evaluated 125 mg MDMA ($n = 24$), the 2 h time point is missing. Criteria for grouping subjects at least >90, 100 and 110 mmHg for diastolic and >140, 160 and 180 mmHg for systolic hypertension grade I–III, respectively. Tachycardia was defined as >100 beats/min. Hyperthermia and hyperpyrexia were defined as tympanic body temperature >38°C and 40°C, respectively.

Acute and subacute adverse effects were assessed using the list of complaints (Hysek et al., 2012a; Zerssen, 1976). The scale consisted of 66 items, yielding a total adverse effects score (non-weighted sum of the item answers) that reliably measures physical and general discomfort. Bruxism (item 66, a common side effect of MDMA) was included in the List of Complaints that was used in 134 subjects. The List of Complaints was administered before and 3–6 (acute adverse effects up to 6 h) and 24 h (subacute adverse effects up to 24 h) after MDMA or placebo administration. Additionally, participants were asked at the beginning of each study session and at the EOS visit to report any adverse events for the periods from 24 h until 14 days after administration.

Plasma concentrations of MDMA

Blood samples were collected 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4 and 6 h after administration of MDMA or placebo. Plasma concentrations of MDMA were determined as previously described (Hysek et al., 2012d). Peak plasma concentrations (C_{max}) were obtained directly from the observed data. The area under the concentration-time curve (AUC) from 0 to 6 h after dosing (AUC_6) was calculated using the linear-log trapezoidal method in Phoenix WinNonlin 6.4 (Certara, Princeton, NJ, USA).

Blood sampling and EOS visit

Blood chemistry and blood cell count tests were performed at the screening visit at the start of the study and at the EOS visit, which were separated by 88 ± 50 days. The EOS visit including the blood sampling took place at variable time intervals (29 ± 22 days) after the last MDMA administration and after one or two administrations of MDMA with or without pretreatments. The analyses were performed using standard assays according to Good Laboratory Practice by the Laboratory Medicine Department of the hospital. The glomerular filtration rate was determined by the Cockcroft–Gault Equation using plasma creatinine concentrations, age and sex of the subject. At the EOS visit, the participants were asked to retrospectively rate the duration of the subjective response to MDMA, whether the experience was positive or negative, whether the controlled clinical setting influenced their experience, and whether they considered taking MDMA again and in what setting. The participants were also asked whether they experienced 'flashbacks'. These questions were asked in 141 subjects.

Statistical analyses

The statistical analyses were performed using Statistica 12 software (StatSoft, Tulsa, OK, USA). Repeated-measures analyses of variance (ANOVAs) with drug (MDMA alone without pretreatment *vs*. placebo) as the within-subjects factor and dose (75 *vs*. 125 mg) as the between-subjects factor were used to evaluate all the effects of MDMA compared with placebo (main effect of drug) and dose–response effects (drug × dose interactions). Sex differences were explored by adding sex as an additional between-subjects factor to the analyses. Tukey post hoc tests were used based on significant main effects or interactions in the ANOVA. Finally, dose per body weight and peak plasma concentrations of MDMA were used as a covariate to test whether sex differences were confounded by dose per body weight or plasma concentrations of MDMA, respectively. The latter analysis also accounted for potential differences in metabolism (Schmid et al., 2016, Vizeli et al., 2017) and non-linear pharmacokinetics. Fisher's exact tests were used to compare proportions. Differences in kidney and liver function and blood cell counts between the screening and EOS visit measures were analysed using paired *t*-tests. The level of significance was set to $p < 0.05$.

