J Psychopharmacol OnlineFirst, published on October 2, 2008 as doi:10.1177/0269881108097631

Psychopharm

Journal of Psychopharmacology
00(00) (2008) 1–8

ISSN 0269-8811
SAGE Publications Ltd,
Los Angeles, London,
New Delhi and Singapore
10.1177/0269881108097631

Ecstasy (MDMA) and high prevalence psychiatric symptomatology: somatic anxiety symptoms are associated with polydrug, not ecstasy, use

G Bedi *School of Psychology, Psychiatry and Psychological Medicine, Monash University, Melbourne, Australia.*
NT Van Dam *Department of Psychology, University at Albany, SUNY, New York, USA.*
J Redman *School of Psychology, Psychiatry and Psychological Medicine, Monash University, Melbourne, Australia.*

Abstract

Although previous studies have examined anxiety and depression in ecstasy (±3,4-methylenedioxymethamphetamine; MDMA) users, it remains unclear whether symptoms are associated specifically with ecstasy or with polydrug use in general. We compared mean symptomatology and clinically significant symptoms in 45 ecstasy polydrug, 48 cannabis polydrug and 40 legal drug users, who completed standardised self-report anxiety and depression symptom measures. We further examined whether group differences were secondary to increased somatic symptom reporting, which may reflect acute/subacute drug effects. Anxiety and depression scores were higher in polydrug than legal drug users, with no difference between ecstasy and cannabis groups. There was no difference in numbers meeting criteria for clinically significant depression or 'moderate' or 'severe' anxiety, but the polydrug group contained more individuals reporting at least 'mild' anxiety symptoms than the legal drug control. Multivariate analyses indicated that anxiety alone was sufficient to discriminate groups. Polydrug users reported more somatic anxiety symptoms than legal drug users, but endorsed equivalent numbers of non-somatic symptoms. High prevalence psychiatric symptomatology in ecstasy polydrug users may be associated with polydrug rather than ecstasy use. Higher ratings in polydrug users appear to be secondary to increased somatic symptom reporting, suggesting possible impacts of drug effects on symptom endorsement.

Key words

anxiety; depression; ecstasy; MDMA; polydrug

Introduction

±3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') damages serotonergic neurons in rodents and non-human primates (Ricaurte, *et al*., 2000). Although the applicability of these findings to humans has been debated (e.g. Cole, *et al*., 2002a), preclinical outcomes have led researchers to investigate possible functional sequelae of putative neurotoxic changes in human ecstasy users. Cognitive function, sleep architecture and mood symptomatology, functional domains thought to be affected by serotonergic neurotransmission (Lucki, 1998), have all been investigated in relation to ecstasy use (for review see Parrott, 2001).

High prevalence psychiatric symptoms such as anxiety and depression have been assessed in a number of previous ecstasy-focused studies (e.g., MacInnes, *et al*., 2001; Morgan, *et al*., 2002; Parrott, *et al*., 2002; McCardle, *et al*., 2004, Lamers, *et al*., 2006). Findings in this area are mixed, appearing to be even more variable than evidence regarding other functional domains such as cognition (see Hoshi, *et al*., 2007; Bedi and Redman, 2008). Some studies have reported an association between ecstasy use and anxiety (e.g., Parrott, *et al*., 2002; Lamers, *et al*., 2006) and/or depression (e.g., MacInnes, *et al*., 2001; Parrott, *et al*., 2002; McCardle, *et al*., 2004; Lamers, *et al*., 2006), whereas others have found that increased symptomatology is more related to use of other drugs commonly consumed by ecstasy users (e.g., Medina and Shear, 2007; Durdle, *et al*., 2008). Other studies have reported that ecstasy users do not differ from controls on measures of anxiety or depression (e.g., Halpern, *et al*., 2004; Hoshi, *et al*., 2004), and one study found ecstasy users to have lower depression scores than non-users (de Almeida and Silva, 2005).

Such inconsistencies are likely to be partly due to methodological issues, a number of which have been raised in relation

Corresponding author: Gillinder Bedi, D Psych, Human Behavioral Pharmacology Laboratory, Department of Psychiatry, University of Chicago, MC3077, 5841 S. Maryland Ave, Chicago, IL 60637, USA. Email: gbedi@bsd.uchicago.edu

to ecstasy-focused research (see Curran, 2000; Cole, *et al*., 2002a). Limitations include inadequate control for other drug use, small sample sizes and lack of control for effects of demographic and lifestyle differences (see Cole, *et al*., 2002a; Halpern, *et al*., 2004; Sumnall and Cole, 2005). One particular difficulty involves separating chronic effects, such as those arising from neurotoxicity, from subacute drug effects that are characteristic of the 'come down' period occurring in the days after acute intoxication (see Curran, 2000). The problem of subacute effects may be particularly relevant in the assessment of psychiatric symptomatology, given that psychiatric symptoms are commonly rated using self-report checklists, whereas other domains such as cognitive function are more frequently assessed with objective performance measures. Self-report checklists require individuals to rate their symptoms retrospectively over the period before assessment, meaning that regular drug users must describe symptomatology over periods when acute and subacute drug effects are likely (Cole, *et al*., 2002b; see also Bedi and Redman, in press).

