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Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms

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Previous work has indicated recreational use of methylenedioxymethamphetamine (MDMA or ecstasy) is associated with elevated scores on self-report measures of depression. We sought to examine the long-term effects of consumption on depression in a group of individuals who had consumed large quantities of the drug in the past, but were now leading relatively drug free lives. Respondents to this study (n = 29) had consumed an average of 1.5 ecstasy tablets in the last month, 8.4 in the last 6 months and 23.3 in the last 12 months. The estimated total consumed was 527 tablets, indicating that these respondents were indeed former chronic users of the drug. None of the respondents had consumed ecstasy in the last 14 days. Levels of depression (Beck's Depression Inventory) were significantly ($p < 0.01$) elevated compared to a matched non-drug using control group. Within the group of former chronic users, these levels of depression were not significantly affected by current use of alcohol, cannabis or amphetamine, but were positively correlated with an external locus of control ($p < 0.05$), infrequent but severe- ($p < 0.05$) and frequent but mild- ($p < 0.005$) self-report measures of life stress. Multiple regression indicated that levels of frequent but mild life stress ($p < 0.005$) and the quantity of ecstasy tablets respondents consumed over a 12-h period ($p < 0.05$) were the only variables that were significant predictors of self-reported levels of depression. The results of this study indicate that former chronic ecstasy users report higher levels of depression than their matched controls.

Key words: BDI; depression; ecstasy; former chronic; human; life stress; locus of control; MDMA; serotonin

Introduction

Recent studies have indicated that recreational use of the neurotoxic drug 'ecstasy' (3,4-methydioxy-methamphetamine, MDMA) is associated with increased scores on self-report measures of depression (Curran and Travill, 1997; Gerra *et al.*, 2000). With one exception (Parrott *et al.*, 2000), results from studies which assess the depressive feelings of ecstasy users in the days or weeks after consumption indicate levels of depression are elevated from matched controls (Curran and Travill, 1997; Gerra *et al.*, 1998; Parrott, 1998; Parrott and Lasky, 1998; Montgomery *et al.*, 1999; Gamma *et al.*, 2000; Gerra *et al.*, 2000). One recent study examined depression in former ecstasy users (i.e. individuals who had not consumed the drug for 12 months) and these former users reported elevated levels of depression compared to controls (Gerra *et al.*, 2000). However, this study had a small number ($n < 16$) of respondents who had consumed a relatively small amount of the drug (maximum 95 exposures; Gerra *et al.*, 2000). We therefore thought it important to examine the long-term effects of consumption on indicators of depressed mood in a somewhat larger group of former chronic users who had consumed large (at least 100 tablets) quantities of the drug in their past but were now leading relatively drug free lives.

MDMA demonstrates a broad range of affinities at a number of brain recognition sites (Battaglia *et al.*, 1988). But it is on serotonin (5-hydroxytryptamine, 5-HT) transmission that MDMA exerts its most significant effects. Ingestion of the drug, through a number of mechanisms, produces a long-term (> 36 h) decrease in central nervous system levels of 5-HT (McKenna and Peroutka, 1990). MDMA has been shown to be associated with a reduction in rodent 5-HT neurone terminal density (Ricaurte *et al.*, 1988; McKenna and Peroutka, 1990). Recent research has shown non-human primates to be more sensitive to terminal degeneration than rodents (Fischer *et al.*, 1995). In humans, recent Positron Emission Tomography (PET) and single photon emission computed tomography (SPECT) studies have confirmed that recreational abuse of the drug is associated with a reduction in binding sites associated with 5-HT terminals (McCann *et al.*, 1998; Semple *et al.*, 1999).