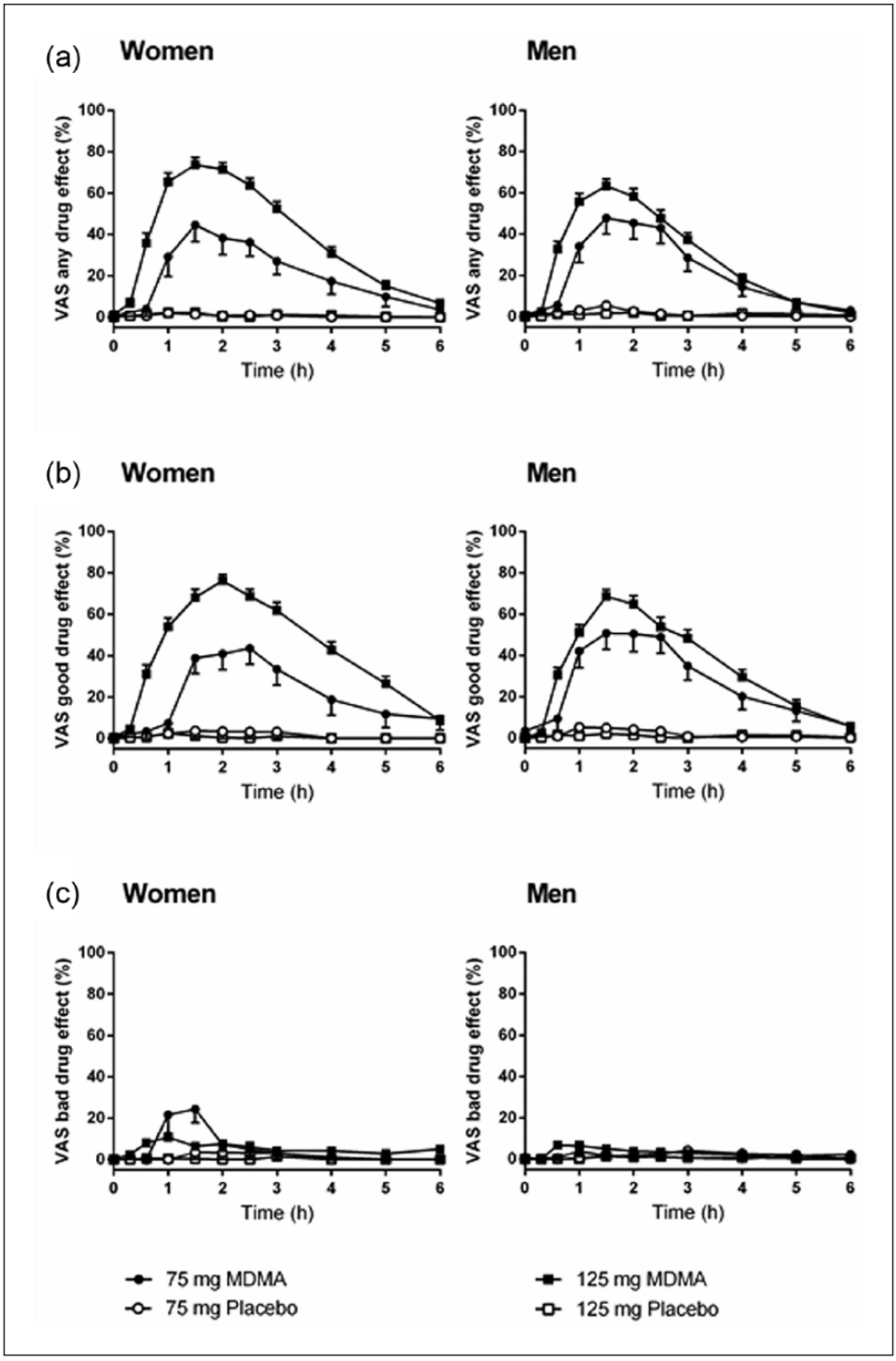

Figure 1. Subjective effects of MDMA. (a) The overall subjective effect ('any drug effect') began after a mean time of 33 min, reached its peak after 1.6 h, and lasted 4.2 h (effect duration from onset to offset with a threshold of 10% of the peak). (a), (b) MDMA produced greater 'any drug effect' and 'good drug effect' ratings at 125 mg compared with 75 mg. (c) MDMA produced moderate and transient 'bad drug effect' ratings that were not dose-dependent but greater in women than in men. The data are expressed as the mean ± SEM in 15 women and 15 men for the 75 mg dose and 68 women and 68 men for the 125 mg dose.

MDMA: 3,4-methylenedioxymethamphetamine; VAS: visual analogue scale.

Results

Acute subjective effects of MDMA

The time course of the subjective response to MDMA alone is shown in Figure. 1. The onset of effects and peak effect were 33 ± 24 min (mean ± SD) and 1.6 ± 0.8 h after MDMA administration, respectively. The duration of the subjective drug effects was 4.2 ± 1.3 h (range: 1.4–8.2 h). No sex or dose differences were found in the duration of the subjective effects. At the EOS visit, the subjects retrospectively indicated that the duration of their subjective response to MDMA was 4.0 ± 2.9 h. MDMA significantly increased ratings of 'any drug effect' and 'good drug effect' compared with placebo (Table 1, Figure 1). The 125 mg dose of MDMA produced higher 'any drug effect' and 'good drug effect' ratings compared with the 75 mg dose of MDMA (Table 1, Figure 1). A nearly significant drug × sex interaction in the ANOVA indicated that women tended to give greater 'any drug effect' ratings than men (Table 1, Figure 1). MDMA increased ratings of 'bad drug effect'. 'Bad drug effect' ratings were not dose-dependent in contrast to 'good drug effect' ratings. 'Bad drug effect' ratings were greater in women than in men. When we accounted for the higher mg/kg dose in women by adding it as a covariate in the analysis, women still gave significantly greater 'bad drug effect' ratings than men after MDMA administration compared with placebo ($F_{1,162} = 20.0$; $p < 0.001$). The sex difference also remained significant after correcting for differences in peak plasma concentrations of MDMA ($F_{1,162} = 21.5$; $p < 0.001$).

