Psychopharmacology (2002) 161:23–31
DOI 10.1007/s00213-001-0995-9

ORIGINAL INVESTIGATION

Suzanne L. Verheyden · Joanne Hadfield · Tara Calin
H. Valerie Curran

Sub-acute effects of MDMA (±3,4-methylenedioxymethamphetamine, "ecstasy") on mood: evidence of gender differences

Received: 23 May 2001 / Accepted: 13 November 2001 / Published online: 6 March 2002

Abstract *Rationale*: Research with animals suggests that central 5-hydroxytryptamine (5-HT) function may be attenuated for a period following a single dose of ±3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). If the same is true in humans, then functions thought to be modulated by 5-HT may differ in MDMA users compared with non-users a few days after the drug is taken. *Aims*: The present study therefore investigated both acute and sub-acute effects of MDMA on mood of recreational users. A second aim was to determine whether these effects differ for females and males. *Design*: A parallel group design was used to compare 40 participants who reported taking MDMA with 40 participants who reported using illicit substances excluding MDMA (polydrug controls). Participants were assessed on the night of drug use (day 0) and again 4 days later. *Results*: Female MDMA users showed higher depression scores mid-week than male users or male or female controls. Mid-week depression in female users was correlated with the amount of MDMA taken on day 0. MDMA users rated lower levels of aggression than controls on the night of drug use but significantly higher levels of aggression mid-week, and in males change in aggression correlated with the amount of MDMA taken on the weekend. There was no association between mood and measures of long-term use of MDMA (e.g. years of use). *Conclusion*: Women are more susceptible than men to mid-week low mood following weekend use of MDMA; however, both men and women show increased self-rated aggression. These results are interpreted in terms of an attenuation of 5-HT function for a period following acute use of MDMA.

S.L. Verheyden (✉) · J. Hadfield · T. Calin · H.V. Curran
Psychopharmacology Laboratories,
Sub-department of Clinical Health Psychology,
University College London, Gower Street, London WC1E 6BT, UK
e-mail: s.verheyden@hotmail.com
Tel.: +44-20-87764657, Fax: +44-20-87764659

Keywords Ecstasy · MDMA · Gender difference · Depression · Aggression · Residual effect

Introduction

MDMA (±3,4-methylenedioxymethamphetamine, 'ecstasy') is a popular recreational drug taken for its acute effects, which include euphoria, increased sociability and energy. Its particular psychological effects have led to the suggestion that MDMA represents a new class of compounds called 'entactogens'. This term derives from the Greek meaning 'touching within' (Nichols 1986) and has parallels with one of users' own terms for MDMA, the 'hug drug'. A few studies have administered single doses of MDMA to humans and described its acute psychological effects (Vollenweider et al. 1998; Cami et al. 2000). However, little attention has been paid to the potential residual effects of MDMA on psychological function in the days immediately after consumption.

In animals, MDMA is neurotoxic to 5-hydroxytryptamine (5-HT) neurons. Animals administered MDMA develop persistent losses in 5-HT axonal markers including 5-HT, 5-hydroxyindoleacetic acid, tryptophan hydroxylase and the 5-HT transporter (Battaglia et al. 1988; Green et al. 1995; O'Shea et al. 1998; Ricaurte et al. 2000). In non-human primates, loss of 5-HT axonal markers persists for several years beyond acute dosing (Hatzidimitriou et al. 1999). Humans who have recently used MDMA show decreased global and regional brain 5-HT transporter binding compared with non-using controls, and this decrement correlates to some degree with extent of use of the drug (McCann et al. 1998).

Acutely, MDMA causes a temporary attenuation of central 5-HT following the initial efflux of stored serotonin from nerve terminals (Schmidt et al. 1986). MDMA has a threefold mechanism of action that results in this temporary reduction in central 5-HT: it causes the release of stored 5-HT from nerve terminals, prevents reuptake of excess 5-HT from the synaptic cleft and inhibits tryptophan hydroxylase, thereby inhibiting the syn-

thesis of replacement 5-HT (McKenna and Peroutka 1990). This effect of MDMA on tryptophan hydroxylase activity means that the attenuation of central 5-HT may persist for days after an acute dose. This attenuation may have implications for the psychological functioning of MDMA users for a period of days after acute dosage. It is possible that the depletion of brain 5-HT caused by MDMA results in impairment to functions modulated by 5-HT.

5-HT is thought to be involved in the modulation of a variety of functions and particularly in the regulation of mood. Indeed, 5-HT has been identified as the key neurotransmitter in the aetiology of depressive illness. For example, rapid depletion of central 5-HT by tryptophan depletion causes relapse of depression in women who had previously recovered from clinical depression (Delgado et al. 1994; Smith et al. 1997), and the mechanism of action of antidepressants may involve increasing the availability of central 5-HT (Goodwin et al. 1985; Cowen 1991). Thus the depletion of 5-HT for a period following ingestion of MDMA may be associated with depressed mood. Indeed, two studies have reported that recreational users of MDMA have low mood several days after an acute dose when compared with controls (Curran and Travill 1997; Parrott and Lasky 1998).

