Is Recreational Ecstasy (MDMA) Use Associated with Higher Levels of Depressive Symptoms?

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Abstract—Due to potential serotonergic deficits, 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) may cause long-term mood disruptions in recreational Ecstasy users. The purpose of this review is to evaluate the evidence for a relationship between recreational Ecstasy use and higher levels of depressive symptoms. Eleven out of 22 studies initially have reported significantly higher depression scores in Ecstasy users in comparison to control participants. However, only three studies ultimately have revealed significantly higher depression scores in comparison to cannabis or polydrug controls. Furthermore, most studies have suffered from methodological weaknesses, and the levels of depressive symptoms that have been found in Ecstasy users have not been shown to be much higher than those found in normative groups. The evidence for an association specifically between Ecstasy use and higher levels of depressive symptoms is currently unconvincing, but the frequent concomitant use of Ecstasy and other illicit drugs has been shown to be associated with higher levels of depressive symptoms. Possible causes include polydrug use in general, MDMA-induced serotonergic deficits, individual effects of illicit drugs besides Ecstasy, combined effects of MDMA and other illicit drugs, and preexisting differences in the levels of depressive symptoms in Ecstasy users.

Keywords—3,4-methylenedioxymethamphetamine, 5-HT, depression, Ecstasy, MDMA, serotonin

Experimental studies have shown that 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) causes lasting serotonin (5-hydroxytryptamine, 5-HT) system deficits in rats and monkeys at certain doses. These deficits have been evidenced through the use of antibody staining (Wilson, Ricaurte & Molliver 1989; O'Hearn et al. 1988) and radioligand binding (Scanzello et al. 1993; Ricaurte et al. 1992; Battaglia, Yeh & De Souza 1988; Commins et al. 1987), as well as through the observation of long-term reductions in 5-HT (Scanzello et al. 1993; Slikker et al. 1989, 1988; Stone, Hanson & Gibb 1987; Stone et al. 1987), 5-hydroxyindoleacetic acid (Scanzello et al. 1993; Slikker et al. 1989, 1988; Stone, Hanson & Gibb 1987; Stone et al. 1987), and tryptophan hydroxylase (Stone, Hanson & Gibb 1987; Stone et al. 1987). MDMA is likely to cause persistent serotonergic alterations in humans as well, but the issue of at what dose this takes place is complicated by variation in species sensitivity to the toxic effects of drugs (Campbell 1996) and differences in the frequency and route of administration of MDMA (Ricaurte et al. 1988). In relation to this issue, brain imaging studies that have employed either PET or SPECT consistently have revealed less SERT (serotonin transporter) binding in the brains of heavy Ecstasy users in comparison to Ecstasy-naive controls. Several of these studies have revealed modest regional brain differences in the range of 5% to 15% (Buchert et al. 2004, 2003; Thomasius et al. 2003; Reneman et al. 2001a, b; Semple et al. 1999), while others have revealed larger differences in the range of 10% to 70% (McCann et al. 2005, 1998). Interestingly, PET or SPECT studies have not revealed any differences in SERT binding in the brains of moderate Ecstasy users or Ecstasy users who had been abstinent for 20 weeks or longer (Buchert et al. 2004, 2003; Thomasius et al. 2003; Reneman et al. 2001a, b).

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Serotonin is involved in the regulation of mood in humans. If MDMA induces persistent serotonergic deficits in humans, then long-term mood disruptions may be seen in recreational Ecstasy users. The purpose of this review is to evaluate the evidence of a relationship between Ecstasy use and higher levels of depressive symptoms. At least 21 studies have searched for a relationship between Ecstasy use and higher levels of depressive symptoms. Each study will be evaluated in terms of statistical significance, and then the studies that reported statistically significant results will be critiqued and examined further in order to ascertain what levels of depressive symptoms have been found in Ecstasy users.

STUDIES THAT HAVE USED THE HAMILTON RATING SCALE FOR DEPRESSION

The Hamilton Rating Scale for Depression (HAM-D) is a clinician-rating instrument that was constructed in order to assess the severity of depression in patients diagnosed with major depression (Hamilton 1960). Although the HAM-D is composed of a total of 21 items, the first 17 items also are commonly used as a rating scale for depression. Both versions of the HAM-D have been established as reliable and valid instruments (Leentjens et al. 2000; Hedlund & Vieweg 1979). Items address the presence of typical symptoms of depression at the time of testing (Hamilton 1960). Responses to items are weighted numerically, with each item having a minimum value of 0 and a maximum value ranging from 2 to 4. An item value of 0 indicates the absence of a certain symptom, and the maximum value for an item indicates the most severe form of that symptom. The highest possible score for the 17-item HAM-D is 53, and the highest possible score for the 21 item HAM-D is 66.

