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Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis

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Abstract

National drugs information strategies convey the message that use of Ecstasy is associated with an increase in both the incidence and severity of major depressive disorder. However, very little primary research supports this. Unlike apparent deficits in higher cognitive functions, most published studies have found no difference in self-reported depressive symptomatology between Ecstasy users and controls. To investigate this further, we conducted a meta-analysis of studies investigating depressive symptomatology in recreational users of Ecstasy. According to selection criteria, we identified 25 relevant studies. A statistically significant effect size (ES) of 0.31 (95% confidence interval 0.17–0.37, $p < 0.001$) was calculated. Significance remained after examining the small number of studies that controlled for cannabis use ($n = 9$, $p < 0.001$) but, in general, drug histories were poorly reported. There was an association between ES and lifetime Ecstasy exposure ($p < 0.001$), but not for other use parameters or abstention ($p > 0.05$). These data indicate that there is an association between Ecstasy use and depressive symptomatology, but this is small and unlikely to be clinically relevant. In addition, the self-report scales used may be heavily confounded by the somatic effects of substance misuse. Public health strategies derived from psychopharmacological investigations should acknowledge the potential negative effects of substance misuse but qualify the difficulties in interpreting research studies.

Keywords

depression, Ecstasy, meta-analysis, review, substance misuse

Introduction

Despite fluctuations in general population prevalence, Ecstasy remains popular in young people, with tablets costing as little as £2 in some urban areas of the UK (Condon and Smith, 2003; Johnston *et al*., 2003; Sumnall *et al*., 2004a). Eliciting powerful prosocial and entactogenic effects, the drug epitomises the contemporary recreational pharmacopoeia (Cole and Sumnall, 2003). However, it is apparent that Ecstasy is just one drug amongst many in the 'pick and mix' repertoire (Sumnall *et al*., 2004b) although, until recently, most studies examining this population have failed to adopt an appropriate analytical design.

Scientific discussion of Ecstasy has mainly concerned the neurotoxic effects of 3,4-methylenedioxymethamphetamine (MDMA), although the two compounds are not necessarily synonymous (Cole *et al*., 2002a). In experimental animals, repeated high-dose regimens of MDMA produce characteristic changes in markers in serotonergic function, and neuronal responses to acetylcholine, glutamate and dopamine; for a recent review, see Green *et al*. (2003). There is great speculation as to whether these changes also occur in humans (Green, 2004), but the data are inconsistent (Kish, 2002), and extrapolation is complicated by dose scaling, species differences in metabolism and thermogenic response to MDMA (Green *et al*., 2003). Furthermore, recent work in non-human primates suggests that self-administered MDMA, a more accurate model of human use behaviour than non-contingent administration, is not neurotoxic to serotonergic and dopaminergic systems (Fantegrossi *et al*., 2004). These data have lead to the study of functional consequences of MDMA and Ecstasy, with a particular focus upon higher cognitive function, social behaviours and affective states (e.g. (McGregor *et al*., 2003; Verbaten, 2003).

Reviewers have tended to the conclusion that use of Ecstasy

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results in depressed mood (Morgan, 2000; Parrott, 2001). Evidence cited has been in the form of community surveys (Cohen, 1995), clinical assessments (Schifano, 2000), structured interviews (Topp *et al*., 1999), web based questionnaires (Parrott *et al*., 2002), and within-subjects (Curran and Travill, 1997) and cross-sectional studies (Verkes *et al*., 2001). Government drugs information initiatives such as FRANK in the UK (www.talktofrank.com) and NIDA Club Drugs in the USA (www.clubdrugs.org) affirm this message. However, closer inspection of primary research studies (Table 1) shows that there is an inconsistent literature, with the majority of studies showing no significant association with Ecstasy, and depressive symptomatology is often dependent upon confounding covariables such as recent substance use, education and age-related psychiatric disorder (Cole and Sumnall, 2003). Further evaluation of these studies is therefore warranted to support effective drug information campaigns.

Meta-analysis is a set of statistical procedures designed to accumulate experimental results across independent studies and is a widely accepted method of research synthesis (Lipsey and Wilson, 2001). We therefore conducted a meta-analysis to provide a quantitative review of self-reported depressive symptomatology in substance misusers who reported Ecstasy use. Furthermore, as is standard practice in collecting primary data for meta-analysis, a methodological log was compiled. These observations formed the basis of brief recommendations that we hope will contribute to improvements in research methodology in this area.