Aggression in humans has also been linked to deficits in 5-HT (Brown et al. 1979; Coccaro et al. 1989; Linnoila and Virkkunen 1992; Linnoila et al. 1993). Studies that have manipulated brain 5-HT using rapid tryptophan depletion have shown an inverse correlation between measures of 5-HT function and levels of hostility and aggression (Bond et al. 1995; Cleare and Bond 1997). Acute release of 5-HT by MDMA would thus be associated with the opposite of aggression (empathy), but several days later, depletion of 5-HT may be associated with aggression. To our knowledge, no study has examined the effects of MDMA on aggression in humans a few days after acute dosage. However, Gerra et al. (1998) found that male MDMA users who had not used MDMA for 3 weeks scored higher than MDMA-naive controls on measures of direct aggressiveness and novelty-seeking behaviour. McCann et al. (1994), in contrast, reported that MDMA users had lower indirect hostility scores and were less impulsive than non-user controls. There could be various reasons for discrepant results, including time since last dose of MDMA, and other methodological differences such as the inclusion of female participants in the McCann et al. study. Thus there is clearly a need to determine the nature of the relationship between MDMA use and aggression.

Aggression has often been seen as ‘anger out’ in contrast to depression seen as ‘anger in’ (Nunn and Thomas 1999; Newman et al. 1999). Depression is more common amongst females than males (Frackiewicz et al. 2000; Murphy et al. 2000), whereas aggression is more common in males. It is conceivable that there are gender differences in the effects of MDMA on depressed mood and/or aggression. To date, only two studies have reported gender differences in MDMA users. McCann et al. (1994) found that 12 female MDMA users had lower levels of 5-hydroxyindoleacetic acid (the metabolite of 5-HT) in cerebrospinal fluid than 18 male MDMA users. Recently Liechti et al. (2001) analysed data from three studies in which acute doses (1.35–1.8 mg kg^{-1}) of MDMA were administered to MDMA-naive subjects. Equal doses of MDMA per kilogram body weight produced stronger subjective effects in women than men. Women reported more anxiety than men on an adjective mood-rating scale, and women’s anxiety scores correlated with the dose of MDMA they had been administered. Thus there is some evidence suggesting that women may have increased susceptibility to the psychological effects of MDMA.

The present study sought to test two hypotheses. The first hypothesis was that female MDMA users would be more susceptible to residual depression in the days following MDMA than male users. This was based on four lines of evidence:

i. Animal studies showing attenuated 5-HT function for a period after an acute dose of MDMA.
ii. Human studies suggesting that females have increased susceptibility to MDMA.
iii. Mid-week low mood a few days after use of MDMA.
iv. Depression is more prevalent in women than in men.

The second related hypothesis was that men would be more likely than women to show increased aggression a few days after taking MDMA. This was based on:

i. The same animal studies showing attenuated 5-HT function after MDMA.
ii. Links between 5-HT function and aggression in humans.
iii. Preliminary evidence of increased self-reported aggression in male MDMA users.

In summary, it was predicted that MDMA users would exhibit elevated mood and decreased aggression relative to controls whilst on drug, but that, 4 days later, this would be reversed such that MDMA users would show increased depression and aggression compared with controls. Gender differences in the sub-acute psychological effects of weekend MDMA consumption were also predicted.

Methods

Participants

Eighty volunteers aged between 18 years and 35 years were recruited using the snowball technique (Solowij et al. 1992) in party settings on successive Friday or Saturday nights over a 5-month period. Participants were recruited in two groups:

i. Forty regular MDMA users who had consumed MDMA that evening.
ii. Forty polydrug controls with little or no previous exposure to MDMA.

For inclusion in the MDMA group, participants had to have taken MDMA on at least 20 occasions during the previous year and have taken MDMA at the party. The polydrug control group were rec-

reational drug users with little or no experience of MDMA who had not taken MDMA that evening. Exclusion criteria for both groups included past or present psychiatric history, major illness, pregnancy, opiate or alcohol dependence. The study had approval from the institutional ethics committee, and all participants gave written, informed consent prior to the study on each of the two test days.

Procedure

Participants were assessed on the evening of the party (day 0) and again 4 days later (day 4). On day 0 volunteers were taken individually to a quiet area where they informed the experimenter whether or not they had taken MDMA that evening. They then completed the assessments detailed below and arrangements were made to meet up 4 days later. Participants were asked to abstain from alcohol and recreational drugs between the two test sessions.

The follow-up test session on day 4 was carried out at the participants home, in a room with minimal distraction. Participants were asked again to give written informed consent. They then completed the same assessments as on day 0 along with some additional trait measures and a detailed drug-use questionnaire. Participants were also asked to report the amount of MDMA and any other drugs consumed on day 0.

Assessments: day 0 and day 4

Mood was assessed using a modified state version of the Beck depression inventory (BDI, Beck 1978). The standard 21-item depression inventory was modified by changing the instructions at the top of the inventory asking participants to rate the items which best described how they had been feeling over the past 3 days (Curran and Travill 1997). The BDI can also be divided into cognitive and somatic items.