Five studies have used the HAM-D in order to compare Ecstasy users to control participants. Gamma and colleagues (2001) found that a group of Ecstasy users scored significantly higher than polydrug controls (users of illicit drugs besides Ecstasy) on the 17-item HAM-D. Similarly, three other studies reported that Ecstasy users scored significantly higher than drug-naive controls (nonusers of illicit drugs) on the 21-item HAM-D (Gerra et al. 2002, 2000, 1998). In contrast, Halpern and colleagues (2004) reported that Ecstasy users did not score significantly higher than control participants on the 21-item HAM-D. Four out of five studies that have used the HAM-D have found significantly higher depression scores in Ecstasy users in comparison to control participants.

STUDIES THAT HAVE USED THE SYMPTOM CHECKLIST 90 OR THE SYMPTOM CHECKLIST 90, REVISED

The Symptom Checklist 90 (SCL-90) is a self-report instrument that was designed to assess the severity of psychopathological symptoms in psychiatric outpatients (Derogatis, Lipman & Covi 1973). The reliability and validity of the SCL-90 have been supported empirically (Derogatis, Rickels & Rock 1976). The questionnaire is composed of items that are descriptive of typical clinical symptoms, and the depression subscale contains 13 of its total 90 items. Test-takers are instructed to rate the degree of each symptom on a scale of 0 to 4 in accord with the past week of their lives (0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, and 4 = extremely). The highest possible raw score for the SCL-90 depression subscale is 52. Researchers sometimes report psychopathology scores for the SCL-90, which are the per item averages for each subscale. In the case of the depression subscale, the psychopathology score is the raw score divided by 13. The Symptom Checklist 90, Revised (SCL-90-R) is an updated version of the SCL-90 (Derogatis 1994). The reliability and validity of the SCL-90-R have been supported empirically in much the same way as its predecessor. The basic format and scoring procedures remain the same.

Four studies have used the SCL-90 in order to compare Ecstasy users to control participants. Parrott, Sisk and Turner (2000) failed to find significantly higher depression scores in light or heavy Ecstasy users in comparison to polydrug controls. Dughiero, Schifano, and Forza (2001) failed to find significantly higher depression scores in Ecstasy users in comparison to polydrug controls. Parrott and colleagues (2001) recruited 768 participants and then separated them into six groups: the first group was composed of participants who had not used legal or illegal recreational drugs; the second group was composed of legal drug users; the third group was composed of cannabis users who also had used legal drugs; the fourth group was composed of Ecstasy-naive polydrug users; the fifth group was composed of polydrug users who had used Ecstasy lightly; and the sixth group was composed of polydrug users who had used Ecstasy heavily. Parrott and colleagues failed to find any significant differences in depression scores among the six groups. Using the same sample of participants as in the previous study, Milani and colleagues (2004) further divided the six groups into males and females. They failed to find any significant differences in depression scores when groups of males were compared to each other or when groups of females were compared to each other. None of the studies that have used the SCL-90 have revealed significantly higher depression scores in Ecstasy users in comparison to control participants.

Five studies have used the SCL-90-R in order to compare Ecstasy users to control participants. Daumann and colleagues (2001) recruited a group of Ecstasy users who had limited their illicit drug use to Ecstasy and cannabis, and they then compared this group of users to a group of cannabis users who were matched for cannabis use. The researchers failed to find significantly higher depression scores in Ecstasy users. Morgan and colleagues (2002) failed to

find significantly higher depression scores in former Ecstasy users (abstinent from Ecstasy use for at least six months) in comparison to drug-naive and polydrug controls, but they did find significantly higher depression scores in current Ecstasy users, although this finding lost significance after treating cannabis use as a covariate. Thomasius and colleagues (2003) found significantly higher depression scores in current and former Ecstasy users (abstinent from Ecstasy use for at least 20 weeks) in comparison to drug-naive controls, but not in comparison to polydrug controls. Halpern and colleagues (2004) strictly recruited rave attendees who had little exposure to drugs in general, with the exception of Ecstasy use on 20 or more occasions in some participants. They failed to find significantly higher depression scores in Ecstasy users in comparison to nonusers. Finally, Daumann and colleagues (2004) failed to find significantly higher depression scores in Ecstasy users in comparison to mostly drug-naive controls. In summary, two out of five studies that have used the SCL-90-R initially have revealed significantly higher depression scores in Ecstasy users in comparison to control participants.

STUDIES THAT HAVE USED THE BECK DEPRESSION INVENTORY

The Beck Depression Inventory (BDI) is a self-report instrument that was constructed in order to assess the severity of depression in patients diagnosed with a psychiatric disorder (Beck et al. 1961). The test contains 21 items that are descriptive of typical symptoms of depression. Test-takers are asked to rate the intensity of each symptom on a scale of 0 to 3 in accord with the past week of their lives. The highest possible score for the BDI is 63. Although the BDI was revised in 1978, most researchers have cited only the 1961 reference and have not indicated which version of the BDI was used in their particular study (Beck, Steer & Garbin 1988). However, Lightfoot and Oliver (1985) used both versions of the BDI and obtained a mean score of about 7 on each version for the same group of college students, which suggests that one version will give close to the same score as the other for the same level of depressive symptoms.