A number of persistent neuropsychological deficits have been associated with the recreational abuse of MDMA, particularly in terms of reduced attention and short-term memory (Parrott *et al.*, 1998; McCann *et al.*, 1999; Morgan, 1999). Ecstasy consumption

Table 1 Descriptive statistics for former chronic ecstasy users

	Total		Females		Males		
	Mean ± SD*	Range	Mean ± SD	Range	Mean ± SD	Range	Significance
Weeks since last use of 'ecstasy'	26 ± 41	2–159	15 ± 21.6	2–159	31 ± 47	2–157	NS
Number consumed in the last month	1.5 ± 2.0	0–6	1.9 ± 2.3	0–6	1.3 ± 1.9	0–6	NS
Number consumed in the last 6 months	8.4 ± 12.9	0–50	9.1 ± 15.9	0–50	8.1 ± 11.7	0–50	NS
Number consumed in the last 12 months	23.3 ± 33	0–125	19.7 ± 11	0–125	24.9 ± 31	0–100	NS
Total number consumed (total 'E')	527 ± 259	100–1000	481 ± 251	200–900	547 ± 267	100–1000	NS
Maximum consumed in 12 h (12-h 'E')	5.4 ± 2.6	1–10	5.6 ± 2.2	2–9	5.4 ± 2.8	1–10	NS
Alcohol (units)	13.9 + 11.7	0–50	14.5 ± 8.57	0–25	13.6 ± 13.1	50–100	NS
Locus of control	13.1 ± 3.5	8–20	16 ± 2.8	13–20	11.8 ± 3.0	8–17	$p < 0.05$
Daily Hassles scale	30.3 ± 21.5	5–83	38.4 ± 26.6	6–80	26.6 ± 18.3	5–83	NS
Life stress units	262 ± 199	0–885	370 ± 256	167–885	214 ± 151	0–522	$p < 0.05$

*Mean ± SD; p represents two-tailed significance (males versus females).

has also been associated with increased obsessive–compulsive disorder symptomatology (Cole *et al.*, 1999), impulsivity (Morgan, 1998), anxiety and depression (Curran and Travill, 1997; Montgomery *et al.*, 1999; Gerra *et al.*, 2000). Case studies report a similar pattern and, although the severity and presence of psychotic symptoms varies between individuals, almost all report the presence of depression (Peroutka *et al.*, 1988; Benazzi and Mazzoli, 1991; McCann and Ricaurte, 1991; Winstock, 1991; McGuire *et al.*, 1994; Schifano and Magni, 1994; Schifano *et al.*, 1998).

Although it is plausible to suggest that a history of chronic use could explain any current levels of depression found in former chronic ecstasy users, we felt it important to examine this in the context of other psychological aspects that have been associated with the disorder. Previous studies have noted that high levels of psychological stress are associated with ecstasy consumption (McGuire *et al.*, 1994; Schifano and Magni, 1994). Life changes or life stress can be seen in terms of events that are infrequent but severe (Holmes and Rahe, 1967) or frequent but mild (Kanner *et al.*, 1981) and both are strongly associated with the onset of illness, particularly depression (Rahe *et al.*, 1964; Rahe *et al.*, 1971; Paykel, 1979; Kanner *et al.*, 1981; Weinberger *et al.*, 1987). Furthermore, psychological studies report that depressives exhibit a negative attributional style, i.e. they are prone to expect an upsetting event to occur and feel that they can exert no control over these events, and such belief structures have been shown to be prominent in modulating the disorder (Hammen *et al.*, 1981, 1985).

Hence, the present work attempted to assess the severity of depressive symptoms in individuals with a history of previous chronic ecstasy consumption in relation to their previous pattern of use, current indices of life stress and attributional style.

Methods

Participants

Twenty-nine former chronic ecstasy users who had a lifetime consumption of 100 or more ecstasy tablets were recruited by the 'snowball peer network technique' (Solowij *et al.*, 1992) and responded initially to a postal questionnaire. Respondents reporting ecstasy use in the 14 days prior to the study were excluded. Any participant who had previously sought psychiatric help and/or was consuming a drug deemed to have potential for invalidating the result was excluded, including any with an established role in altering monoamine function (Royal Pharmaceutical Society, 1999). Twenty-nine controls, matched by age, ethnicity, educational standard (university degree, A level, GCSE or equivalent) and gender to the former chronic users were recruited through a central UK city public library (n = 8) and the undergraduate population of a UK university (n = 21) by advertisement. Since additional matching of controls on drug usage (current or historical) was not a realistic proposition, control group respondents were screened to exclude any who had, or were currently, consuming an illegal drug or prescribed medication, by self-report; and the influence of substance use on depressive symptoms was explored within the former ecstasy user group.