Four visual analogue scales were used so that participants could self-rate the acute effects of MDMA whilst on drug. These included the mood-rating scale (MRS, Bond and Lader 1974), the aggression-rating scale (ARS, Bond and Lader 1986), the impulsivity self-rating scale (ISRS, Bond and Lader 1974) and a bodily symptoms scale (BSS, Bond and Lader 1974). All visual analogue scales were 100-mm long and anchored at each end with contrasting descriptions of mood/aggression/impulsivity/bodily symptoms. For each scale participants rated how they felt at that moment in time by placing a mark across the line. Three factors were extracted from the MRS: alertness, contentedness and calmness. The BSS included somatic symptoms known to be associated with MDMA.

Pulse rate was taken on both day 0 and day 4. It was expected that this would provide physiological evidence as to whether MDMA had been taken, with higher pulse rates on day 0 suggesting use of MDMA.

Assessments: day 4 only

Trait measures of depression and aggression were carried out on day 4. The hospital anxiety and depression scale (HADS, Zigmond and Snaith 1983) was used to assess trait anxiety and epression. The aggression questionnaire (AQ, Buss and Perry 1992) was used to measure trait aggression.

A substance use questionnaire was constructed to obtain information about participants' drug-use patterns. Amount, frequency and length of use of all recreational drugs were recorded, along with the drugs that were used in conjunction with MDMA. Units of alcohol consumed were calculated by the experimenter from participant's reported drinking.

Statistical analyses

Changes in scores from day 0 to day 4 were analysed using repeated-measures analysis of variance (ANOVA) with day (0 or 4) as the within-subjects factor and group and gender as between-subjects factors. Age was entered as a covariate in these analyses as an independent samples *t*-test revealed a significant age difference in groups (see below). All data satisfied the assumptions necessary to carry out repeated-measures ANOVAs (normality, sphericity, equality of variance). Drug use patterns were compared using Mann-Whitney U-tests as these data were not normally distributed.

The internal consistency of the 13 variables comprising the visual analogue scale for aggression was assessed using Cronbach's alpha. The scale had a high internal consistency on both day 0 (α=0.89) and day 4 (á=0.95), so a total aggression score was calculated and used in subsequent analysis in order to reduce the possibility of type-I errors. The same procedure was used for the 20 items in the ISRS. Again, the scale had a high internal consistency on both day 0 (α=0.81) and day 4 (á=0.92), so a total impulsivity score was used. Pearson product–moment correlations were carried out to examine relationships between drug consumption and change in mood. All data were analysed using SPSS for Windows (release 9.0).

Results

Demographics

There were similar number of males and females in each group (MDMA group: 19 females, 21 males; control group, 21 females, 19 males, Table 1). Participants were aged between 18 years and 35 years (mean 21.38± 2.88 years). Those in the MDMA group were older (by approximately 2 years) than those in the polydrug control group (t_{60}=–3.02, P<0.005), and males in the MDMA group were older (again by approximately 2 years) than females in the MDMA group (t_{26}=–2.41, P<0.05). Males and females in the control group were of a similar age.

In the control group, three males and five females had taken MDMA in the previous 6 months but were not regular users of MDMA (i.e. they used less than once a month). None had taken MDMA in the previous 21 days. Within the MDMA group (i.e. those who had taken the drug on day 0), there were no gender differences in frequency of MDMA use. However, there were significant gender differences in typical dose of MDMA, length of MDMA use and a cumulative measure of lifetime use. As seen in Table 1, men took an average of one MDMA tablet more than women per session (t_{37}=–2.60, P<0.05) and had used MDMA for an average of 2 years more than women (t_{28}=–2.19, P<0.05). A measure of cumulative use of MDMA (typical dose × frequency of use × years of use) showed that men had taken more MDMA tablets over their lifetime than women (t_{22}=–2.76, P<0.05). Mann-Whitney U-tests showed no significant differences between male and female MDMA users for lifetime use of all other drugs. However, men had a tendency towards higher lifetime use of alcohol (U=132.00, P=0.07) and tobacco (U=91.00, P=0.07) than women (Table 2).

Although MDMA users reported higher lifetime use of cocaine, ketamine, lysergic acid diethylamide (LSD) and benzodiazepines, too few of the control group reported use of these drugs to make meaningful comparisons (Table 2). Moreover few, if any, of the MDMA

Table 1 Age and patterns of ±3,4-methylenedioxymethamphetamine (MDMA) use (mean±SD)

	Age	Typical dose (per session)	Frequency (days/month)	Length of use (years)	Lifetime use (dose × years × frequency)
MDMA males (*n*=21)	23.43±4.20	3.55±1.99	4.63±3.58	5.30±3.57	1171.58±1158.53
MDMA females (*n*=19)	21.05±1.54	2.26±0.87	4.00±2.29	3.34±1.75	397.26±391.45
Total MDMA (*n*=40)	22.30±3.41	2.92±1.66	4.32±2.98	4.35±2.97	784.42±938.85
Control males (*n*=19)	20.26±1.56	–	–	–	–
Control females (*n*=21)	20.62±2.11	–	–	–	–
Total control (*n*=40)	20.45±1.85	–	–	–	–

Table 2 Mean (SD) lifetime drug use in ±3,4-methylenedioxymethamphetamine (MDMA) and control groups. *LSD* lysergic acid diethylamide, *GHB* γ-hydroxybutyrate