Subacute drug effects commonly include prominent somatic symptoms, such as alterations to appetite and sleep, dizziness, heart palpitations and physical fatigue (e.g., see Liechti, *et al*., 2001). Many of these symptoms overlap with somatic symptoms of psychiatric disorders such as anxiety and depression (American Psychiatric Association, 1994). It is possible, therefore, that previous findings indicating elevated anxiety and depression symptomatology in ecstasy users represent transient subacute effects of drug use in general, rather than evidence of MDMA-induced neurotoxicity (see Sumnall and Cole, 2005). Although such symptoms could be expected to have impacts on daily functioning in regular drug users regardless of their aetiology, implications for treatment and long-term outcomes would differ based on whether they represent transient or chronic effects of drug use.

The existing literature contains suggestive evidence that psychiatric symptom ratings in ecstasy users may be partly due to somatic subacute drug effects. Many of the studies reporting associations between ecstasy and anxiety and/or depression have used self-report questionnaires including substantial somatic components (e.g., MacInnes, *et al*., 2001; McCardle, *et al*., 2004, Lamers, *et al*., 2006). Conversely, studies using the Hospital Anxiety and Depression Scale (HADS), a self-report measure that is not confounded by somatic effects (Sumnall and Cole, 2005), do not report ecstasy users to have elevated anxiety or depression scores (e.g., Verheyden, *et al*., 2002; Hoshi, *et al*., 2004; Cole, *et al*., 2006). Interestingly, a recent report found that although polydrug users (both ecstasy and non-ecstasy) endorsed more symptoms of depression than non-drug controls (on a measure including somatic symptoms), they did not display the negative attentional bias characteristic of 'true' depression (Roiser and Sahakian, 2004).

There is also, however, some previous evidence arguing against differences in symptomatology between ecstasy and non-ecstasy users being due primarily to somatic subacute symptoms of drug use. Three previous studies assessing symptoms of depression have divided scores into somatic and cognitive subscales (Verheyden, *et al*., 2002; McCardle, *et al*., 2004; Roiser and Sahakian, 2004). McCardle, *et al*. (2004) and Roiser and Sahakian (2004) reported that differences in overall depressive ratings were due to both somatic and cognitive symptoms, with subscale scores mirroring overall total scores. Verheyden, *et al*. (2002) reported that cognitive but not somatic subscores differed between ecstasy users and controls. To our knowledge, no previous study has examined contributions of somatic symptoms to levels of anxiety symptom endorsement in ecstasy users.

Given the mixed findings of previous studies, further research examining the relationship between anxiety and depression and ecstasy use, and contributions of somatic symptomatology to symptom ratings, appears warranted. The present article presents analyses that were undertaken to investigate these questions. The first question was whether high prevalence psychiatric symptoms are associated with ecstasy use specifically or with polydrug use more generally. We assessed group differences in mean symptom ratings, as well as number of individuals meeting criteria for clinically significant symptomatology, which is an important public health consideration (Cole and Sumnall, 2002). Given overlaps between anxiety and depressive symptomatology, we also examined whether anxiety or depression symptom ratings better differentiated drug-using groups. The final question extended previous research by investigating whether any group differences identified were secondary to increased somatic symptom reporting. We hypothesised that ecstasy use would be associated with more anxiety and depressive symptoms, but that these differences would reflect increased somatic symptom endorsement.

Methods and materials

Participants

Participants were 45 ecstasy polydrug users (EP; lifetime use of ecstasy and cannabis ≥10 times), 48 cannabis polydrug users (CP; use of cannabis ≥10 times) and 40 legal drug users (LD; use of alcohol, caffeine and/or tobacco, use of cannabis ≤5 times, any other illicit drug except ecstasy ≤1 time), all over 18 years old. No CP or LD participant reported any previous ecstasy use.

Participants responded to advertisements placed in local universities, shops, 'street' press and on ecstasy-specific websites (e.g., http://www.pillreports.com), and were encouraged to contact others who might be interested (the 'snowballing' technique; Parrott, *et al*., 1998).