Measures

Depressive symptoms were assessed in both former chronic user and control groups using the 'Beck Depression Inventory' (BDI) (Beck *et al.*, 1961). Psychological aspects and substance use were explored within the former chronic user group. Table 1 shows the information gathered on history of ecstasy use. Current alcohol use was recorded in standard units. Current use (more than once a week) of other illicit substances (HMSO, 1971) was recorded by substance as either present or absent.

The former chronic drug users completed a Locus of Control scale (Rotter, 1966) which gauges the extent to which respondents attribute control to themselves or to external factors. The severity and frequency of life stress in terms of infrequent but severe or frequent but mild were assessed by the Social Readjustment Rating scale (SRRS), which yields a Life Stress Unit (LSU) tally, and the 'Daily Hassles scale', respectively (Holmes and Rahe, 1967; Kanner *et al.*, 1981).

Statistical analysis

Statistical analysis was conducted on the Statistical Package for the Social Sciences (SPSS) (SPSS Inc, Chicago, IL, USA). The characteristics of the former chronic user and control groups were compared using a Mann–Whitney test. Further analysis of the former chronic user group included a correlational analysis (Pearson's r), and a multiple regression with BDI score as the dependent variable using SPSS default parameters in which all variables were entered simultaneously. Alpha was set at $p = 0.05$.

Results

Descriptive statistics

Of the original 60 questionnaires distributed, 38 were returned. Four questionnaires were incomplete. One respondent was

Table 2 Characteristics of former chronic ecstasy users

	Former chronic abusers			Controls		
	Total	Female	Male	Total	Female	Male
Number	29	9	20	29	9	20
Age (years)	26.6 ± 4.3	27.3 ± 4.8	26.2 ± 4.1	26.7 ± 4.1	27.3 ± 4.8	26.5 ± 3.9
Weight (kg)	60.6 ± 9.0	52.2 ± 4.7	64.4 ± 7.8	62.0 ± 6.5	55.2 ± 4.9	65.1 ± 4.3

*Mean ± SD.

currently engaged in psychiatric counselling; two were currently prescribed fluoxetine and two respondents had not consumed more than 100 ecstasy tablets. The characteristics of the 29 participants admitted to the study are shown in Table 1 and comparison to matched controls is shown in Table 2.

Twenty percent of the former ecstasy users were educated to University degree level, 27% to 'A' level standard and 48% to GCSE. Only one participant (3%) had no educational qualifications. In comparison, 21% of the control group were educated to University degree level, 45% to 'A' level standard and 34% to GCSE. All participants were White.

As shown in Table 1, the former chronic users had not consumed ecstasy for an average of 26 weeks. The female former chronic users had taken the drug more recently then the males (15 versus 31 weeks, respectively) but this difference was non-significant (see Table 1). The data on consumption over the 1, 6 and 12 months was consistent with the ecstasy users' consumption decreasing. Taken in conjunction with the average number of tablets consumed to date (for the whole group 527, for females 481 and males 547), the data suggests the participants were indeed former chronic ecstasy users. Two participants had consumed in excess of 1000 tablets and nine (31%) in excess of 700, whereas only three respondents had consumed 200 tablets or less. These relatively large totals are also reflected in the 'total number of ecstasy tablets consumed in 12 h' reported by respondents. As a group, respondents had consumed 5.4 tablets in 12 h. There were no significant differences between male and female former chronic users on the indices of ecstasy use. Current alcohol consumption was low within the former chronic user group (Table 1). Nineteen (66%) currently used cannabis, four (13%) were consuming amphetamine and one of these amphetamine users also currently used heroin and ketamine.

Depressive symptoms in former chronic ecstasy users and controls

Former chronic users exhibited significantly higher scores on the BDI than their matched non-drug using controls and this difference was still present when males and females were contrasted separately (Table 3). Within the former chronic users, there was no relationship between BDI scores and alcohol intake ($r = 0.132$, $p > 0.5$). Current cannabis use (19 respondents) also failed to influence the BDI scores (median: cannabis 8; no cannabis 8.5; $p > 0.6$). BDI scores in the former ecstasy users who were ($p < 0.001$) and/or were not ($p < 0.01$) using cannabis were both significantly different from controls (Kruskal–Wallis ANOVA with post-hoc Dunn's test). The four respondents currently using amphetamine had BDI scores of 7, 14, 14 and 24 (the last being the above-mentioned multi-drug user) with a median score of 14; although higher than the non-amphetamine using remainder (median 8), the difference was not statistically significant.