Methods

Literature review and data selection

An initial search (conducted for the period 1914 to 1 March 2004) was conducted in the Web of Knowledge, PSYCINFO, and MAPS MDMA databases, using the search Key words: 'Ecstasy' or 'MDMA', combined in turn with each of 'human', 'self report', 'depressive' and 'depression'. Web of Science is a research platform operated by Thomson ISI, and is a multidisciplinary citation database. PSYCINFO is maintained by the American Psychological Association and covers the field of psychology and psychological aspects of related disciplines, such as medicine, psychiatry, sociology and education. The MAPS MDMA bibliography (www.maps.org) is a searchable database of MDMA/Ecstasy

Table 1 Self reported depressive symptomatology studies included in meta-analysis

Study	Test	μ_1	n_1	SD_1	μ_2	n_2	SD_2	ES ± SE	95% confidence interval (upper – lower)	Reported as statistically significant?[a]	Clinically relevant symptomatology?[b]
Curran *et al.* (2004) (+7 days)	BDI	6.2	29	4.4	6.1	32	4.4	0.03 ± 0.26	−0.48–0.53	No	No
Daumann *et al.* (2001)	SCL-90R	7.9	28	8.1	5.5	28	5.2	0.34 ± 0.27	−0.18–0.87	No	–
Daumann *et al.* (2004)	SCL-90R	8.2	60	7.1	7.9	38	8.6	0.03 ± 0.21	−0.37–0.44	No	–
Daumann *et al.* (2004)	SCL-90R	8.2	38	8.6	5.9	30	4.3	0.32 ± 0.25	−0.16–0.80	No	–
De Win *et al.* (2004) (ex users)	BDI	6.4	16	6.0	2.1	13	2.5	0.88 ± 0.39	0.11–1.64	No	No
De Win *et al.* (2004) (heavy)	BDI	6.2	23	7.0	2.1	13	2.5	0.69 ± 0.36	−0.01–1.39	No	No
De Win *et al.* (2004) (moderate)	BDI	2.6	15	3.3	2.1	13	2.5	0.16 ± 0.38	−0.58–0.91	No	No
Dughiero *et al.* (2001)	SCL-90	0.8	43	0.7	0.6	77	0.6	0.25 ± 0.19	−0.13–0.62	No	–
MacInnes *et al.* (2001)	BDI	9.2	29	5.9	5.2	29	3.9	0.79 ± 0.27	0.25–1.32	Yes	No
Morgan *et al.* (2002) (current)	SCL-90R	1.1	17	1.1	0.4	15	0.4	0.71 ± 0.37	−0.01–1.42	Yes	–
Morgan *et al.* (2002) (ex users)	SCL-90R	0.9	15	0.9	0.4	15	0.4	0.64 ± 0.37	−0.09–1.38	No	–
Parrott *et al.* (2000) (light users)	SCL-90	16.0	16	11.4	10.5	22	9.1	0.53 ± 0.35	−0.12–1.19	No	–
Parrott *et al.* (2000) (heavy users)	SCL-90	16.4	12	10.6	10.5	22	9.1	0.60 ± 0.37	−0.12–1.32	No	–
Parrott *et al.* (2001) (heavy)	SCL-90	0.9	119	0.7	0.9	102	0.7	0.03 ± 0.13	−0.24–0.29	No	–
Parrott *et al.* (2001) (light)	SCL-90	0.9	115	0.7	0.9	102	0.7	−0.07 ± 0.14	−0.34–0.20	No	–
Roiser and Sahakian (2004) (current)	BDI	7.9	30	6.5	6	30	5.4	0.31 ± 0.26	−0.20–0.82	No	No
Roiser and Sahakian (2004) (ex users)	BDI	12.6	20	9.5	6	30	5.4	0.89 ± 0.30	0.30–1.48	No	No
Smith *et al.* (unpublished data)	BDI	4.5	209	4.3	3	20	2.7	0.36 ± 0.23	−0.10–0.82	No	No
Sumnall *et al.* (2004b) (reanalysis)	CESD	14.1	64	8.1	12.1	36	10.2	0.23 ± 0.21	−0.18–0.63	No	No
Verkes *et al.* (2001) (heavy)	BDI	7.0	21	6.3	3	20	3.7	0.75 ± 0.32	0.12–1.39	No	No
Verkes *et al.* (2001) (moderate)	BDI	3.9	21	3.3	3	20	3.7	0.25 ± 0.31	−0.36–0.87	No	No
von Geusau *et al.* (2004)	SCL-90	21.4	26	4.8	20.8	33	4.5	0.13 ± 0.26	−0.39–0.64	No	–
Curran and Travill (1997)*	BDI	11.8	12	7.2	6.2	12	4.1	0.92 ± 0.43	0.08–1.76	No	No
Gamma *et al.* (2001)*	HAM-D	11.7	16	9.2	5	17	6.1	0.84 ± 0.36	0.13–1.56	Yes	Mild
Verheyden *et al.* (2002)*	BDI	10.5	40	6.7	7.0	40	7.1	0.50 ± 0.23	0.06–0.94	Yes	No