More detailed exclusion criteria have been presented elsewhere (Bedi and Redman, in press). In summary, exclusion was based on medical and psychiatric illness (with the exception of depression and anxiety), drug dependence except ecstasy, cannabis, or nicotine, regular use of drugs other than ecstasy and cannabis (defined as benzodiazepine use at least weekly for six or more months; intravenous opiate use; current use of greater than three standard units of alcohol per day

more than five times per week, of cocaine more than once per month, or of opiates or amphetamines more than once per week), positive alcohol breathalyser reading (measured with Lion Alcometer S-D2; Lion laboratories Ltd, Barry, UK), and positive urinalysis except cannabis metabolites (immunoassay tests for opiates, amphetamines including MDMA, cannabis metabolites, benzodiazepines and cocaine were conducted by Dorovich Pathology, Melbourne, Australia). We did not exclude based on cannabis metabolites because they may remain in the body for several days after last use, and we only requested participants to abstain from cannabis for 24 h before testing (for further discussion, see below; see also Simon and Mattick, 2002).

Participants with a psychiatric disorder other than depression or anxiety were excluded from analyses because symptomatology of other psychiatric conditions can overlap with depression and anxiety. For example, participants with schizophrenia could endorse symptoms of depression that are actually attributable to the negative symptoms of psychosis (see Addington, *et al*., 1996). Participants with a history of diagnosis and/or treatment for depression and anxiety were included to allow generalisation to a broader population of illicit and legal drug users, given the high prevalence of these conditions (American Psychiatric Association, 1994). Moreover, because these analyses investigated clinically significant symptoms of depression and anxiety, it was important to include individuals most likely to experience symptoms at or above diagnostic threshold (i.e., those with previous diagnoses/treatment histories).

Procedure

Participants attended two sessions for which they were reimbursed AU$40. During the first session, they provided written informed consent. They then provided demographic and drug-use information and completed self-report measures of memory. Session two consisted of neuropsychological testing and the anxiety and depression self-report measures presented here. Neuropsychological findings have been reported elsewhere (Bedi and Redman, 2008; in press).

Participants were requested to abstain from alcohol for 24 h and from ecstasy and other recreational drugs except for cannabis for 10 days. They were requested to abstain from cannabis for 24 h (Fox, *et al*., 2001; see limitations for further discussion of these abstinence requirements). Participants supplied a breathalyser reading at each session. Urine samples were collected and a randomly selected subset ($N = 40$) of session two samples were screened for drugs of abuse as described above. Participants were asked to avoid major change to their sleeping patterns or nutritional intake before attendance.

Measures

Demographic/drug-use information A demographic and drug-use history was taken using a structured interview format. Substance dependence was assessed using questions based on DSM-IV criteria (American Psychiatric Association, 1994). EP participants provided information about ecstasy-use patterns using a contextually based timeline (Bedi and Redman, 2006). All participants provided information about use of other drugs such as alcohol, cannabis, stimulants and hallucinogens.

Anxiety symptoms Anxiety symptoms were measured with the Beck Anxiety Inventory (BAI; Beck and Steer, 1993), which has previously been used with 'dance' drug users (Sumnall, *et al*., 2004). Clinical significance of symptomatology was assessed with suggested cut-off scores of 16+ for at least 'moderate' anxiety and 8+ for at least 'mild' anxiety (Beck and Steer, 1993).

Depressive symptoms Depression symptoms were rated using the Center for Epidemiologic Studies Depression Scale – Revised (CESD-R; Eaton, *et al*., 2004), which has previously been used with 'dance' drug users (Sumnall, *et al*., 2004). The CESD has been shown to be a more discriminative measure of depression severity than other scales measuring depressive symptomatology (e.g., Beck Depression Inventory), particularly in non-clinical samples (Santor, *et al*., 1995). Clinically significant symptoms were assessed with the suggested cut-off score of 16+ for a depressive 'case' (Eaton, *et al*., 2004).

Statistical analyses

Differences in demographics and drug use were investigated with *t*-tests, chi-square tests of independence and analyses of variance (ANOVAs) followed by post-hoc comparisons with Bonferroni corrections where necessary.

Discriminant Function Analysis (DFA) assessed whether anxiety or depressive symptoms and/or a combination of the two differentiated between groups. Where a significant function was yielded, stepwise DFA determined the minimum number of variables necessary to discriminate. The discriminative value of individual variables was assessed by ANOVA followed by post-hoc comparison as necessary. In the case that either anxiety or depression scores differentiated groups, follow-up analyses were conducted with scores separated into somatic and non-somatic subscores.

Group differences in numbers meeting criteria for clinically significant symptomatology on the BAI and CESD-R were evaluated using chi-square tests of independence. Analyses were performed using Statistical Package for the Social Sciences version 15.0 (SPSS 15.0; SPSS Inc., Chicago, Illinois, USA).

Results

Drug screening

No positive breath alcohol reading was detected. One EP urine sample tested positive for opiates and this data set was excluded. A second sample recorded a low creatinine level.

Because this indicated the possibility that the participant had diluted the sample with water to hide recent drug use (Wilkins, 1997), this dataset was also excluded. Three EP samples tested positive to cannabis metabolites, as did two CP samples (these datasets were not excluded, see discussion and Simon and Mattick, 2002).