Drug	Lifetime use of drug (years of use × dose × frequency)							
	MDMA males	*n*	MDMA females	*n*	Control males	*n*	Control females	*n*
Alcohol (units)	13,182.86±11,984.70	21	6726.32±3802.14	19	7809.47±8824.16	19	6898.28±6778.3	21
Tobacco (cigarettes)	43,353.33±25,928.95	18	27,457.50±22,326.20	16	17,481.82±14,964.01	11	25,602.35±15,024.82	17
Cannabis (oz)	115.37±127.72	18	47.59±56.96	18	89.72±123.34	16	39.36±70.17	18
Amphetamine (g)	101.00±101.99	6	178.50±267.45	4	96.00	1	192.00	1
Cocaine (g)	162.00±226.21	13	38.77±32.09	13	12.00	1	48.86±105.68	7
Ketamine (g)	153.00±202.18	7	34.20±30.27	5	–	0	–	0
LSD (trips)	540.00±84.85	7	–	0	24.00	1	72.00	1
GHB (mg)	–	0	–	0	–	0	–	0
Benzodiazepines (mg)	192.00	1	–	0	–	0	–	0

Table 3 Drugs other than ±3,4-methylenedioxymethamphetamine (MDMA) used on day 0. *LSD* lysergic acid diethylamide, *GHB* γ-hydroxybutyrate

Drug	Number of participants reporting use of drug			
	MDMA males (*n*=21)	MDMA females (*n*=19)	Control males (*n*=19)	Control females (*n*=21)
Alcohol	19	19	17	21
Cannabis	9	6	13	9
Amphetamine	0	1	0	0
Cocaine	5	0	0	1
Ketamine	3	1	0	0
LSD	0	0	0	0
GHB	0	0	0	0
Benzodiazepines	1	0	0	0

group used LSD, γ-hydroxybutyrate (GHB) or benzodiazepines on a regular basis. Of the drugs used regularly by both groups, the MDMA group had higher lifetime use of alcohol (U=582.50, $P<0.05$) and tobacco (U=333.50, $P<0.05$) than the control group.

There was no significant gender difference in the amount of MDMA taken on day 0. Female MDMA users took an average of 1.8 tablets whereas male MDMA users took an average of 2.1 tablets. There were no group or gender differences in amount of alcohol consumed on day 0. MDMA males reported drinking 5.3 units on average compared with 5.0 units reported by control males. Female MDMA users drank an average of 3.7 units on day 0 compared with 5.4 units reported by females in the control group.

MDMA and control groups were well matched for drugs other than MDMA used on day 0, although rather more controls took cannabis on day 0 (Table 3). Despite being asked to abstain from drug use between test days, many participants used alcohol and cannabis between day 0 and day 4. Nevertheless, the only drugs used by participants between day 0 and day 4 were alcohol and cannabis. A similar number of MDMA users (50%) and controls (55%) drank alcohol between test sessions. Slightly more MDMA users used cannabis between day 0 and day 4 than controls (45% versus 25%, respectively).

Subjective ratings

Beck depression inventory

BDI scores showed a significant 3-way interaction of group × gender × day ($F_{1,75}=4.37$, $P<0.05$). As seen in Fig. 1, female MDMA users showed a larger increase in BDI scores than male MDMA users between day 0 and day 4. Control males and females showed only a slight de-

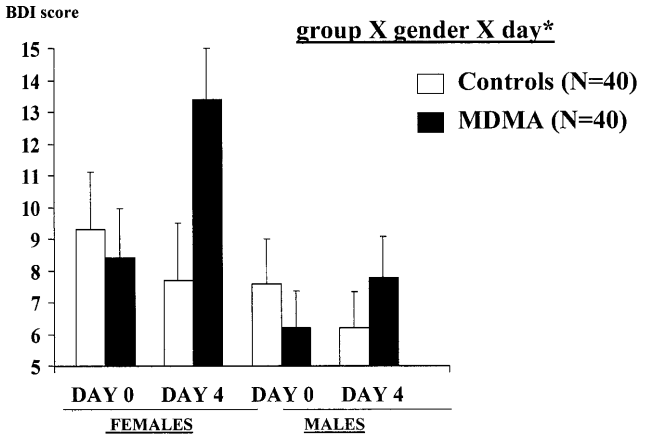

Fig. 1 Depression scores [mean Beck depression inventory (BDI), standard error] on day 0 and day 4 for males and females in the ±3,4-methylenedioxymethamphetamine (MDMA) and control groups (***P<0.001, *P<0.05)