BDI, Beck Depression Inventory); CESD, Centre for Epidemiological Studies Depression scale; SCL-90, Symptom Check List; R, Revised. μ, mean, SD, standard deviation; ES, bias corrected standardized effect size. [a]By original study authors or through reanalysis; [b]by reference to patient populations. Raw SCL-90R scores are meant to be standardized and compared to tables of norms to identify. No study using these measures reported these scores, hence decision about clinical status could not be made. *Additional data included in analysis of ecstasy abstention

documents dating back to 1914. The reference lists of the initially retrieved set of articles also served as sources for further relevant articles, which subsequently served as additional sources. This process was continued for as long as pertinent references could be found. Research active authors were also contacted for details of, in press work, although only one study was forthcoming (Smith *et al*., 2004). Data included in conference abstracts were excluded because these do not generally undergo peer review, details are incomplete, and often concern pilot studies and undergraduate student projects without adequate methodological rigour. Unpublished work was not included. Although this would have resulted in a more complete analysis, it would not have been possible to secure data from all unpublished studies. These steps were adhered to for methodological consistency but introduced a source of study selection bias common to all meta-analyses; 'negative' findings often remain in abstract/unpublished form as authors and journal editors are more likely to publish 'positive' reports.

Studies were considered for inclusion if they assessed self-reported depressive symptomatology, using validated measures, in community samples of Ecstasy users. Twenty-five suitable studies were identified, concerning 40 assessments. Of these, two assessments were excluded for failing to incorporate control groups, four because they concerned clinical populations, three because detailed data were not reported (and corresponding authors failed to respond to data requests). Two studies were excluded from the initial meta-analysis because they examined sub-acute effects of recent (< 1 week) consumption (Curran and Travill, 1997; Verheyden *et al*., 2002). One study was excluded for utilizing an observer rated rather than self-reported assessment (Gamma *et al*., 2001). However, these three studies were only included in analysis of Ecstasy abstention to provide a wide-ranging data source. Within studies, where more than one assessment of depression was made, measures common to other studies in the meta-analysis, or the most commonly used inventories (via literature cross reference, e.g. Beck Depression Inventory chosen over Hospital Anxiety and Depression Scale) were selected. In the event of failure of this strategy, a mean effect size was computed for all the assessments used.

Meta-analysis

Meta-analysis followed methods described by Lipsey and Wilson (2001), using SPSS macros written by Professor D. W. Wilson (Department of Criminology and Criminal Justice, University of Maryland). For each study, mean scale score, its SD, and group

Table 2 Ecstasy use characteristics, and matching (versus controls) on other drug characteristics

	Ecstasy use parameters				Matched on ...?			
Study	Estimated lifetime use (tablets)	Abstention (weeks)	Duration (weeks)	Estimated usual dose (tablets)	Cannabis ('joints' in last year)	Cocaine	Amphetamine	Alcohol (units/week)
Daumann *et al.* (2001)	93.4	5.9	108	1.4	Yes (–)	–	–	–
Daumann *et al.* (2004)	292.4	31.2	114	2	No (–)	–	–	–
Daumann *et al.* (2004)	271.3	29.4	149.8	1	No (–)	–	–	–
De Win *et al.* (2004) (ex)	268.1	116.2	4.55	2.1	Yes (538.8)	–	Yes	Yes (6.2)
De Win *et al.* (2004) (heavy)	530.1	9.1	288.0	2.2	Yes (326.6)	Yes	No	Yes (9.6)
De Win *et al.* (2004) (moderate)	28.6	14.6	212.2	1.4	Yes (214.3)	No	No	Yes (13.1)
Dughiero *et al.* (2001)	233	–	–	1.5	–	–	–	–
Gamma *et al.* (2001)	270	1	–	–	–	–	–	–
MacInnes *et al.* (2001)	527	26	–	–	–	–		
Morgan *et al.* (2002) (current)	303	4.1	228.8	2.2	Yes (519.0)	Yes	Yes	Yes (21.1)
Morgan *et al.* (2002) (former)	498.1	112.2	212.5	1.67	Yes (785)	Yes	Yes	Yes (8.9)
Parrott *et al.* (2000) (light users)	6.8	–	–	–	No (–)	No	No	
Parrott *et al.* (2000) (heavy users)	371	–	–	–	No (–)	No	No	
Parrott *et al.* (2001) (heavy)	–	–	–	–	No (–)	No	No	No (–)
Parrott *et al.* (2001) (light)	10	No (–)	No	No	No (–)			
Roiser and Sahakian (2004) (current)	273.4	10.7	–	3.8	Yes (421.1)	Yes	Yes	Yes (16.9)
Roiser and Sahakian (2004) (ex users)	792	145.9	–	4	Yes (493.2)	No	Yes	Yes (10.8)
Smith *et al.* (unpublished data)	33	–	–	–	–	–	–	–
Sumnall *et al.* (2004b)	133.6	12.9	94.8	1.4	No (–)	No	No	No (20.4)
Verkes *et al.* (2001) (heavy)	741	1.3	234	3.1	No (–)	No	No	Yes (0.9)
Verkes *et al.* (2001) (moderate)	169	2.2	228.8	2	No (–)	No	No	Yes (1.4)
von Geusau *et al.* (2004)	46.3	2	117.8	–	No (99.2)	No	No	No (–)
Curran and Travill (1997)	–	0.7	–	–	–	–	–	–
Verheyden *et al.* (2002)	784.4	0.6	226.2	2.9	Yes (–)	No	Yes	No (–)
Curran *et al.* (2004) (+7 days)	207.9	1	141.4	2.7	Yes (–)	No	Yes	Yes (–)