Demographics and drug use

Demographic and drug use information is presented in Table 1. Groups did not differ in age, gender or number of current university students. They differed in rates of previous affective disorder diagnosis, with no significant difference between EP and CP users, but the combined polydrug group reporting higher rates of previous diagnosis than LD users (see Table 1).

Groups were matched in lifetime dose of alcohol. There were no differences between EP and CP groups in lifetime dose of cigarettes, cannabis or LSD, but EP users had higher use of amphetamines. Number of participants reporting regular use (four or more times per week) of cannabis in the month before participation did not differ between EP and CP groups. The combined EP and CP groups had higher lifetime use of cigarettes than LD users. Although the LD and CP groups reported no ecstasy use, the EP group reported total lifetime ecstasy use ranging from 13.5 to 2407 pills ($M = 170.6$, SD = 362.8).

Anxiety and depression scores

Anxiety and depression scores are presented in Table 2. For the combined anxiety and depression analysis, the first function significantly discriminated groups (Wilks' $\lambda = 0.91$, χ^2 (4) = 12.37, $P = 0.015$), accounting for 79% of between-group variability. Univariate analyses indicated that anxiety and depression scores differed between groups. In both cases, there were no differences between EP and CP groups, but the combined EP and CP group endorsed more symptoms than the LD group. When stepwise DFA was undertaken, BAI emerged as sufficient to differentiate groups (Wilks' $\lambda = 0.93$, χ^2 (2) = 9.61, $P = 0.008$), suggesting that the discriminative utility of CESD-R scores might be due to overlapping variance with BAI scores (correlation between BAI and CESD-R: $r = 0.64$, $P < 0.001$). Because of the potential impact of nicotine on anxious and depressive symptomatology (Strine, *et al.*, 2008) and because polydrug users differed from LD users on this measure (see Table 1), we examined relationships between tobacco use and BAI, and tobacco use and CESD-R. Cigarette use was not significantly correlated with BAI total score ($r = 0.11$, $P = 0.22$). A small positive correlation was found between ciga-

Table 1 Participant demographics and patterns of drug use

	Ecstasy polydrug, *N* = 45	Cannabis polydrug, *N* = 48	Legal drug, *N* = 40	Overall differences	EP vs CP	EP + CP vs LD
	Mean (SD)	Mean (SD)	Mean (SD)			
Age	22.8(3.0)	21.7 (3.5)	23.1 (3.7)	$F(2,130) = 2.13$	—	—
Sex, female (%)	21 (47)	22 (46)	19 (48)	$\chi^2(2) = 0.02$	—	—
Current university student, *N* (%)	30 (67)	37 (77)	32 (80)	$\chi^2(2) = 2.26$	—	—
Previous affective disorder diagnosis or treatment[a], *N* (%)	13 (29)	7 (15)	2 (5)	$\chi^2(2) = 8.96$*	$\chi^2(1) = 2.82$	$\chi^2(1) = 5.52$*
Lifetime dose	Mean (SD)	Mean (SD)	Mean (SD)	*F* (df)	*t* (df)	*t* (df)
Cigarettes	12266.2 (20510.7)	8845.4 (20005.9)	1204.0 (3637.1)	5.52* (2,130)	1.03 (91)	4.60* (102.02)
Alcohol (standard units[b])	4033.8 (5746.8)	3175.0 (3249.4)	1990.8 (3865.1)	2.87 (2,130)	—	—
Cannabis (g)	355.6 (616.9)	360.4 (634.2)	0.1 (0.3)	—	0.01 (91)	—
LSD (tabs[c])	76.9 (328.4)	22.1 (146.7)	0 (0)	—	1.50 (91)	—
Amphetamines (g)	23.5 (68.4)	0.3 (1.1)	0 (0)	—	2.68* (44.02)	—
Regular heavy cannabis use in preceding month[d], *N* (%)	4 (9)	5 (10)	0 (0)	—	$\chi^2(1) = 0.06$	—

F, *F*-test resulting from ANOVA; χ^2, chi-square test of independence; *t*, independent samples *t*-test; *N*, sample size; SD, standard deviation; df, degrees of freedom.

[a]Previous diagnosis of unipolar depression, and/or any anxiety disorder or any previous treatment for depression or anxiety.

[b]A standard unit of alcohol was defined by Australian Government standards as any drink containing 10 g of alcohol.

[c]A street dose of lysergic acid diethylamide (LSD), a blotter containing variable amounts of active drug.

[d]Defined as use 4 or more times per week.

*$P < 0.05$, statistics were conducted with Bonferroni corrections where necessary.