Acute effects of MDMA on vital signs

MDMA alone acutely increased blood pressure, heart rate and body temperature (Table 2). A significant dose–response effect of MDMA on blood pressure but not heart rate or body temperature was found (Table 2). The acute effect of MDMA on systolic blood pressure, heart rate and body temperature peaked after 1.7 ± 0.9 h, 2.0 ± 1.4 h and 2.4 ± 1.2 h, respectively. No sex differences in the effects of MDMA on vital signs were observed. However, when we accounted for the lower mg/kg dose in males compared with females by adding it to the analysis (i.e. dose normalization), men presented greater increases in systolic blood pressure compared with women ($F_{1,164} = 6.08$; $p < 0.05$). Blood pressure increases were also greater in men than women when correcting for plasma concentrations of MDMA ($F_{1,164} = 8.28$; $p < 0.01$). After MDMA administration, 54 subjects (33%) and seven subjects (4%) had systolic blood pressure >160 mmHg and 180 mmHg, respectively. The proportion of subjects with systolic blood pressure >160 mmHg was significantly greater after 125 mg MDMA administration compared with 75 mg ($p < 0.01$). Forty-eight subjects (29%) presented tachycardia (heart rate >100 beats/min). The proportion of subjects with heart rate >100 beats/min was significantly greater after 125 mg MDMA administration compared with 75 mg ($p < 0.05$). MDMA increased body temperature to >38°C in 32 subjects (19%), up to a maximum of 39.1°C. The proportion of subjects with body temperature >38°C was significantly greater after 125 mg MDMA administration compared with 75 mg ($p < 0.01$). The mean room temperature was 22.7 ± 0.6°C. The effects of co-administering MDMA with other medications on vital signs are shown in Supplementary Table S1. No hypertensive urgencies or incidents of hyperpyrexia (>40°C) occurred. The maximal diastolic and systolic blood pressure values among the 166 administrations of MDMA alone were 130 and 196 mmHg, respectively. The maximal diastolic and systolic blood pressure values among the 112 administrations of MDMA plus a pretreatment were 119 and 200 mmHg, respectively. The maximal observed body temperature value among all 278 administrations of MDMA alone or with pretreatment was 39.1°C.

Adverse effects of MDMA

MDMA produced significant acute and subacute adverse effects on the List of Complaints compared with placebo (Tables 1 and 2). The 125 mg dose of MDMA increased acute and subacute List of Complaints total scores significantly more than the 75 mg dose (Table 2). MDMA increased acute List of Complaints ratings more in women (8.8 ± 5.9) than in men (6.4 ± 6.8; Table 1). MDMA also increased subacute List of Complaints scores more in women (5.4 ± 5.5) than in men (3.0 ± 5.0; Table 1). The difference in the acute and subacute adverse effects between women and men remained significant after correcting for differences in the mg/kg dose of MDMA ($F_{1,162} = 6.27$; $p < 0.05$ and $F_{1,162} = 6.21$; $p < 0.05$, respectively) or differences in the plasma concentration of MDMA ($F_{1,162} = 6.13$; $p < 0.05$ and $F_{1,162} = 4.63$; $p < 0.05$, respectively).

Frequent and relevant complaints after MDMA and placebo administration are shown in Table 3. The most frequent acute adverse effects after MDMA administration included lack of appetite, dry mouth, difficulty concentrating, cold feet, sweating, bruxism, restless legs, dizziness and hot flushes. Significant subacute (24 h) adverse effects of MDMA included headache, lack of appetite, lack of energy, dry mouth, difficulty concentrating and bruxism. Acute dry mouth, difficulty concentrating, sweating and bruxism were more frequently observed after 125 mg MDMA compared with 75 mg. Acute anxiety was reported by nine subjects (6%) after the 125 mg dose and none of the subjects after the 75 mg dose (Supplementary Table S2). No serious adverse events were reported. Additional adverse events that were reported for the periods from 24 h until 7–14 days after drug administration included the following (0% if not mentioned): headache, 6% after 125 mg MDMA, 7% after 75 mg MDMA, and 5% after placebo; depressed mood, 4% after 125 mg MDMA; common cold: 2% after 125 mg MDMA, 4% after placebo; dysmenorrhoea: 10% after 75 mg MDMA; diarrhoea: 2% after 125 mg MDMA; dizziness: 2% after 125 mg MDMA; gastroenteritis: 3% after 75 mg MDMA, 1% after placebo; emesis: 2% after 125 mg MDMA; toothache: 2% after 125 mg MDMA; jaw muscle soreness: 1% after 125 mg MDMA; migraine: 1% after 125 mg MDMA; back pain: 1% after 125 mg MDMA; sinusitis: 1% after 125 mg MDMA; abdominal pain: 1% after 125 mg MDMA, 1% after placebo; flu: 1% after 125 mg MDMA; bronchitis: 3% after 75 mg MDMA. These adverse events were not reported significantly more frequently after MDMA administration compared with placebo. There were several adverse events that occurred only after placebo: sleep walking, herpes zoster, insomnia, syncope, upper ankle joint distortion, pneumonia, nausea, inflamed mosquito bites, infection of the eye, dry cough, and abscess in the inguinal region combined with tinea of the body (each in 1% of the subjects). In the studies that used 125 mg MDMA, a total of 12 subjects (9%) reported flashbacks 1–3 times and eight times in

Table 1. Subjective effects and adverse effects in men and women.