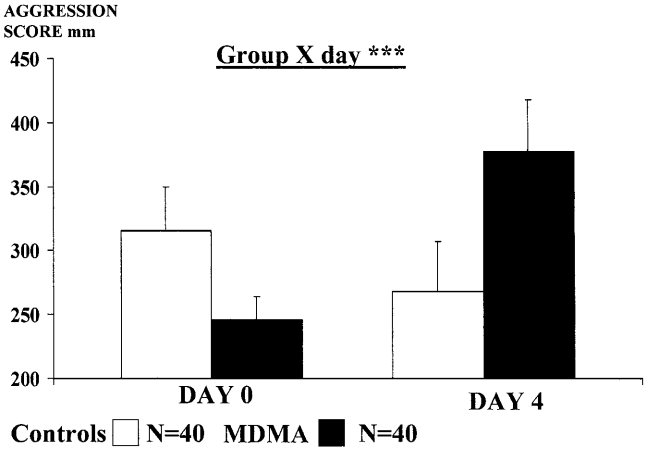

Fig. 2 Subjective aggression scores [mean aggression-rating scale (ARS), standard error] on day 0 and day 4 for males and females in the ±3,4-methylenedioxymethamphetamine (MDMA) and control groups

crease in scores from day 0 to day 4. There was also a significant day × group interaction ($F_{1,75}$=23.52, P<0.001) and day × gender interaction ($F_{1,75}$=3.82, P=0.05). There was a group × day interaction on the BDI cognitive scale ($F_{1,75}$=11.58, P<0.005). The control group had slightly higher cognitive depression scores than the MDMA group on day 0, but by day 4 the MDMA group had much higher scores than the control group. There were no significant main effects or interactions on the BDI somatic scale.

Mood rating scale

There was also a group × gender × day interaction on the MRS 'contentedness' factor ($F_{1,74}$=4.82, P<0.05). This paralleled results on the BDI: female MDMA users showed an increase in discontentment over time whilst controls did not show any change (Table 4). Female MDMA users also showed a larger increase in discontentment than male MDMA users. There was also a group × day interaction ($F_{1,74}$=17.59, P<0.001) again reflecting an increase in discontentment from day 0 to day 4 in MDMA users but not controls. There was a main effect of gender on the calmness factor ($F_{1,75}$=5.34, P<0.05) with females having lower calmness scores than males. There was also a main effect of day on the alertness factor ($F_{1,74}$=4.35, P<0.05) whereby participants were more alert on day 4 than on day 0.

Aggression rating scale

This showed a very significant group × day interaction ($F_{1,75}$=14.28, P<0.001). As seen in Fig. 2, MDMA users showed an increase in aggression scores from day 0 to day 4, whereas controls showed a decrease in aggression scores over time. MDMA users had lower scores than controls on day 0, but on day 4 this pattern was reversed (Table 4). There were no gender differences.

Impulsivity

There was only a main effect of group on the ISRS ($F_{1,75}$=10.18, P<0.005) whereby MDMA users had higher impulsivity scores than the control group. There were no gender main effects or interactions (Table 4).

Bodily symptoms scale

As this scale comprises 13 separate items, a conservative alpha level of 0.01 was adopted to reduce the likelihood of type I errors. There were four group × day interactions: palpitations ($F_{1,75}$=7.57, P<0.01), visual sensitivity ($F_{1,75}$=8.80, P<0.005), loss of appetite ($F_{1,75}$=42.61, P<0.001) and muscular tension ($F_{1,75}$=18.43, P<0.001). The pattern of effects on each was the same: MDMA users scored higher than controls on day 0, but groups did not differ on day 4.

There were also group × day interactions on the anxiety ($F_{1,75}$=29.54, P<0.001) and depression items ($F_{1,75}$=28.27, P<0.001, Table 5). Here, the MDMA group had lower anxiety and depression scores than the control group on day 0, but had higher scores than the control group by day 4. There was also a day × gender interaction on the depression scale ($F_{1,75}$=10.30, P<0.005) whereby females had lower depression scores than males on day 0 but higher scores than males on day 4. There was a main effect of group on two items: MDMA users had higher ratings of memory impairment ($F_{1,75}$=7.22, P<0.01) and of poor concentration ($F_{1,75}$=8.72, P<0.005) than controls.

Pulse rate

This was recorded for half the sample as one of the two experimenters omitted to record this. There was a highly significant group × day interaction ($F_{1,38}$=81.78, P<0.001)

Table 4 Mean (±SD) Beck depression inventory (BDI) and visual analogue scores on day 0 and day 4. *MDMA* ±3,4-methylenedioxymethamphetamine, *MRS* mood-rating scale, *ARS* the aggression-rating scale, *ISRS* the impulsivity self-rating scale

	MDMA				Controls			
	Male		Female		Male		Female	
	Day 0	Day 4	Day 0	Day 4	Day 0	Day 4	Day 0	Day 4
BDI (total)	6.19±5.36	7.86±5.93	8.37±6.79	13.37±7.38	7.63±6.08	6.16±4.96	9.29±8.30	7.71±8.63
BDI (cognitive)	5.14±4.78	6.52±6.02	6.84±6.14	10.11±6.86	5.95±5.15	4.58±3.96	7.29±6.85	5.19±4.93
BDI (somatic)	1.04±1.24	1.71±1.19	1.58±2.09	3.05±3.10	1.79±1.78	1.63±1.57	2.00±2.14	2.52±6.28
MRS (alert)[a]	43.77±15.49	28.86±13.96	52.06±13.80	37.60±20.03	49.07±15.94	33.88±20.10	47.33±18.37	29.13±13.31
MRS (content)[a]	18.68±8.91	33.35±14.66	16.15±9.68	41.22±16.96	28.68±16.86	30.61±17.65	31.51±12.27	31.10±11.55
MRS (calm)[a]	24.10±17.90	27.24±13.74	33.21±18.02	34.18±14.04	24.95±21.79	30.84±19.62	33.76±17.76	30.62±14.70
ARS	241.10±130.87	351.86±177.30	250.89±154.27	406.68±238.35	334.89±243.33	276.79±236.04	297.67±155.17	276.95±128.81
ISRS	1018.19±293.89	751.10±271.75	1081.11±191.10	773.26±351.59	846.21±284.20	615.37±336.48	920.57±167.22	605.71±242.83