Table 2 Anxiety and depression scores

	Ecstasy polydrug, *N* = 45	Cannabis polydrug, *N* = 48	Legal drug, *N* = 40	Overall differences	EP vs CP	EP + CP vs LD
	Mean (SD)	Mean (SD)	Mean (SD)	*F* (df)	*t* (df)	*t* (df)
Anxiety – BAI	8.6 (7.9)	8.1 (6.0)	4.7 (4.0)	4.99* (2,130)	0.32 (91)	3.89* (121.49)
BAI – somatic anxiety	4.7 (4.6)	4.8 (3.7)	2.3 (2.3)	6.06* (2,130)	0.05 (91)	4.32* (122)
BAI – non-somatic (Cognitive) anxiety	3.9 (4.1)	3.4 (2.8)	2.4 (2.5)	2.41 (2,130)	—	—
Depression – CESD-R	12.2 (9.7)	14.0 (9.0)	9.4 (6.3)	3.38* (2,130)	0.94 (91)	2.39* (131)
	N (%)	*N* (%)	*N* (%)	χ^2 (df = 2)	χ^2 (df = 1)	χ^2 (df = 1)
BAI – moderate or severe anxiety	7 (16)	5 (10)	1 (3)	4.13	—	—
BAI – mild, moderate, or severe anxiety	19 (42)	21 (44)	8 (20)	6.44*	0.88	6.42*
CESD-R – depressive 'case'[a]	15 (33)	13 (27)	5 (13)	5.13	—	—

BAI, Beck Anxiety Inventory; *F*, *F*-test resulting from ANOVA; χ^2, chi-square test of independence; *t*, independent samples *t*-test; *N*, sample size; SD, standard deviation; df, degrees of freedom; CESD-R, Center for Epidemiologic Studies Depression Scale – Revised.

[a]A depressive case is defined as a score ≥16 on the CESD-R.

*$P < 0.05$, statistics were conducted with Bonferroni corrections where necessary.

rette use and total score on the CESD-R ($r = 0.17$, $P = 0.045$). Because there was no relationship with BAI score, which was the only variable necessary to differentiate groups, we did not include cigarette use in the DFA model.

Clinically significant symptomatology

Number of individuals meeting the CESD-R cut-off score of 16+ were not found to vary across groups. Using the BAI score for at least 'moderate' anxiety (16+), groups did not differ in numbers meeting criteria. However, when criteria were expanded to include individuals with 'mild' anxiety symptoms (8+), the combined polydrug group was found to contain more individuals meeting criteria than the LD group, with no difference between EP and CP groups (details are reported in Table 2).

Somatic symptoms of anxiety

To assess possible influences of somatic symptoms on the discriminative utility of BAI scores, the BAI was divided into two subscores, reflecting somatic (e.g., 'Numbness and tingling') and non-somatic/cognitive (e.g., 'Fear of the worst happening') symptoms, based on previous factor analysis in a community sample (Creamer, *et al*., 1995). Although non-somatic subscores were similar between groups, a one-way ANOVA showed significant differences between groups in somatic subscores. EP and CP groups had similar somatic anxiety scores, but the combined polydrug group had significantly higher mean somatic symptom ratings than LD users (details are reported in Table 2).

Discussion

The hypothesis that ecstasy use would be associated with anxiety and depression was not supported, but illicit drug use in general was related to higher levels of symptomatology. There were no significant differences between ecstasy and cannabis polydrug groups on any symptom indicators, whereas the combined polydrug group had higher rates of previous diagnosis with an affective disorder, higher mean anxiety and depression scores, and more individuals meeting criteria for at least 'mild' anxiety than people not reporting illegal drug use.

This is contrary to some findings that ecstasy use is associated with increased anxiety and mood symptoms (e.g., MacInnes, *et al*., 2001; Morgan, *et al*., 2002; Parrott, *et al*., 2002; McCardle, *et al*., 2004). It is, however, consistent with a number of other reports indicating that high prevalence psychiatric symptomatology is more closely related to other drug use than to use of ecstasy (Daumann, *et al*., 2004; Medina and Shear, 2007; Durdle, *et al*., 2008). The findings emphasise the need to control for other drug use in investigations of the effects of drugs that are commonly used as part of a broader polydrug use repertoire (Medina and Shear, 2007; Van Dam, *et al*., 2008).

Interestingly, although both anxiety and depressive symptoms differed between groups, anxiety was sufficient alone to discriminate in multivariate analyses, suggesting that differences in depression scores may have been secondary to shared variance with anxiety symptoms. It is further noteworthy that the discriminative capacity of anxiety scores appeared due primarily to increased numbers of people meeting criteria for 'mild' anxiety, rather than higher rates of 'moderate' or 'severe' symptomatology. Therefore, although average

symptom endorsement was higher in the polydrug groups, these findings do not appear to reflect clinically significant symptoms in the majority of individual polydrug users.