Indices of life-stress in former ecstasy users

Female former chronic users reported significantly elevated life stress units and locus of control scores compared to males but scores on the Daily Hassles scale were not significantly different (Table 1). As shown in Table 4, the BDI scores positively correlated with 'maximum tablets consumed in 12 h' but not with the total number of tablets consumed, although maximum

Table 3 Beck Depression Inventory scores (mean, SDs and levels of significance) for former chronic ecstasy abusers compared with non-drug using controls

	Former chronic users			Non-drug users			
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR	Significance
Total population ($n = 29$)	9.2 ± 5.9	8.0	5.5	5.2 ± 3.9	3.0	2.5	$p < 0.01$
Female ($n = 9$)	11 ± 8.2	8.0	8.5	4.8 ± 3.6	3.0	2.0	$p < 0.05$
Male ($n = 20$)	8.4 ± 4.7	8.0	4.5	5.3 ± 4.2	3.0	3.75	$p < 0.01$

*Mean ± SD. IQR, Interquartile range.

Table 4 Correlation coefficients between depression and psychological variables in the former chronic users

	Daily Hassles scale	Life stress units	Locus of control	12-h 'E'	Total 'E'
BDI	0.8382**	0.5622*	0.5476*	0.4530*	0.2373
Daily Hassles scale		0.6347*	0.5219*	0.4287*	0.3681*
Life stress units			0.4772**	0.1533	–0.0065
Locus of control				0.1334	0.1500
12-h 'E'					0.6962**

Two-tailed significance: *$p < 0.05$; **$p \leq 0.005$. BDI, Beck Depression Inventory.

Table 5 Standardized regression coefficients (Beta), zero order correlations (*r*), partial correlation coefficients (*pr*) and semipart correlation coefficients (*sr*) for multiple regression

Independent variable	Beta	*r*	*pr*	*sr*	*t*	Significance
Life stress units	–0.0449	0.5622	–0.0664	–0.0318	–0.319	NS
Total 'E'	–0.2818	0.2372	–0.3708	–0.1911	–1.91	NS
Locus of control	0.1831	0.5475	.3010	0.1511	1.51	NS
12-h 'E'	.3144	0.4530	0.4112	0.2159	2.16	$p < 0.05$
Daily Hassles scale	0.7401	.8381	0.7034	0.4737	4.74	$p < 0.005$

consumption in 12 h was significantly related to total consumption. Locus of control scores, Daily Hassles scores and LSU significantly correlated with depression, as assessed by the BDI. Scores on the Daily Hassles, LSU and Locus of Control scales were significantly intercorrelated, although only Daily Hassles and LSU showed a significant relation to the ecstasy consumption variables.

Further exploration of the relationships between these variables using multiple regression revealed that only two significantly predicted BDI scores after removing the effect of the other variables from each measure (Table 5). The model was a good fit to the data [$F(5,28) = 15.47$, $p < 0.0001$], as confirmed by analysis of residuals which showed that the model could be accepted as adequate [normality, Durbin-Watson (1.623), Leverage (0.1724), Cooks D (mean 0.0745) and Mahalanobis distance were within acceptable limits]. The multiple correlation coefficient, *r*, was 0.88 and r^2 0.77; thus, the independent variables accounted for 77% (adjusted for shrinkage 72%) of the variance in BDI. The standardized regression (Beta) coefficients show that Daily Hassles had the highest predictive power followed by 'number of ecstasy tablets consumed in 12 h'. The unique component of predictive power of these two measures was strong, as denoted by their semipartial coefficients. The remaining variables (Locus of Control, LSU and total tablets consumed) did not make significant contributions to prediction of the BDI score.