[a] A higher score indicates lower levels of alertness, contentedness and calmness

whereby the MDMA group showed a higher pulse rate than the control group on day 0 and a similar pulse rate to the control group by day 4. The MDMA group showed an increase in pulse rate of 30 beats per minute (bpm) on day 0 compared with day 4, whereas the control group showed only a slight increase (2 bpm) on day 0 compared with day 4.

Aggression questionnaire

There were no significant differences between groups for trait aggression. On day 4, the MDMA group had a mean score of 76.18 (±17.59), whilst the control group scored 71.08 (±14.94).

Hospital anxiety and depression scale

There were no significant group differences on either the anxiety or depression sub-scales on day 4. The MDMA group had a mean anxiety score of 6.43 (±2.99), whilst the control group had a mean score of 6.49 (±3.90). On the depression scale, the MDMA group had a mean score of 2.83 (±2.67), and the control group had a mean score of 2.54 (±2.23).

Correlations

Within the MDMA group, there was an overall positive correlation between number of MDMA tablets taken on day 0 and change in total ARS scores (r=0.43, $P<0.01$). Separate correlations for male and female users showed that in males there was a strong positive correlation between number of MDMA tablets taken on day 0 and change in total ARS scores (r=0.66, $P<0.005$). Thus the greater number of MDMA tablets taken on day 0, the larger the increase in aggression scores from day 0 to day 4. However, for female MDMA users there was no significant correlation between number of tablets taken and change in ARS scores. Amount of alcohol consumed on day 0 had no association with change in ARS score for male or female MDMA users. Furthermore, there were no significant correlations between lifetime MDMA consumption, amount of MDMA used in a typical session or length of MDMA use and change in ARS scores for either men or women.

Females showed a positive correlation between number of tablets consumed on day 0 and change in BDI scores (r=0.46, $P<0.05$). Thus for females, the more MDMA tablets taken on day 0, the greater the increase in BDI scores by day 4. For male MDMA users, there was no significant correlation between change in BDI scores and number of tablets taken. However, for male users there was a negative correlation between amount of alcohol consumed on day 0 and change in BDI scores (r=–0.49, $P<0.05$), so the higher the dose of alcohol the smaller the change in BDI score. There were no signifi-

Table 5 Mean (±SD) pulse rate (beats per minute) and scores on the *BSS* (bodily symptoms scale). *MDMA* ±3,4-methylenedioxymethamphetamine

	MDMA		Controls	
	Day 0	Day 4	Day 0	Day 4
Pulse rate (*n*=20)	106.30±8.83	76.35±4.12	79.80±12.40	76.65±9.73
BSS item (*n*=40)				
Anxiety	15.35±14.05	31.60±20.92	31.60±20.74	21.95±16.83
Depression	11.45±11.78	34.48±21.12	25.18±19.21	23.58±18.09
Memory impairment	54.93±24.00	28.80±25.64	38.20±28.15	17.70±17.68
Palpitations	42.93±27.24	7.88±9.90	25.50±25.71	11.95±15.27
Visual sensitivity	49.03±27.97	16.00±19.65	30.98±25.68	16.75±21.65
Loss of appetite	72.95±23.09	21.73±24.63	17.60±26.99	18.25±23.93
Muscular tension	50.53±27.92	19.63±22.05	18.38±23.01	20.50±23.42
Loss of concentration	60.50±24.98	30.68±21.49	43.50±28.32	18.63±21.21

cant correlations between lifetime MDMA consumption, amount of MDMA used in a typical session or length of MDMA use and change in BDI scores for either men or women.

Discussion

A main finding of the present study was gender differences in depression scores 4 days after the use of MDMA. Female MDMA users showed evidence of mild to moderate depression in the days following MDMA use compared with either male users or female or male controls. A parallel pattern of effects emerged on discontentment scores on the MRS. Over one-third of female MDMA users in the present study scored in the range for mild to moderate clinical depression on day 4. The change over days in depression scores of female MDMA users was significantly associated with the amount of MDMA reported taken on the previous weekend. Depression scores were not associated with lifetime use or other variables (years of use, frequency of use) reflecting long-term use and possible neurotoxic effects of the drug. Further, there were no group differences in trait depression scores. Taken together, these findings suggest that the 'mid-week low' is related to amount of MDMA taken on the night rather than longer-term patterns of MDMA consumption or potential neurotoxicity. The association between dose of MDMA taken on day 0 and mid-week mood suggests that the mid-week low phenomenon is the product of temporary 5-HT depletion rather than a longer-term neurotoxicity. Males and females in our study had taken similar amounts of MDMA on day 0, although males had taken MDMA in higher quantities over a longer period of time than females. Thus the present study expands on previous research that has suggested gender differences in the effects of MDMA (McCann et al. 1994; Liechti et al. 2001).