Congruent with our hypothesis that group differences would be secondary to increased somatic symptom endorsement (Sumnall and Cole, 2005), illegal drug users reported more somatic but not more cognitive anxiety symptoms than did non-illegal drug users. Given the possibility that somatic symptoms represent transient effects of drug use in addition to, or instead of, genuine psychiatric symptoms (Sumnall and Cole, 2005), this finding calls into question the use, with drug-using populations, of psychiatric symptom measures including substantial somatic components. It is important to note that somatic symptoms, even if they do not represent chronic sequelae of ecstasy use, may still affect day to day functioning. However, public health and treatment implications differ based on whether symptomatology arises because of chronic or transient drug effects.

A number of limitations of this study warrant comment. The cross-sectional design restricts possible causal interpretations. Additionally, we relied on self-report measures of psychopathology; however, our results were generally congruent with those of a recent study using clinician-rated scales (Durdle, *et al*., 2008). Future research could valuably examine whether somatic symptoms as measured with clinician ratings also contribute to differences between polydrug and legal drug users.

There were inevitable compromises made in our approach to controlling for acute and subacute effects of substance use on the day of testing. Withdrawal effects because of disruption of drug use may have increased symptom endorsement rates. However, we required participants to abstain for set periods because acute drug effects might mask symptoms of depression and anxiety (Weiss, *et al*., 1992). Moreover, participants were excluded on the basis of regular use of drugs other than ecstasy, cannabis and nicotine, reducing the possibility of withdrawal syndromes for drugs other than these. In terms of ecstasy, it is possible that withdrawal effects may last longer than 10 days, and some studies of neurocognitive function have required longer abstinence periods (e.g., McCann, *et al*., 1999). However, this abstinence period was selected because previous evidence suggests that withdrawal mood effects of ecstasy resolve 7 days after use (Curran, *et al*., 2004).

In terms of withdrawal effects from cannabis, less than 10% of participants in the two polydrug groups reported heavy use of cannabis (four or more times per week) in the month before participation, suggesting that relatively few participants would have experienced withdrawal symptoms after the 24 h cannabis abstention period required. Conversely, the abstention period selected for alcohol and cannabis (24 h) may have been insufficient to prevent subacute drug effects. With regards to alcohol, subacute or 'hangover' effects would be expected to increase symptom endorsement. However, the 24-h period was selected so that participants would not consume alcohol the night before assessment, limiting possible 'hangover' effects that typically occur the morning after consumption (e.g., see Finnigan, *et al*., 1998). Furthermore, no participant tested positive for breath alcohol at the time of psychological screening, which might be expected in at least some participants if they had consumed high levels of alcohol the night before participation.

The 24-h cannabis abstention period was selected to limit acute drug effects. Subacute effects of cannabis can only reliably be avoided after abstention of approximately 28 days (see Pope and Yurgelun-Todd, 1996; Pope, *et al*., 2001). A primary concern was that recruitment of polydrug users prepared to abstain from cannabis for 28 days might alter the sample composition. Furthermore, withdrawal effects are likely to affect outcomes, if abstention periods longer than 1 day but less than 28 days are required of regular cannabis users (see Kouri and Pope, 2000). We selected 24 h as a compromise between these factors, meaning that subacute cannabis effects on the day of testing are possible.

In addition, participants who tested positive for cannabis metabolites were included because metabolites can remain in the body for several days after use. This approach has previously been taken in ecstasy-related research (e.g., Simon and Mattick, 2002). Because we did not assay all participants' urine samples, the possible impact of cannabis metabolites on outcomes could not be analysed. In the subset of participants screened, a relatively small number ($N = 5$) tested positive to cannabis metabolites, providing some indication that a minority of participants in the whole sample would have provided positive drug screens. Any subacute effects of cannabis would likely affect the two polydrug groups equally given similar drug-use histories and similar numbers testing positive for cannabis metabolites in the EP and CP groups. However, it is possible that subacute cannabis effects at the time of testing contributed to differences between polydrug users and legal drug controls.

A related limitation was that biochemical confirmation of drug-free status for substances other than alcohol was only conducted for a subset of participants because of resource limitations. Participants were not informed that only a subset of samples would be tested, which may have encouraged compliance. In addition, drug screening of the subset (approximately 30% of sample) led to the exclusion of only two data sets (5% of samples tested), suggesting that the majority of participants complied with drug-related requirements. However, it is possible that the subset selected for testing was unrepresentative of the overall sample.

An additional limitation is that participants were informed before testing that the study involved measures of mood symptoms. If they deduced that the study was focused on possible negative effects of substance use, this could have created a bias. However, it is difficult to control for the high face validity of self-report mood symptom questionnaires (see Pincus, *et al*., 2004). We included subjects with a history of depression or anxiety diagnoses, whereas previous diagnosis with other psychiatric conditions was cause for exclusion. Although these criteria may have affected endorsement of depression and anxiety symptoms, they were selected to minimise effects of symptom overlap between the psychiatric conditions studied

and other syndromes, while maximising the extent to which clinically significant symptoms of depression and anxiety would be recorded. A final limitation was that although participants were requested to avoid major change to their sleeping patterns before testing, we did not fully control for possible effects of differences in sleep amount or quality between groups.