E_{max}, mean ± SD	Women				Men				Drug		Drug × Dose		Drug × Sex		Drug × Dose × Sex	
	75 mg *n* = 15		125 mg *n* = 68		75 mg *n* = 15		125 mg *n* = 68		$F_{1,162}$	*p* =	$F_{1,162}$	*p* =	$F_{1,162}$	*p* =	$F_{1,162}$	*p* =
	Placebo	MDMA	Placebo	MDMA	Placebo	MDMA	Placebo	MDMA								
Any drug effect	3 ± 6	59 ± 29***	4 ± 8	85 ± 20***###	6 ± 9	56 ± 32***	4 ± 13	73 ± 24***#	652	<0.001	20	<0.001	3.4	0.068	0.2	NS
Good drug effect	6 ± 13	60 ± 28***	3 ± 10	82 ± 25***##	7 ± 12	57 ± 33***	4 ± 15	77 ± 23***##	585	<0.001	20	<0.01	0.9	NS	0.04	NS
Bad drug effect	4 ± 13	35 ± 33***	2 ± 10	24 ± 24***	6 ± 16	7 ± 11+++	2 ± 10	13 ± 22***+	44	<0.001	0.001	NS	16	<0.001	3.6	0.059
List of complaints score, mean ± SD																
Before, *n*	1.5 ± 1.6	2.1 ± 2.5	1.6 ± 2.0	1.6 ± 1.8	0.7 ± 1.4	0.7 ± 1.3	1.4 ± 2.4	1.2 ± 1.8	0.1	NS	0.7	NS	0.5	NS	0.2	NS
Acute, up to 6 h, *n*	2.2 ± 2.2	8.2 ± 4.6**	2.2 ± 2.3	11.6 ± 6.1***	1 ± 1.7	3 ± 2.4+	1.1 ± 2.1	8.5 ± 6.9***##++	99	<0.001	12	<0.001	5.9	<0.05	0.6	NS
Subacute, up to 24 h, *n*	0.9 ± 1.5	4.1 ± 5.2	1.2 ± 2.1	7.1 ± 5.7***	1 ± 1.6	1.6 ± 2.4	0.6 ± 2.3	4.2 ± 5.1***+++	41	<0.001	7.3	<0.01	5.8	<0.05	0.02	NS
MDMA plasma concentration, mean ± SD									Dose		Sex		Dose × Sex			
C_{max}, ng/mL	133 ± 27		252 ± 40###		116 ± 29		195 ± 37###+++		180.97	<0.001	24.99	<0.001	7.5	<0.01		
AUC_6, ng*h/mL	547 ± 127		1058 ± 185###		493 ± 113		838 ± 160###+++		164.85	<0.001	16.79	<0.001	6.14	<0.05		

**$p < 0.01$, ***$p < 0.001$ compared with placebo.

#$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ compared with 75 mg.

+$p < 0.05$, ++$p < 0.01$, +++$p < 0.001$ compared with women.

n: number of subjects; SD: standard deviation; E_{max}: maximal effect; MDMA: 3,4-methylenedioxymethamphetamine; C_{max}: peak plasma concentration; AUC_6: area under concentration-time curve.

Table 2. Maximal effects on vital signs and adverse effects.

MDMA dose	Placebo	MDMA	Placebo	MDMA	Drug		Drug × dose	
	75 mg		125 mg		$F_{1,165}$	p =	$F_{1,164}$	p =
	n = 30		n = 136					
Diastolic blood pressure, mean ± SD, mmHg	77 ± 5	84 ± 8**	79 ± 8	93 ± 10***###	292	<0.001	17.9	<0.001
>90, *n* (%)	0 (0)	7 (23)*	13 (8)	83 (61)***###				
>100, *n* (%)	0 (0)	1 (3)	1 (1)	30 (23)***#				
>110, *n* (%)	0 (0)	0 (0)	0 (0)	4 (3)				
Max, mmHg	90	101	104	130				
Systolic blood pressure, mean ± SD, mmHg	131 ± 11	145 ± 14***	133 ± 15	157 ± 15***###	486	<0.001	15.2	<0.001
>140, *n* (%)	7 (23)	19 (63)**	32 (24)	122 (90)***###				
>160, *n* (%)	0 (0)	3 (10)	8 (6)	51 (38)***##				
>180, *n* (%)	0 (0)	0 (0)	0 (0)	7 (5)*				
Max, mmHg	153	176	175	196				
Heart rate, mean ± SD, beats/min	69 ± 9	83 ± 17***	76 ± 12	95 ± 17***	267	<0.001	2.38	NS
>100, *n* (%)	0 (0)	3 (10)	3 (2)	45 (33)***#				
Max, beats/min	95	134	117	145				
Body temperature, mean ± SD, °C	37.0 ± 0.3	37.2 ± 0.3	37.4 ± 0.5	37.7 ± 0.5***	44.4	<0.001	2.43	NS
>38, *n* (%)	0 (0)	0 (0)	12 (9)	32 (24)**##				
Max, °C	37.7	37.6	38.7	39.1				
List of complaints score								
before, mean ± SD, *n*	1.1 ± 1.5	1.4 ± 2.1	1.5 ± 2.2	1.4 ± 1.8	0.01	NS	0.66	NS
acute, up to 6h, mean ± SD, *n*	1.6 ± 2.1	5.6 ± 4.5**	1.7 ± 2.3	10.0 ± 6.6***###	93.0	<0.001	11.9	<0.001
subacute, up to 24h, mean ± SD, *n*	0.9 ± 1.5	2.9 ± 4.1	0.9 ± 2.2	5.7 ± 5.6***##	35.5	<0.001	6.91	<0.01

n: number of subjects/complaints; SD: standard deviation; MDMA: 3,4-methylenedioxymethamphetamine; NS: not significant.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with placebo.
#$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ compared with 75 mg.

one subject. Flashbacks reportedly occurred 26 ± 15 h after MDMA administration (range: 8–50 h). No sex differences were found in the reports of adverse events or flashbacks.