The elevated BDI scores of MDMA users were not due to the somatic effects of MDMA (e.g. insomnia) as there were no significant main effects or interactions for somatic items. It is also possible that the MDMA group had pre-existing high depression scores although this seems unlikely as no group differences were found on the HADS. Thus it seems more likely that the susceptibility of the MDMA-using females to mid-week lows reflects temporary depletion of 5-HT caused by weekend use of MDMA rather than pre-existing differences. There is also the possibility that the low mood reported by MDMA users following weekend use is simply a psychological reaction to the 'high' of the weekend. However, this seems unlikely in that males did not show the same pattern.

The second main finding of the present study was that MDMA users rated increased aggression mid-week compared with controls. As expected, on the night of drug use MDMA users' self-ratings showed less aggression than controls, but this pattern was reversed on day 4. Thus in terms of subjective ratings, the 'hug drug' on day 0 produced the opposite effect ('thug drug') on day 4. This finding is consistent with the inverse correlation between measures of 5-HT function and levels of aggression found by Bond and colleagues (Bond et al. 1995; Cleare and Bond 1997). This result has important implications for MDMA users who need to be aware that they may be prone to aggression in the days following MDMA consumption. Whilst corroborating the findings of Gerra et al. (1998), these findings contrast with those of McCann et al. (1994), who found evidence of reduced hostility in MDMA users. This difference may be due to the fact that participants in the McCann study had not used MDMA for an average of 18 weeks (range 2–104 weeks) and therefore would not be subject to depleted 5HT following an acute dose.

Unlike our original hypothesis, there was no difference between male and female MDMA users in aggression ratings. The present study used a self-rating aggression scale, and results may have been different had objective measures of aggression been employed. Interestingly, there was some indication of gender differences in residual responses to MDMA in that there was a positive correlation between amount of MDMA consumed increased mid-week aggression scores in male but not female MDMA users. As expected, MDMA users were more impulsive than controls and this did vary over day of testing. This is consistent with previous findings of elevated impulsivity in MDMA users (Morgan 1998, 1999).

Methodologically, there are clear difficulties inherent in studying recreational drug users compared with controlled laboratory studies (Curran 2000). Importantly, we cannot be sure what the tablets taken by the MDMA users contained. Tablets sold as MDMA often contain other amphetamine analogues, such as 3,4-methylenedioxyethylamphetamine or 3,4-methylenedioxyamphetamine, or a range of other compounds including ketamine or caffeine, and even pure MDMA tablets vary considerably in dosage (Wolff et al. 1995). Nevertheless, analysis of the bodily symptoms scale showed that MDMA users reported physical symptoms known to be associated with the consumption of MDMA including palpitations, visual sensitivity, loss of appetite and muscular tension (Peroutka et al. 1988; Liester et al. 1992). Moreover, the rise in pulse rate in the MDMA group on day 0 was consistent with that reported in laboratory studies (Mas et al. 1999). As with the majority of studies of recreational users, the MDMA users had higher levels of polydrug use than the control group. More MDMA users reported using amphetamine, cocaine and ketamine than the control group. Of the drugs that were used by both groups, the MDMA group had higher lifetime use of alcohol and tobacco than the control group. However, there were no differences between groups in terms of alcohol consumed on day 0. This is important given the known association between alcohol and aggression (Bond and Lader 1986). Further, with regard to the gender effects discussed above, male and female MDMA users were well matched for lifetime use of all drugs.

The gender differences found in the present study should ideally be investigated in a study which controls for hormonal differences linked to the menstrual cycle of female MDMA users (Halbreich and Tworek 1993). In particular, further research is required to address the question of whether gender differences in mid-week mood indicate a pharmacological sensitivity to depletion of 5-HT following MDMA in female users. Although difficult in a club environment, it would have been useful to include objective measures of aggression such as a competitive reaction-time task (Bond et al. 1995). Future studies should also include more comprehensive measures of anger, aggression and hostility. Multidimensional measures of aggression, and in particular of anger attributional styles, may have revealed differential reactions to MDMA in men and women.

In summary, the present study found that female MDMA users were more likely than male users to display low mood a few days after taking MDMA and that mood change was correlated with the amount of MDMA females had taken at the weekend. Mood change was not related to measures of long-term use of MDMA. Additionally, MDMA users were more susceptible than controls to mid-week aggression. These findings suggest that future studies should take into account the gender of MDMA users. That MDMA users are vulnerable to low mood and aggression mid-week has implications for the functioning and well being of the very large numbers of people who take this drug at weekends.

Acknowledgement Suzanne Verheyden was supported by a MRC studentship.