These limitations notwithstanding, these data suggest that symptoms of depression and anxiety in ecstasy polydrug users may be associated with factors other than putative MDMA-related serotonergic neurotoxicity. Although ecstasy polydrug users endorsed more high prevalence psychiatric symptoms than legal drug controls, there was no difference in symptom endorsement rates between ecstasy polydrug users and polydrug users who did not use ecstasy. This lends credence to an association between symptomatology and polydrug use generally, rather than ecstasy use in particular. Although both depression and anxiety differed between polydrug and legal drug users, anxiety symptoms were sufficient to discriminate alone. These differences were secondary to increased numbers of people meeting criteria for mild rather than more severe anxiety symptom levels among the polydrug users. Moreover, somatic but not non-somatic anxiety symptoms differed between groups. These findings warrant consideration when examining previous evidence indicating links between ecstasy use and high prevalence psychiatric symptoms, particularly where somatically oriented symptom measures were used. Further investigation is needed to better understand the contributions of transient somatic symptoms to ratings of psychiatric symptomatology in polydrug-using populations.

Conflicts of Interest

None declared.

Acknowledgements

Thanks to Lydia Windisch for practical assistance, Emeritus Professor Kim Ng for methodological consultation and Drs Jon Cole, Mitch Earleywine and Brady Reynolds for comments on this article. We also thank the participants. G.B. was supported by an Australian Postgraduate Award, and the project was funded by Monash University, School of Psychology, Psychiatry, and Psychological Medicine.

References

Addington, D, Addington, J, Atkinson, M (1996) A psychometric comparison of the Calgary Depression Scale for Schizophrenia and the Hamilton Depression Rating Scale. Schizophr Res *19*: 205–212.

American Psychiatric Association (1994) DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. MD, USA: American Psychiatric Association.

Beck, AT, Steer, RA (1993) Beck Anxiety Inventory Manual. San Antonio, USA: The Psychological Corporation.

Bedi, G, Redman, J (2006) Self-reported ecstasy use: the impact of assessment method on dosage estimates in recreational users. J Psychopharmacol *20*: 432–436.

Bedi, G, Redman, J (2008) Ecstasy use and higher-level cognitive functions: weak effects of ecstasy after control for potential confounds. Psychol Med *38*: 1319–1330.

Bedi, G, Redman, J (in press) Metamemory in recreational ecstasy polydrug users: what do self-reports of memory failures mean? J Psychopharmacol.

Cole, JC, Michailidou, K, Jerome, L, Sumnall, HR (2006) The effects of stereotype threat on cognitive function in ecstasy users. J Psychopharmacol *20*: 518–525.

Cole, JC, Sumnall, HR (2002) The BDI of the beholder. J Psychopharmacol *16*: 103.

Cole, JC, Sumnall, HR, Grob, CS (2002a) Sorted: ecstasy facts and fiction. Psychologist *15*: 464–467.

Cole, JC, Sumnall, HR, Wagstaff, GF (2002b) Methodological problems with ecstasy and the SCL-90. Psychopharmacology *162*: 215–217.

Creamer, M, Foran, J, Bell, R (1995) The Beck Anxiety Inventory in a non-clinical sample. Behav Res Ther *33*: 477–485.

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, Rees, H, Hoare, T, Hoshi, R, Bond, A (2004) Empathy and aggression: two faces of ecstasy? A study of interpretative cognitive bias and mood change in ecstasy users. Psychopharmacology *173*: 425–433.

Daumann, J, Hensen, G, Thimm, B, Rezk, M, Till, B, Gouzoulis-Mayfrank, E (2004) Self-reported psychopathological symptoms in recreational ecstasy (MDMA) users are mainly associated with regular cannabis use: further evidence from a combined cross-sectional/longitudinal investigation. Psychopharmacology *173*: 398–404.

de Almeida, SP, Silva, MTA (2005) Characteristics of ecstasy users in Sao Paulo, Brazil. Subst Use Misuse *40*: 395–404.

Durdle, H, Lundahl, LH, Johanson, CE, Tancer, M (2008) Major depression: the relative contribution of gender, MDMA, and cannabis use. Depress Anxiety *25*: 241–247.

Eaton, WW, Smith, C, Ybarra, M, Muntaner, C, Tien, A (2004) Center for Epidemiologic Studies Depression Scale: review and revision (CESD and CESD-R). In: Maruish, ME, (ed), The Use of Psychological Testing for Treatment Planning and Outcomes Assessment, vol. 3: Instruments for Adults (pp. 363–377). NJ, USA: Lawrence Erlbaum Associates.

Finnigan, F, Hammersley, R, Cooper, T (1998) An examination of next-day hangover effects after a 100mg/100ml dose of alcohol in heavy social drinkers. Addiction *93*: 1829–1838.