–, Represents missing data or where it was not possible to calculate variable from available data. Too few studies reported informative measures of cocaine and amphetamine use to warrant reporting units.

sizes were extracted. Weighted means and pooled SD were calculated where results were reported by gender. An independent set of bias corrected (Hedges) standardized effect sizes, standard errors, and 95% confidence interval were computed. Comparison was made between Ecstasy users and controls. Where more than one experimental group existed (e.g. author defined 'heavy' and 'light' users), effect size was calculated for all independent subgroups. Whereas some authors have argued that inclusion of subgroups from studies may lead to dependent data points (Wolf, 1990), these effects are likely to be small (Lipsey and Wilson, 2001) and, in the current set of studies, represent independent populations. This approach also allowed more complete examination of patterns of use. Where more than one control group existed (e.g. drug naïve, cannabis users), the effect size was determined by comparison of Ecstasy users with polysubstance users rather than drug naïve controls. The combined effect size (fixed effects model) for Ecstasy users and controls was calculated and tested for homogeneity of variance. Weighted meta-regression analyses were performed to explore the associations between effect size and derived Ecstasy and use variables (estimated lifetime consumption, abstention, usual dose, duration of use). All data were analysed using SPSS for Windows (version 11.0; SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

Characteristics of study populations, psychopathological data, and drug use variables included in the analyses are displayed in Tables 1 and 2.

For the 22 studies that included abstention criteria of at least 7 days, the weighted fixed-effects mean effect size (ES) of 0.26 was statistically significant [$Z = 4.94$, d.f. = 21, $p < 0.001$; 95% confidence interval (CI) 0.15–0.36] (Fig. 1). The index of homogeneity was non-significant ($Q = 30.00$, d.f. = 21, $p = 0.0919$); hence, the variance in the selected studies was not greater than would be expected from sampling error alone. Calculation of I^2, considered an intuitive measure of consistency for meta-analyses of small sample studies (Higgins *et al*., 2003) showed that there was low to moderate (32.4%) heterogeneity between studies. Furthermore, as the power of Q in detecting heterogeneity is low in meta-analyses containing a small number of studies, utilizing a more conservative significant p-value ($p < 0.1$), the homogeneity hypothesis was rejected. However, an additional analysis in which random effects were corrected ES (0.31) remained significant ($Z = 4.76$, d.f. = 21, $p < 0.001$; 95% CI 0.18–0.44). In those studies that reported the variable ($n = 22$), weighted regression analysis showed that lifetime Ecstasy use significantly predicted ($r^2 = 0.353$) model variance ($\beta = 0.6845$, $Z = 3.72$, $p < 0.001$). Only 11 studies reported additional data on duration of Ecstasy use and usual dose per episode, which may explain why a subsequent weighted regression model including all three independent variables was non-significant ($\beta = 0.7058$, $Z = 1.466$; $\beta = 0.085$, $Z = 0.228$; $\beta = -0.274$, $Z = -0.629$, respectively, all $p > 0.05$). This was supported by two further independent weighted meta regressions which showed that both duration of Ecstasy use ($n = 14$; $\beta = 0.403$, $Z = 1.367$, $p > 0.05$) and usual dose per episode ($n = 16$; $\beta = 0.400$, $Z = 1.515$, $p > 0.05$) did not explain any of the model variance.

ES remained significant for the 17 studies reporting abstention data (< 7 days abstention; ES = 0.39, $Z = 5.65$, d.f. = 16, $p < 0.001$;