References

Battaglia G, Yeh SY, de Souza EB (1988) MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. Pharmacol Biochem Behav 29:269–274

Beck AT (1978) The Beck depression inventory (BDI). The Psychological Corporation, Harcourt Brace Jovanovitz, USA

Bond AJ, Lader MH (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol 47:211–218

Bond AJ, Lader MH (1986) A method to elicit aggressive feelings and behaviour via provocation. Biol Psychol 22:69–79

Bond AJ, Curran HV, Bruce MS, O'Sullivan G, Shine P (1995) Behavioural aggression in panic disorder after 8 weeks' treatment with alprazolam. J Affect Disord 35:117–123

Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF (1979) Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1:131–139

Buss AH, Perry M (1992) The aggression questionnaire. J Personality Social Psychol 63:452–459

Cami J, Farre M, Mas M, Roset PN, Poudevida S, Mas A, San L, de la TR (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. J Clin Psychopharmacol 20:455–466

Cleare AJ, Bond AJ (1997) Does central serotonergic function correlate inversely with aggression? A study using D-fenfluramine in healthy subjects. Psychiatry Res 69:89–95

Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL (1989) Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. Arch Gen Psychiatry 46:587–599

Cowen PJ (1991) Serotonin receptor subtypes: implications for psychopharmacology. Br J Psychiatry Suppl 12:7–14

Curran HV (2000) Is MDMA ('Ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research. Neuropsychobiology 42:34–41

Curran HV, Travill RA (1997) Mood and cognitive effects of +/-3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. Addiction 92:821–831

Delgado PL, Price LH, Miller HL, Salomon RM, Aghajanian GK, Heninger GR, Charney DS (1994) Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. Archiv Gen Psychiatry 51:865–874

Frackiewicz EJ, Sramek JJ, Cutler NR (2000) Gender differences in depression and antidepressant pharmacokinetics and adverse events. Ann Pharmacother 34:80–88

Green AR, Cross AJ, Goodwin GM (1995) Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or 'Ecstasy'). Psychopharmacology 119:247–260

Goodwin GM, DeSouza RJ, Green AR (1985) Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. Nature 317:531–533

Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, Caccavari R, Delsignore R (1998) Serotonergic function after (+/-)3,4-methylene-dioxymethamphetamine ('Ecstasy') in humans. Int Clin Psychopharmacol 13:1–9

Halbreich U, Tworek H (1993) Altered serotonergic activity in women with dysphoric premenstrual syndromes. Int J Psychiatry Med 23:1–27

Hatzidimitriou G, McCann UD, Ricaurte GA (1999) Altered serotonin innervation patterns in the borebrain of monkeys treated with (±)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. J Neurosci 19:5096–5107

Liechti ME, Gamma A, Vollenweider FX (2001) Gender differences in the subjective effects of MDMA. Psychopharmacology 154:161–168

Liester MB, Grob CS, Bravo GL, Walsh RN (1992) Phenomenology and sequelae of 3,4-methylenedioxymethamphetamine use. J Nerv Ment Dis 180:345–352

Linnoila M, Virkkunen M (1992) Biologic correlates of suicidal risk and aggressive behavioral traits. J Clin Psychopharmacol 12:19S–20S

Linnoila M, Virkkunen M, George T, Higley D (1993) Impulse control disorders. Int Clin Psychopharmacol 8[Suppl 1]:53–56

Mas M, Farre M, de la Torre R, Roset PN, Ortuno J, Segura J, Cami J (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. J Pharmacol Exp Ther 290:136–145

McCann UD, Ridenour A, Shaham Y, Ricaurte GA (1994) Serotonin neurotoxicity after (+/-)3,4-methylenedioxymethamphetamine (MDMA; "ecstasy"): a controlled study in humans. Neuropsychopharmacology 10:129–138

McKenna DJ, Peroutka SJ (1990) Neurochemistry and neurotoxicity of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). J Neurochem 54:14–22

Morgan MJ (1998) Recreational use of ecstasy (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19:252–264

Morgan MJ (1999) Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology 141:30–36

Murphy JM, Laird NM, Monson RR, Sobol AM, Leighton AH (2000) Incidence of depression in the Stirling County Study: historical and comparative perspectives. Psychol Med 30:505–514

Newman JL, Gray EA, Fuqua DR (1999) Sex differences in the relationship of anger and depression: an empirical study. J Counsel Dev 77:198–203

Nichols DE (1986) Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. J Psychoactive Drugs 18:305–313

Nunn JS, Thomas SL (1999) The angry male and the passive female: the role of gender and self-esteem in anger expression. Soc Behav Pers 27:145–154

O'Shea E, Granados R, Esteban B, Colado MI, Green AR (1998) The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA ('ecstasy'). Neuropharmacology 37:919–926

Parrott AC, Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology 139:261–268

Peroutka SJ, Newman H, Harris H (1988) Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. Neuropsychopharmacology 1:273–277

Ricaurte GA, Yuan J, McCann UD (2000) (+/-)3,4-Methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: studies in animals. Neuropsychobiology 42:5–10

Schmidt CJ, Wu L, Lovenberg W (1986) Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analogue. Eur J Pharmacol 124:175–178

Smith KA, Fairburn CG, Cowen PJ (1997) Relapse of depression after rapid depletion of tryptophan. Lancet 349:915–919

Solowij N, Hall W, Lee N (1992) Recreational MDMA use in Sydney: a profile of 'Ecstacy' users and their experiences with the drug. Br J Addict 87:1161–1172

Vollenweider FX, Gamma A, Liechti M, Huber T (1998) Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. Neuropsychopharmacology 19:241–251

Wolff K, Hay AWM, Sherlock K, Conner M (1995) Contents of "ecstasy". Lancet 346:1100–1101

Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 67:361–370