Fox, HC, Toplis, AS, Turner, JJD, Parrott, AC (2001) Auditory verbal learning in drug-free Ecstasy polydrug users. Human Psychopharmacol *16*: 613–618.

Halpern, JH, Pope, HG, Sherwood, AR, Barry, S, Hudson, JI, Yurgelun-Todd, D (2004) Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. Drug Alcohol Depend *75*: 135–147.

Hoshi, R, Bisla, J, Curran, HV (2004) The acute and sub-acute effects of 'ecstasy' (MDMA) on processing of facial expressions: preliminary findings. Drug Alcohol Depend *76*: 297–304.

Hoshi, R, Mullins, K, Boundy, C, Brignell, C, Piccini, P, Curran, HV (2007) Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naïve controls. Psychopharmacology *194*: 371–379.

Kouri, EM, Pope Jr, HG (2000) Abstinence symptoms during withdrawal from chronic marijuana use. Exp Clin Psychopharmacol *8*: 483–492.

Lamers, CTJ, Bechara, A, Rizzo, M, Ramaekers, JG (2006) Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. J Psychopharmacol *20*: 302–311.

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

Lucki, I (1998) The spectrum of behaviors influenced by serotonin. Biol Psychiatry *44*: 151–162.

MacInnes, N, Handley, SL, Harding, GFA (2001) Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms. J Psychopharmacol *15*: 181–186.

McCann, UD, Mertl, M, Eligulashvili, V, Ricaurte, GA (1999) Cognitive performance in +/-3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. Psychopharmacology *143*: 417–425.

McCardle, K, Luebbers, S, Carter, JD, Croft, RJ, Stough, C (2004) Chronic MDMA (ecstasy) use, cognition and mood. Psychopharmacology *173*: 434–439.

Medina, KL, Shear, PK (2007) Anxiety, depression and behavioral symptoms of executive dysfunction in ecstasy users: contributions of polydrug use. Drug Alcohol Depend *87*: 303–311.

Morgan, MJ, McFie, L, Fleetwood, LH, Robinson, JA (2002) Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence. Psychopharmacology *159*: 294–303.

Parrott, AC (2001) Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. Hum Psychopharmacol *16*: 557–577.

Parrott, AC, Buchanan, T, Scholey, AB, Heffernan, T, Ling, J, Rodgers, J (2002) Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. Hum Psychopharmacol *17*: 309–312.

Parrott, AC, Lees, A, Garnham, NJ, Jones, M, Wesnes, K (1998) Cognitive performance in recreational users of MDMA or 'ecstasy': evidence for memory deficits. J Psychopharmacol *12*: 79–83.

Pincus, T, Williams, AC, Vogel, S, Field, A (2004) The development and testing of the depression, anxiety, and positive outlook scale (DAPOS). Pain *109*: 181–188.

Pope Jr, HG, Gruber, AJ, Hudson, JI, Huestis, MA, Yurgelun-Todd, D (2001) Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry *58*: 909–915.

Pope Jr, HG, Yurgelun-Todd, D (1996) The residual cognitive effects of heavy marijuana use in college students. JAMA *275*: 521–527.

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

Roiser, JP, Sahakian, BJ (2004) Relationship between ecstasy use and depression: a study controlling for poly-drug use. Psychopharmacology *173*: 411–417.

Santor, DA, Zuroff, DC, Ramsay, JO, Cervantes, P, Palacios, J (1995) Examining scale discriminability in the BDI and CES-D as a function of depression severity. Psychol Assess *7*: 131–139.

Simon, NG, Mattick, RP (2002) The impact of regular ecstasy use on memory function. Addiction *97*: 1523–1529.

Strine, TW, Mokdad, AH, Dube, SR, Balluz, LS, Gonzalez, O, Berry, JT, *et al.* (2008) The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. Gen Hosp Psychiatry *30*: 127–137.

Sumnall, HR, Cole, JC (2005) Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis. J Psychopharmacol *19*: 84–92.

Sumnall, HR, Wagstaff, GF, Cole, JC (2004) Self-reported psychopathology in polydrug users. J Psychopharmacol *18*: 75–82.

Van Dam, NT, Earleywine, M, DiGiacomo, G (2008) Polydrug use, cannabis, and psychosis-like symptoms. Hum Psychopharmacol. *23*: 475–485.

Verheyden, SL, Hadfield, J, Calin, T, Curran, HV (2002) Sub-acute effects of MDMA ±3,4-methylenedioxymethamphetamine, "ecstasy" on mood: evidence of gender differences. Psychopharmacology *161*: 23–31.

Weiss, RD, Griffin, ML, Mirin, SM (1992) Drug abuse as self-medication for depression: an empirical study. Am J Drug Alcohol Abuse *18*: 121–129.

Wilkins, JN (1997) Quantitative urine levels of cocaine and other substances of abuse. NIDA Res Monogr *175*: 235–252.