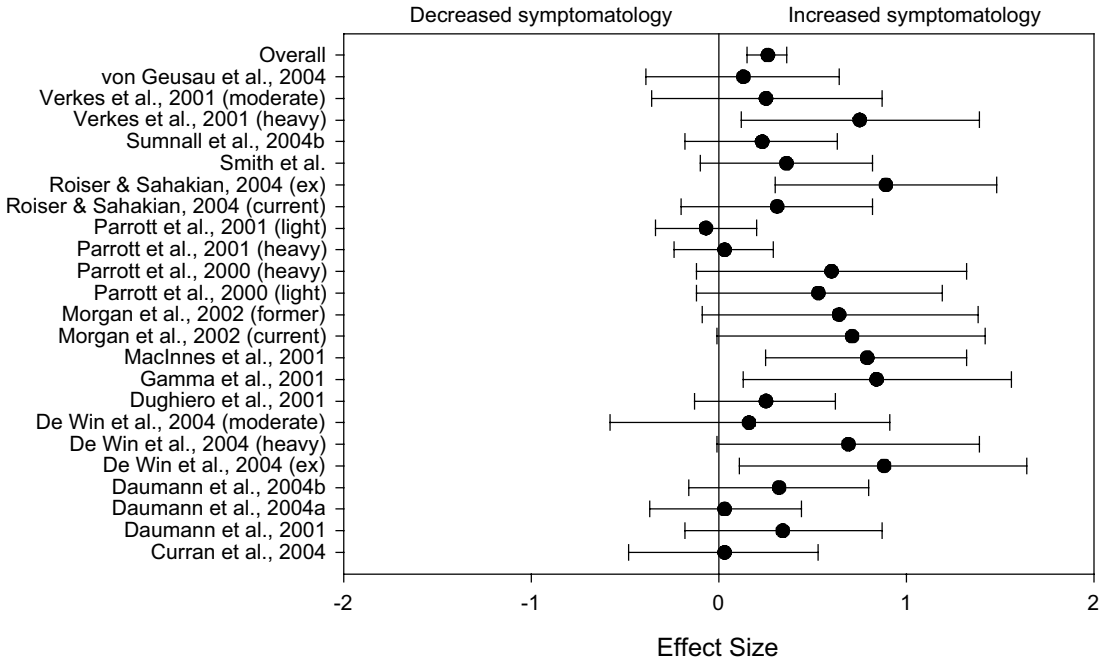

Figure 1 Error bar chart with effect sizes ± 95% confidence intervals from community studies investigating self reported depressive symptomatology in ecstasy users (at least 7 days abstention)

95% CI 0.26–0.53). Because there was a significant index of homogeneity ($Q = 18.43$, d.f. = 16, $p = 0.058$; $I^2 = 13.2\%$), correction for random effects was applied, but ES remained significant (ES = 0.35, $Z = 5.47$, $p < 0.001$; 95% CI 0.23–0.48). However, weighted meta regression analysis performed on all studies reporting abstention data ($n = 19$) showed that this variable did not provide any significant explanation of ES variance ($\beta = 0.003$, $Z = 1.787$, $p > 0.05$).

In those studies that controlled for cannabis use ($n = 9$) ES remained significant (ES = 0.46, $Z = 4.386$, d.f. = 8, $p < 0.001$; 95% CI 0.25–0.67; non-significant index of homogeneity $Q = 8.18$, d.f. = 8, $p > 0.1$; $I^2 = 2.2\%$). Weighted meta regression on the subset of studies providing details of cannabis use in the previous year showed no significant contribution to model variance ($n = 8$; $\beta = 0.721$, $Z = 1.858$, $p > 0.05$). In those studies that controlled for alcohol use ($n = 12$) ES remained significant (ES = 0.50, $Z = 5.27$, d.f. = 11, $p < 0.001$; 95% CI 0.31–0.68; non-significant index of homogeneity $Q = 9.31$, d.f. = 11, $p > 0.1$; $I^2 = 0\%$). Weighted meta regression on studies reporting alcohol units consumed/week ($n = 10$) showed no significant contribution to model variance ($\beta = -0.580$, $Z = -1.598$ $p > 0.05$). Examining only those studies that controlled for amphetamine use ($n = 6$), ES remained significant (ES = 0.49, $Z = 3.865$, $p < 0.001$; non-significant index of homogeneity $Q = 6.92$, d.f. = 5, $p > 0.1$; $I^2 = 27.7\%$). Units of amphetamine used were not reported frequently enough to enable meta regression. Too few studies matched cocaine use between groups ($n = 4$) to justify further investigation.

Meta-analysis of studies using the Beck Depression Inventory (BDI; $n = 10$) produced a statistically significant ES (ES = 0.48, $Z = 5.067$, d.f. = 9, $p < 0.001$; 95% CI 0.29–0.66; non-significant index of homogeneity $Q = 10.19$, d.f. = 9, $p > 0.1$; $I^2 = 11.7\%$). The ES remained significant in those studies using the BDI ($n = 6$) also controlling for cannabis use (ES = 0.44, $Z = 3.439$, d.f. = 5, $p < 0.001$; 95% CI 0.19–0.68; non-significant index of homogeneity $Q = 7.26$, d.f. = 5, $p > 0.1$; $I^2 = 31.1\%$). The ES for those studies utilizing the Symptom Check List (SCL-90) was non-significant ($n = 6$; ES = 0.11, $Z = 1.427$, d.f. = 5, $p > 0.05$; 95% CI –0.04–0.26; non-significant index of homogeneity $Q = 6.76$, d.f. = 5, $p > 0.1$; $I^2 = 26.0\%$), whereas using the revised version (SCL-90R) produced a significant ES ($n = 5$; ES = 0.26, $Z = 2.150$, d.f. = 4, $p < 0.05$; 95% CI = 0.02–0.50; non-significant index of homogeneity $Q = 4.04$, d.f. = 4, $p > 0.05$; $I^2 = 1.0\%$). Too few SCL-90 studies controlled for cannabis use ($n = 2$) to justify further analysis.