Plasma concentrations of MDMA

Plasma concentrations of MDMA for both doses and sexes are shown in Table 1. Peak plasma concentrations of MDMA were significantly and on average 1.8-fold higher after the 125 mg dose (224.1 ng/mL) compared with the 75 mg dose (124.5 ng/mL). Statistical comparison of the dose-normalized C_{max} values revealed a significant difference in the total sample ($F_{1,161} = 4.19$; $p < 0.05$), which was significant only in women ($p < 0.05$), indicating nonlinear pharmacokinetics, but not in men ($p = 1.0$). Peak concentrations were on average 1.9- and 1.7-fold higher after the 125 mg compared with the 75 mg dose in women and men, respectively. At the same 125 mg dose, women showed on average 1.29- and 1.26-fold higher C_{max} and AUC_6 levels compared with men, respectively.

Effects of MDMA on kidney and liver function and changes in blood cell counts

At EOS and 30 ± 22 days after the last of one or two administrations of MDMA plus pretreatments in some of the studies, plasma creatinine levels and the estimated glomerular filtration rate were unchanged compared with the start of the study and before MDMA administration (Table 4). Similarly, plasma levels of aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase were similar at the screening and at the EOS visits. Red blood cell counts and haemoglobin levels decreased, and thrombocyte levels increased during the study. White blood cell counts remained unchanged. Red blood cells and haemoglobin were reduced significantly more in women than in men ($F_{1,159} = 8.12$; $p < 0.01$ and $F_{1,159} = 12.9$; $p < 0.001$). The decrease did not reach statistical significance in men.

Subjects' interest in using MDMA again

Eighty per cent of the subjects were MDMA-naive, and the rest had very limited experience with MDMA (i.e. ⩽4 exposures at most). One hundred and forty-one subjects were asked whether they would consider taking MDMA again. Twenty-seven subjects (19%) reported that they would probably not take MDMA again under any circumstances. Sixty-six subjects (47%) reported that they would not use MDMA in a recreational setting but might consider participating in another study with MDMA administration under controlled conditions. Forty-eight subjects (34%) indicated that they may consider taking MDMA in a recreational setting but only if the identity, purity and dose were known. Twenty-four of these 48 subjects (50%) had taken illicit drugs previously, including MDMA. Only 13 subjects considered taking MDMA in a club setting. Ninety-five subjects (67%) reported a positive overall MDMA experience, 25 subjects (18%)

Table 3. Acute and subacute adverse effects of MDMA (total *n* = 166).

	Placebo			MDMA		
		Acute	Subacute		Acute	Subacute
	0 h	Up to 6 h	24 h	0 h	Up to 6 h	24 h
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Lack of appetite	2 (1)	3 (2)	1 (1)	4 (2)	98 (59)***	52 (31)***
Dry mouth	1 (1)	3 (2)	3 (2)	1 (1)	91 (55)***	37 (23)***
Difficulty concentrating	6 (4)	10 (6)	4 (2)	5 (3)	76 (46)***	35 (22)***
Cold feet	8 (5)	7 (4)	2 (1)	10 (6)	69 (42)***	10 (6)*
Sweating	2 (1)	0 (0)	0 (0)	0 (0)	68 (41)***	7 (4)*
Bruxism[a]	2 (2)	1 (1)	1 (1)	3 (2)	54 (40)***	19 (14)***
Restless legs	1 (1)	2 (1)	2 (1)	2 (1)	62 (37)***	12 (7)*
Dizziness	2 (1)	2 (1)	3 (2)	5 (3)	57 (34)***	12 (7)*
Hot flushes	1 (1)	0 (0)	0 (0)	1 (1)	52 (31)***	12 (7)***
Headache	9 (5)	27 (16)	25 (15)	8 (5)	42 (25)	55 (33)***
Heart palpitation	1 (1)	2 (1)	1 (1)	1 (1)	40 (24)***	11 (7)**
Lack of energy	9 (5)	23 (14)	5 (3)	8 (5)	38 (23)*	49 (30)***
Nausea	3 (2)	2 (1)	1 (1)	2 (1)	19 (11)***	9 (6)*
Anxiety	0 (0)	0 (0)	0 (0)	2 (1)	9 (6)**	3 (2)

[a]*n* = 134.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with placebo (Fisher's exact test).
MDMA: 3,4-methylenedioxymethamphetamine; *n*: number of subjects.