Discussion

As with all studies of this type, the present study relies on self-report of the amount and nature of illicit drug use. The former chronic user sample showed a wide variation in the total amount of drug consumed, although mean consumption was high in comparison with previous studies. Based on a random sample from an American undergraduate campus, Peroutka *et al.* (1988) reported maximum consumption quantities of 38 tablets. Other American studies, using a self-selecting drug using population, indicate an average of 94.5 exposures over a 5-year period (McCann *et al.*, 1994). Our average participant reports having consumed 541 tablets over an approximately similar time period. Even the results of the British studies are small in comparison (Winstock, 1991; Montgomery *et al.*, 1999; Parrott *et al.*, 2000). Winstock (1991) reports only five individuals, 7% of the sample, had consumed in excess of 100 tablets. Such individuals reported a variety of psychological symptoms, which they attributed to consumption of the drug. The participants in a recent SPECT study report consuming similar 'lifetime totals' of the drug to the present study and these individuals had reduced levels of cortical 5-HT binding (Semple *et al.*, 1999). Unfortunately, respondents were not assessed for the quantity consumed over 12 h.

These high figures are also reflected in the quantity of 'ecstasy' consumed in 12 h by our respondents. The average MDMA content of a typical ecstasy tablet appears to be approximately 100 mg (Peroutka *et al.*, 1988; McCann and Ricaurte, 1991; Henry, 1992). Respondents in the present study report having consumed in excess of 1000 mg or approximately 10 tablets in 12 h. Winstock (1991) records similar figures of 10–20 tablets being consumed in one 'binge'.

The former chronic ecstasy users reported significantly higher levels of depression than their matched controls, as shown by their scores on the BDI. This corroborates previous self-report studies using the depression scale of the Minnesota Multiphasic Personality Inventory which found that users of the drug, who had experienced a maximum of 69.3 (average dose 106 mg) exposures, but had not consumed ecstasy in the last 12 months experienced significantly higher levels of depression than matched controls (Gerra *et al.*, 2000). However, the present study indicates that chronic consumption of the drug is associated with only low levels of depressive symptoms (mean BDI of 9.2) since Beck *et al.* (1961) suggest a score of 9 represents mild depression.

Sixty-six percent of the former chronic user participants were currently consuming cannabis and a smaller number (14%) were currently consuming amphetamine on a regular basis. The majority were also consuming alcohol. Polydrug use within such experimental populations is difficult to control for. The majority of studies that have looked at this area of illicit drug use have also examined respondents that not only use ecstasy, but also cannabis and other illicit drugs (Curran and Travill, 1997; Parrott *et al.*, 1998; Parrott *et al.*, 2000). Morgan (1998) compared polydrug users who had not used ecstasy, polydrug users who had used ecstasy and non-drug users, on a 6-point Likert scale asking respondents to rate how 'depressed/blue' they felt, and found no significant differences. Use of these substances does not appear to account for the higher depression scores in the former chronic user group seen in the present work: cannabis use had no detectable effect on BDI scores within the former chronic users and these scores were significantly higher in the former chronic users than in the controls, irrespective of whether the former were using cannabis. In addition, alcohol or amphetamine use had no significant effect on BDI scores within the former chronic user group.

Within the former chronic user group, this retrospective study found that levels of depression, as measured by BDI, positively and significantly correlated with the measurements of life stress and attributional style (LSU, Daily Hassles and Locus of Control). Such cognitive clustering is consistent with the vulnerability model of depression of Hammen *et al.* (1981, 1985). This could reflect personality styles/traits that were present prior to the onset of ecstasy use, or a colouring of perceptions and recollections by the current mood state. After taking these variables into account in

multiple regression analysis, binge consumption (total number of ecstasy tablets consumed in 12 h) was still a significant independent predictor of BDI scores, allowing the suggestion that there may be some biological basis to the levels of depression reported by respondents. As mentioned above, human SPECT studies have indicated that individuals who have consumed similar total quantities of the drug do experience reduced 5-HT function (Semple *et al.*, 1999). However, it cannot be excluded that personality factors leading to high dosing levels could also be involved in promoting depressive symptomatology.

In summary, the data from this study indicates that a history of chronic ecstasy use is associated with a small but significant elevation of depression scores on the BDI compared to those of a matched control group. Within the study group, depression scores were significantly predicted by a combination of peak usage (maximum ecstasy usage in 12 h) and current levels of perceived life stress (Daily Hassles). The results suggest that these former chronic ecstasy users fulfil the vulnerability model of depression of Hammen *et al.* (1985) and thus may be at risk with regard to the development of a more severe depressive syndrome.

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