Meta regression showed a significant negative association between the number of subjects studied and the derived ES ($\beta = -0.003$, $Z = -2.846$, $p < 0.01$), with only studies with less than 40 subjects producing a significant ES (16 out of the 22 (72.7%) studies included in the analysis studied less than this number). Finally, it was interesting to note that combination of effect sizes from those studies results originally reported as statistically non-significant ($n = 20$) produced a significant ES when combined (ES = 0.23, $Z = 4.241$, d.f. = 19, $p < 0.001$; 95% CI = 0.12–0.33; non-significant index of homogeneity $Q = 23.35$, d.f. = 19, $p > 0.1$; $I^2 = 18.6\%$).

Discussion

Meta-analysis of self-reported depressive symptomatology in community samples of Ecstasy users found a significant ES of 0.31. According to Cohen's estimation of ES magnitude (Cohen, 1988) this represents a relatively small effect (small ES ≤ 0.2; medium = 0.5; large ≥ 0.8). The 95% CI did not contain 0, suggesting that increased depressive symptomatology is a robust finding. Weighted meta regression analysis showed that estimated lifetime Ecstasy use, but not duration of use, usual dose per episode, or abstention predicted ES. Significance remained after partially controlling for reported use of alcohol, amphetamine and cannabis. Calculation of Rosenthal's Fail Safe *N* showed that an additional nine unpublished studies would need to be included to nullify the significant ES. Considering the amount of Ecstasy research that does not advance past conference proceedings alone, it is likely that a large body of unpublished work exists (e.g. Cole *et al*., 1999; Soar *et al*., 2003). Using meta regression, it was found that there was an association between ES and estimated lifetime use of Ecstasy, although not for abstention, duration of use, or usual dose per episode. ES for studies using the BDI or SCL-90R were significant, but not the original version of the SCL-90, indicating that the observed effects may have been dependent upon the type of assessment used (see below). However, because the original SCL-90 has questionable psychometric properties (Derogatis, 1994) this may explain this discrepancy.

This main finding was interesting in that, although only a small positive ES was calculated, it contrasted with the majority of published literature which has, despite most official drugs information (see Introduction), generally shown no association between Ecstasy use and depressive symptomatology (Table 1). Exceptions have been 'current users' in the study of Morgan *et al*. (2002), and the populations studied by Gamma *et al*. (2001) and MacInnes *et al*. (2001). Individually, these studies are difficult to interpret. For example, Ecstasy users in the study of Gamma *et al*. (2001) reported significantly greater other drug use than controls; hence, there was no means of determining specificity of effect. MacInnes *et al*. (2001) reported incomplete drug histories, and BDI scores were within general population norms (Cole and Sumnall, 2002). Indeed, only Gamma *et al*. (2001) reported clinically relevant symptomatology in all of the studies reviewed, and this was through an observer rated scale (Hamilton Depression Scale). The subsequent regression analysis conducted by Morgan *et al*. (2002) also showed that cannabis use was a more accurate predictor of psychopathology than Ecstasy. It is uncertain whether the interpretation of Gamma *et al*. (2001) and MacInnes *et al*. (2001) would remain if they had adopted a similar analytical strategy. The question therefore arises as to why the current investigation produced a significant ES. One explanation is common to all meta-analyses, individual studies were not statistically powerful enough to detect trend effects that only emerged through study combination. However, this was complicated by the association that we found between study sizes and ES (i.e. smaller studies produced larger effect sizes). The derived funnel plot showed asymmetry (Fig. 2),