Table 4. Chronic effects of MDMA on kidney and liver function and blood cell counts.

Kidney and liver function	Screening	EOS	*t*-test	
	n = 164[a]		*t*	*p* =
Creatinine, normal: <97 µm				
Mean ± SD, µm (range)	74 ± 13 (47–115)	73 ± 12 (47–108)	1.89	NS
Glomerular filtration rate C_{CR}, normal: > 90 mL/min				
Mean ± SD, mL/min (range)	122±22 (70–202)	125±24 (64–220)	−1.95	NS
Aspartate aminotransaminase, normal: <34 U/L				
Mean ± SD, U/L (range)	25 ± 7 (14–64)	26 ± 11 (9–131)	−0.93	NS
Alanine aminotransferase, normal: <59 U/L				
Mean ± SD, U/L (range)	19 ± 9 (6–64)	20 ± 10 (5–82)	−0.44	NS
γ-glutamyl transpeptidase, normal: <68 U/L				
Mean ± SD, U/L (range)	19 ± 8 (7–56)	18 ± 8 (7–51)	2.73	< 0.01
Blood cell counts	*n* = 161[b]			
White blood cells, normal: 3.5–10.0 × 10^9/L				
Mean ± SD, ×10^9/L (range)	6.6 ± 1.8 (3.2–14.6)	6.4 ± 1.8 (2.6–16.4)	1.54	NS
Red blood cells, normal: 4.2–6.3 × 10^{12}/L				
Mean ± SD, ×10^{12}/L (range)	4.7 ± 0.4 (3.8–6.1)	4.6 ± 0.4 (3.8–5.8)	4.77	< 0.001
Haemoglobin, normal: 120–180 g/L				
Mean ± SD, g/L (range)	144 ± 12 (121–174)	140 ± 14 (106–181)	6.33	< 0.001
Thrombocytes, normal: 150–450 ×10^9/L				
Mean ± SD, ×10^9/L (range)	263 ± 53 (145–438)	276 ± 56 (164–481)	−4.27	< 0.001

MDMA: 3,4-methylenedioxymethamphetamine; EOS: end of study; *n*: number of subjects; SD: standard deviation; NS: not significant.
[a]Data from two subjects missing.
[b]Data from five subjects missing.

reported a neutral experience and 21 subjects (15%) reported a disappointing or bad experience. No sex differences were observed. Fifty-one subjects (36%) reported that the controlled setting had no impact on their experience, whereas 90 subjects (64%) reported that the controlled setting was important for their type of experience and was reassuring and made them feel safe.

Women rated the setting as significantly more important than men ($F_{1,139} = 12.4$; $p < 0.001$).

Discussion

The present study analysed pooled data from nine placebo-controlled Phase I studies and characterized the acute effects of MDMA in healthy subjects, with a focus on tolerability and clinical safety. The safety considerations included aspects of psychological and physical harm. The present study showed clearly greater positive than negative acute subjective effects. MDMA induced a state of predominantly positive mood across different laboratories (Baggott et al., 2016; Bershad et al., 2016; Dumont and Verkes, 2006; Farre et al., 2007; Hysek et al., 2014a; Kamilar-Britt and Bedi, 2015; Kirkpatrick et al., 2012, 2014a; Kolbrich et al., 2008a; Kuypers et al., 2014; Tancer and Johanson, 2003), with one exception (Parrott et al., 2011). Modest apprehension anxiety was present in some subjects as previously reported (Dumont and Verkes, 2006; Liechti et al., 2001), whereas social anxiety has been shown to decrease (Baggott et al., 2016). In the present study, anxiety was reported in the List of Complaints as an acute adverse effect by 7% of the subjects after 125 mg MDMA administration but not after 75 mg. In our experiments, anxiety could be reduced by verbal support in all of the subjects, and benzodiazepines were not used. There were no cases of severe anxiety or panic attacks. Psychological distress was minimal. Overall positive subjective experiences were retrospectively reported in two-thirds of the participants in the present study, whereas 15% of the subjects were rather disappointed by the effects of MDMA or had bad experiences. In contrast to the findings from the present controlled studies, panic attacks and agitation/aggression are common psychiatric complications in recreational ecstasy users who present to emergency departments (Halpern et al., 2011; Liechti et al., 2005; Wood et al., 2016).

The present study also determined the exact time course of the overall subjective response to MDMA. The average onset time, peak time and effect duration (33 min, 1.6 h and 4.2 h, respectively) were comparable to previous studies (Farre et al., 2004; Hysek and Liechti, 2012; Kolbrich et al., 2008a; Liechti et al., 2001; Mithoefer et al., 2010). The effect duration represented the time an individual experienced a subjective drug effect ⩾10% of his/her own peak response. It has been suggested that the duration of the effect of MDMA (125 mg) could be prolonged by another dose (62.5 mg) 2 h after the initial dose (Mithoefer et al., 2010; Sessa, 2016). However, the short duration of action of MDMA relative to its long plasma half-life (Hysek et al., 2011; Kolbrich et al., 2008b) is attributable to acute pharmacological tolerance. Thus, the subjective effects decline despite high concentrations of MDMA in the body (Hysek et al., 2011, 2012a). Therefore, adding more MDMA to increase the MDMA concentration in the body might not relevantly prolong the limited effect duration and may increase adverse effects (Peiro et al., 2013). In line with this view, the effect duration of the 75 and 125 mg dose of MDMA did not differ in the present study. In contrast to MDMA, acute pharmacological tolerance was not observed with lysergic acid diethylamide (LSD), which is also investigated in substance-assisted psychotherapy (Gasser et al., 2014), and the effect duration of LSD was shown to be dose-dependent (Dolder et al., 2015, 2016).