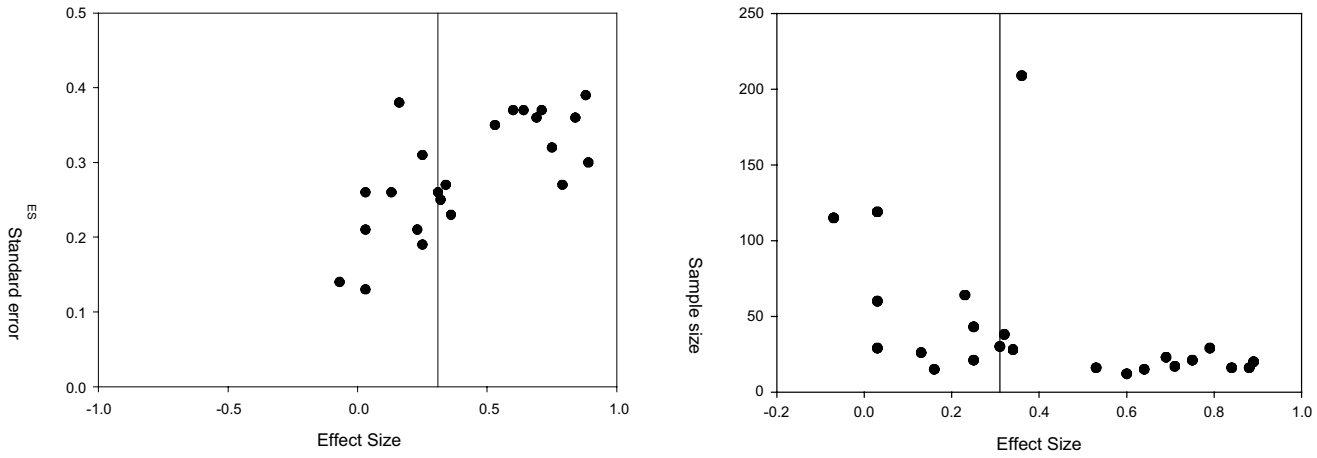

Figure 2 Funnel plots displaying association between individual effect size estimates with the standard error of the estimate (left) and sample size (right). The vertical line indicates ES. A significant regression coefficient of 0.795 was obtained.

and calculation of the regression slope for this plot revealed a non-zero coefficient ($\beta = 0.795$), indicating a strong association between effect and sample size. The three individual studies previously mentioned, for example, included less than 30 Ecstasy users and our analysis showed that only studies of less than 40 subjects produced significant effect sizes. Considered alongside subject selection bias inherent in retrospective studies of this nature (Cole *et al*., 2002b), smaller studies may tend towards type I statistical errors. Publication bias tends to censor small effect sizes, which may lead to under representation of findings derived from larger samples. General population Ecstasy prevalence remains quite high compared to other misused substances [e.g. the British Crime Survey reported a prevalence of 5.4% in the last year (16–24-year-olds) during 2002/2003] (Condon and Smith, 2003), and it should not prove difficult for researchers to recruit relatively large numbers of subjects from community populations. Although this may increase experimental costs, it is imperative considering provision of accurate information to drug users.

The second explanation is more pertinent to the present discussion. The accuracy of meta-analyses depend upon the quality of primary data sources, and adherence to appropriate methodology in the research base. Until recently, this has been problematic. It is not the purpose of this study to offer a detailed critique of individual methodologies as this has been done elsewhere (Curran, 2000; Cole *et al*., 2002b). Despite agreement between researchers about the existence of confounding factors affecting the interpretation of data from retrospective studies of Ecstasy users, little has been done to address them. Table 3 summarizes problems that limit our confidence in the data and, based on the current discussion, offers suggestions as to how they may be more effectively addressed.

Only nine studies of the 23 controlled for use of cannabis between groups, and only eight of these recorded use parameters. This meant that it was not possible to accurately differentiate Ecstasy-related effects from cannabis. Heavy cannabis users, who may smoke the drug every day, may either be intoxicated or in withdrawal when participating in experiments. Work carried out by Morgan *et al*. (2002), Daumann *et al*. (2004) and Sumnall *et al*. (2004b) has reported complex relationships between parameters of polysubstance misuse and self-reported psychopathology. Very few studies reported wider drug histories (e.g. cocaine, alcohol, tobacco,

Table 3 Interpretational difficulties in studies assessing substance misuse associated psychopathology in community samples

Problem	Solution
Description of population assessed. What is an Ecstasy user?	Recognition of polysubstance misuse and incorporation of appropriate analytical strategies
Quantifying drug intake	Drug diary, forensic analysis
Polysubstance misuse	Detailed histories for all substances used, including tobacco and alcohol
Drug free status	Urinalysis; recognition that heavy cannabis users may be intoxicated or in withdrawal. Results of many studies reflect current periods of drug use
Cross sectional design	Move towards longitudinal study or readjustment of interpretations
Appropriate assessment tools	Differentiation of items measuring negative affect and somatic complaints which may result from extra pharmacological factors
Time course of effects	Clear differentiation between sub-acute, short-term, and long-term effects.
Representative population	Problematic users versus community population
Study size	Studies should not be performed with less than 50 subjects

cannabis). This is a largely a product of how this population is classified by the researcher and subsequently studied (i.e. 'Ecstasy users'). A recent behavioural economic investigation of drug choice indicated that although the majority of volunteers self-reported a preference for using Ecstasy, their actual behaviour was discrepant and they valued intoxication over the effects of individual drugs (Sumnall *et al*., 2004a). *A posteriori* classification of most Ecstasy using populations in the present review would, on the basis of drug use behaviours, more accurately define them as having a preference for alcohol and cannabis. It is therefore essential that comprehensive drug histories are collected and this data incorporated into analyses.