In terms of potential physical harm, MDMA induced sympathomimetic activation. MDMA produced at least moderate hypertension (systolic blood pressure >160 mmHg) and tachycardia (heart rate >100 beats/min) in one-third of the participants. Thus, although the participants were resting, they presented changes in vital signs that were similar to moderate physical activity. Transient severe hypertension (systolic blood pressure >180 mmHg) was observed in 5% of the participants who received 125 mg MDMA. Severe hypertension may lead to complications including stroke and heart attacks in vulnerable persons. No other signs or symptoms of hypertensive crises (severe headache, shortness of breath, or nosebleeds) were observed in the present study. Similarly, a previous analysis that included 74 subjects from laboratory studies found systolic blood pressure ⩾160 mmHg and ⩾180 mmHg in 32% and 9% of the subjects, respectively (Liechti et al., 2001). Other stimulant drugs, such as methamphetamine, D-amphetamine and methylphenidate, produced comparable cardiovascular stimulation to MDMA when administered as single oral doses (Bershad et al., 2015; Brauer et al., 1996; Hysek et al., 2014b; Kirkpatrick et al., 2012; Martin et al., 1971; Schmid et al., 2014; Wardle and De Wit, 2012).

The present study also found statistically significant MDMA-induced increases in body temperature, but body temperatures did not increase to >39.1°C, consistent with previous studies (Freedman et al., 2005; Kolbrich et al., 2008a; Liechti, 2014). There can be considerable variance in the thermal reactions to acute MDMA (Kolbrich et al., 2008a; Liechti, 2014). Hyperpyrexia (>40°C) is rare but represents the most important life-threatening complication of recreational MDMA use (Grunau et al., 2010; Halpern et al., 2011; Henry et al., 1992; Liechti, 2014; Liechti et al., 2005; Wood et al., 2016). No controlled clinical study of MDMA has reported MDMA-induced hyperpyrexia, possibly because the participants were treated with moderate single doses at rest, were well-hydrated and were not in a hot or crowed environment, unlike in some recreational settings that are known to increase the risk of hyperpyrexia (Dafters, 1995).

In the present study, the participants reported a series of MDMA-induced acute and subacute adverse effects. These effects were consistent with moderate sympathomimetic toxicity, including lack of appetite, dry mouth, cold feet, sweating, restlessness and heart palpitation. The most frequently reported adverse effects 24 h after MDMA administration were headache, lack of energy and lack of appetite. Depressed mood, including emotional irritability, lack of energy, brooding and bad dreams, has previously been reported in up to one-third of subjects, lasting up to three days in some subjects (Liechti et al., 2001). Anxiety, difficulty concentrating, irritability and loss of appetite were also noted in the week following MDMA use in psychotherapy (Mithoefer et al., 2010; Oehen et al., 2013). Similarly, ecstasy users reported mid-week depression following weekend MDMA use (Verheyden et al., 2002).

Hallucinogen persisting perception disorder has been described following recreational ecstasy use (Litjens et al., 2014). One hundred and forty-one participants in the present study were asked at the end of the study whether they experienced flashbacks. Twelve subjects (9%) reported flashbacks, but only within 8–50 h after drug administration. Thus, our study found no evidence of persisting perceptual alterations after MDMA administration in a controlled setting.

In the present study, MDMA did not influence levels of liver enzymes on average one month after administration. Although direct hepatotoxic effects of MDMA are unlikely at the doses used, there is evidence of rare idiosyncratic hepatotoxicity (Atayan et al., 2015; Ellis et al., 1996; Henry et al., 1992; Maharaj et al., 2015). This type of hepatotoxicity is observed with many marketed medications. The decrease in red blood cells and increase in thrombocytes that were observed over the time course of the present study were attributable to the sampling of blood (400–600 mL) for pharmacokinetic analyses and not a consequence of MDMA use.