It was notable that we found no association between ES and abstention from Ecstasy. In a series of studies, it was reported that during the week following an Ecstasy episode (i.e. abstention < 7 days), users reported short-lasting (resolved after 7 days), detrimental effects on mood (Curran and Travill, 1997; Verheyden *et al*., 2003, 2003). MacInnes *et al*. (2001) did not specifically investigate the relationship between abstention and symptomatology, but argued that ex-users (mean abstention 26.0 weeks) scored more highly on the BDI than non-users, suggestive of long lasting effects. By contrast, Morgan *et al*. (2002) reported that ex-users (mean abstention 112.2 weeks) reported similar depressive symptomatology to current users (mean abstention 4.1 weeks). Our own work (Sumnall *et al*., 2004b) also suggested no relationship between abstention (mean 12.9 weeks) and depressive symptomatology. An important consideration for studies included in the meta regression of abstention was that, although Ecstasy use may have been postponed or stopped, there was continuation of other substance misuse. If concomitant substance misuse is as important a determinant of psychopathology as recent data suggests (Daumann *et al*., 2004), then it is not surprising that there was no linear relationship between abstention and ES. Again, collection of detailed drug use histories would have helped to resolve this.

Recently published work investigating neurocognitive function found that clinically relevant (DSM-IV criteria), rather than purely recreational Ecstasy use was associated with cognitive impairment (Hanson and Luciana, 2004). There was also a trend towards higher BDI scores in this subsample (this work was published after the cut off date for the meta-analysis). As already indicated by typological work undertaken with recreational substance misusers (Smit *et al*., 2002; Fendrich *et al*., 2003), it is likely that there is a heterogeneous Ecstasy using population who consume the drug with differing consequences, despite a similar number of use episodes. The quality of drug histories may therefore be improved by collection of additional data on use disorders rather than reliance on estimated total episodes.

The choice of scales for measuring negative affect and depressive symptomatology are also crucial variables in these analyses. The majority of self-report scales include somatic symptoms, such as loss of appetite and sleep, which can be caused by substance misuse *per se*. Similar problems are experienced with chronically ill patients where the physical effects of their diseases confound measurements of depressive symptomatology (Johnston *et al*., 2000; Lespérance and Frasure-Smith, 2000). In this context, it is common practice to use self-report scales that focus on negative affect. It is interesting to note that, in one publication where more than one depression scale was employed, one such scale (Hospital Anxiety and Depression Scale) proved to be non-significant whereas the scale potentially confounded by the somatic effects of substance misuse (BDI) was significant (Verheyden *et al*., 2003). Future work should consider the use of scales that are not confounded by the physiological effects of ongoing substance misuse.

Epidemiological studies demonstrate that there is a high rate of comorbidity between substance use disorders and other psychiatric disorders (Kushner *et al*., 1990). This indicates that substance use disorders co-occur with psychiatric disorders at rates exceeding those predicted by chance alone. The precise causal relationship is more difficult to determine. This suggests three groups of comorbid substance abuser: (i) those with a primary independent psychiatric condition which predates the substance use; (ii) those with a substance-related psychiatric disorder; and (iii) those who have a predisposition to a psychiatric condition which is exacerbated by substance misuse. It is impossible to distinguish a causal direction using a cross-sectional study design, but one recent prospective longitudinal investigation of temporal patterns of Ecstasy use and psychiatric disorders indicated that drug use is secondary to the onset of psychiatric disorders (Lieb *et al*., 2002). Similarly, childhood abuse and neglect was found to be more common in Ecstasy users (Singer *et al*., 2004). Within this population, there is a close relationship between increasing drug experience and the perceived function that use fulfils (e.g. perceived symptom or negative mood alleviation through drug use) (Boys and Marsden, 2003).

Although the majority of depressed patients would present to a primary health care agency, once substance misuse had been identified, they would probably be referred on to specialist drug agencies (SDA). The number of Ecstasy users presenting to SDA within the EU is very small (EMCDDA, 2003). It is possible that the overwhelming majority would hide their substance misuse but there are no data to substantiate this either way. Because the data from SDA are the only ones available, they are the only ones that can be used to predict the public health consequences of Ecstasy use. One would expect that if Ecstasy use was causing major depressive disorder (MDD) then the ES and the number of users presenting for treatment would both be much higher. This is not to state that the relationship between Ecstasy use and MDD is trivial, rather the relationship between the two is more complicated than is currently portrayed. Effective clinical interventions with this population require a clearer understanding of this relationship.

How then should official drugs information campaigns impart information about the psychopathological consequences of Ecstasy use? Previous strategies pertaining to depression were not evidence-based. As researchers, we should recognize that we are only beginning to be able to start answering this question, and should adopt appropriate caution in our discussion. The current meta-analysis suggested a small quantifiable link but also highlighted the methodological inadequacy of the research base, thus preventing firm conclusions. However, it is clear that because of the drug using behaviours of this population, observed effects may be common to polysubstance misuse in general rather than Ecstasy *per se* (Cole *et al*., 2002b; Sumnall *et al*., 2004b). Users should be informed that substance misuse has both acute and sub-acute

effects that may negatively impact upon health, education, work and relationships.

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