Although the 125 mg dose of MDMA was 1.67-fold higher than the 75 mg dose, it produced 1.8-fold higher C_{max} and AUC_6 values than the 75 mg dose, indicating nonlinear dose-exposure relationship. This finding is in line with previous studies (de la Torre et al., 2000; Kolbrich et al., 2008a; Schmid et al., 2014) but statistically significant only in women and not in men at the doses tested in the present study. At the same fixed 125 mg dose of MDMA, women showed 1.29-fold higher C_{max} levels than men, which could be explained mainly by their 1.24-fold lower body weight. In the present study, subjective 'bad drug effect' ratings and other adverse acute and after-effects were greater in women than in men. These negative effects of MDMA were significantly greater in women than men even when correcting for the higher dose per body weight or significantly higher plasma levels in women compared with men. Similarly, greater acute and subacute adverse effects were previously reported in women compared with men in an analysis of studies that used body weight-adjusted dosing of MDMA (Liechti et al., 2001). Previous studies also found greater MDMA-induced negative subjective effects, including 'fear of loss of body control' and 'thought disorders' (Liechti et al., 2001), as well as dizziness and sedation (Pardo-Lozano et al., 2012), in women than in men. Higher midweek depression scores in women than in men following weekend MDMA use have also been reported (Verheyden et al., 2002). Women may be more susceptible to the adverse effects of MDMA on the serotonin system (Reneman et al., 2001). Men presented higher acute blood pressure responses than women (Liechti et al., 2001), consistent with the greater cardiovascular stimulant effects of MDMA in men than in women, after dose-normalization in the present study. In contrast, women presented higher heart rates than men in another smaller study (Pardo-Lozano et al., 2012). To our knowledge, no other laboratory studies have specifically reported sex differences in the acute subjective and physiological effects of MDMA. The present findings may be useful for dose selection in MDMA-assisted psychotherapy in patients with PTSD. Women had similar adverse effects scores on the List of Complaints after 75 mg MDMA administration compared with men that received 125 mg, suggesting that the lower dose should be used in female patients. However, significantly higher subjective 'good drug effect' ratings and comparable 'bad drug effect' ratings were reported in women after 125 mg MDMA administration compared with 75 mg. Based on our data, we suggest that a fixed dose of 100 mg may be a good choice in women and comparable to the 125 mg dose in men. This dose adjustment would also account for the approximately 1.3 times higher plasma peak levels of MDMA in women compared with men at the 125 mg dose shown in the present study. Doses up to 187.5 mg have been safely used in mostly women in MDMA-assisted psychotherapy (Mithoefer et al., 2010; Oehen et al., 2013). Whether these high doses are indeed needed in female patients to achieve therapeutic effects requires further study.

The present safety data can in part be applied to the use of MDMA in patients. In patients, MDMA is typically used sporadically 2–3 times and spaced several weeks apart in addition to non-substance assisted psychotherapy (Mithoefer et al., 2010; Oehen et al., 2013; Sessa, 2016). The same 125 mg dose of MDMA was used in the present study and in MDMA-assisted psychotherapy (Mithoefer et al., 2010; Oehen et al., 2013). The study participants typically had no or very little previous MDMA experience, similar to patients. In the research setting that is used in our laboratory, a research assistant is always present with the participants, similar to a therapy session (Mithoefer et al., 2010; Oehen et al., 2013), in contrast to some other experimental settings (Kirkpatrick et al., 2014a). However, the subjective response to MDMA may be different in patients with psychiatric disorders compared with subjects who are screened to be psychiatrically healthy. Consistent with the present data, there have been no reports to date of serious adverse reactions in clinical MDMA studies (Doblin et al., 2014; Mithoefer et al., 2010; Oehen et al., 2013).

The present study has limitations. We included only psychiatrically healthy subjects and the risks of using MDMA in persons with psychiatric disorders may be different (Greer and Tolbert, 1986; Parrott, 2007; Vollenweider et al., 1998) and also need to be investigated. For example, the use of MDMA has been reported to acutely induce negative moods and cognitions, and other undesirable psychological effects in psychotherapy, (Greer and Tolbert, 1986; Parrott, 2007). We included mostly young subjects, but older patients with mainly more cardiovascular risk factors may also be treated in MDMA-assisted psychotherapy. Hyponatraemia is frequently observed in ecstasy intoxications (Halpern et al., 2011; Hartung et al., 2002; Rosenson et al., 2007) but was not assessed in the present study. Additionally, we did not evaluate neurocognitive function or any other correlates of neurotoxicity or long-term problems (Kuypers et al., 2016; Mueller et al., 2016; Parrott, 2013b, 2014; Rogers et al., 2009). Laboratory markers of liver and renal function were only assessed at the end of the study and on average one month after the last MDMA administration not excluding short-lasting transient changes in these parameters. Finally, the sample size of the present pooled analysis of 166 administrations of MDMA alone or 278 administrations of MDMA alone or with a pretreatment was too small to exclude infrequent (0.1–1%) or rare (<0.1%) adverse events. For example, we observed no event of hyperpyrexia among the 278 MDMA administrations and the 95% confidence interval for no event among 278 observations calculated using the binomial distribution is 0–1.3%.

Conclusion

Single-dose administration of MDMA was safe in healthy subjects and in a controlled clinical setting. Acute subjective effects were predominantly positive. Subjective adverse effects were more frequently reported in women than in men. A fixed dose of 100 mg is likely more appropriate for women and comparable to the 125 mg dose in men. These safety data do not raise any concerns related to further studies of MDMA as an adjunct to psychotherapy in controlled medical environments. However,

MDMA dose-dependently induced cardiovascular stimulation, which may be greater in men and should be considered a significant risk for patients with cardiovascular disease. Finally, the risks and benefits of using MDMA in patients with psychiatric disorders need further study.

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