Five studies have used the BDI in order to compare Ecstasy users to control participants. Verkes and colleagues (2001) administered the BDI to moderate Ecstasy users, heavy Ecstasy users, and mostly drug-naive controls; they reported that depression scores did not differ significantly among the three groups. In contrast, MacInnes, Handley and Harding (2001) found that Ecstasy users had significantly higher depression scores than drug-naive controls. In another study, de Win and colleagues (2004) administered the BDI to moderate Ecstasy users, heavy Ecstasy users, former heavy Ecstasy users (abstinent from Ecstasy use for at least one year), and polydrug controls. Although they failed to find significantly higher depression scores in moderate or heavy Ecstasy users in comparison to polydrug controls, the researchers did find significantly higher scores in former heavy Ecstasy users. Roiser and Sahakian (2004) found that both current and former Ecstasy users (abstinent from Ecstasy use for at least one year) had significantly higher depression scores in comparison to drug-naive controls, but not in comparison to polydrug controls. Finally, de Almeida and Silva (2005) surprisingly found significantly lower depression scores in Ecstasy users in comparison to polydrug controls. Since the Ecstasy users included in this particular study were required to have taken Ecstasy on only 10 or more occasions, the authors concluded that this unexpected result possibly was due to a lower level of Ecstasy use in relation to other samples. Thus far, three out of five studies that have used the BDI have shown significantly higher depression scores in Ecstasy users in comparison to control participants.

STUDIES THAT HAVE USED THE BECK DEPRESSION INVENTORY, SECOND EDITION

The Beck Depression Inventory, Second Edition (BDI-II) is a self-report instrument that was designed in order to assess the severity of depression in patients diagnosed with major depression (Beck, Steer & Brown 1996). The main reason for the development of the BDI-II was to better match the criteria for a major depressive episode as found in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association 1994). In contrast to the BDI, the BDI-II instructs test-takers to answer questions in accord with the past two weeks of their lives. A time frame of two weeks is consistent with the length of time someone must experience depressive symptoms in order to qualify for a major depressive episode according to the DSM-IV. Beyond this change, four out of 21 items found on the BDI were replaced by new items that are more specific to depressed individuals, and 14 of the remaining 17 items were reworded in order to reduce misunderstanding. The BDI-II asks test-takers to rate the intensity of each symptom on a scale of 0 to 3. The highest possible score for the inventory is 63.

McCardle and colleagues (2004) were the first to use the BDI-II in measuring depressive symptoms in Ecstasy users. The researchers in this study found that Ecstasy users scored significantly higher than mostly drug-naive controls. Guillot and Greenway (2006) also used the BDI-II in measuring depressive symptoms in Ecstasy users. In their study, they found that Ecstasy users did not score significantly higher than mostly drug-naive college students. Lamers and colleagues (2006) recruited a group of Ecstasy users who had limited their use mostly to Ecstasy and marijuana, and they then compared this group of users to marijuana users and mostly drug-naïve controls. After controlling for alcohol and marijuana use, they found that Ecstasy users scored significantly higher than marijuana users and mostly

drug-naïve controls. Currently, two out of three studies have shown significantly higher BDI-II scores in Ecstasy users in comparison to control participants.

A CLOSER EXAMINATION OF THE STUDIES THAT REPORTED SIGNIFICANTLY HIGHER DEPRESSION SCORES IN ECSTASY USERS

Gamma and colleagues (2001) found that a group of Ecstasy users scored significantly higher than polydrug controls on the 17-item HAM-D. Mean HAM-D scores were 5.0 for polydrug controls and 11.7 for Ecstasy users. Gamma and colleagues stated, "HAM-D scores were markedly and significantly higher in our sample of Ecstasy users than in control subjects, although they were lower than the range of scores typical for clinical depression" (p. 70). Unfortunately, no HAM-D studies were found to be published that tested broad community samples, so I cannot provide a comparison group beyond that of the polydrug controls in this particular study. Regardless, the study by Gamma and colleagues suffered from several weaknesses: sample sizes were small (17 polydrug controls and 16 Ecstasy users), and control participants were more educated and had used other illicit drugs less than Ecstasy users.

Gerra and colleagues (1998) found that Ecstasy users scored significantly higher than drug-naive controls on the 21-item HAM-D. They attempted to isolate Ecstasy use as a factor by including only Ecstasy users who had used other illicit drugs infrequently. Mean HAM-D scores were 5.1 for drug-naive controls and 14.9 for Ecstasy users. Using the same methodology as the previous study, Gerra and colleagues (2000) found that Ecstasy users scored significantly higher than drug-naive controls on the 21-item HAM-D. Mean HAM-D scores were 5.1 for drug-naive controls and 16.0 for Ecstasy users. Again using the same methodology, Gerra and colleagues (2002) found that Ecstasy users scored significantly higher than drug-naive controls on the 21-item HAM-D. Mean HAM-D scores were 5.1 for drug-naive controls and 17.1 for Ecstasy users. These three studies consistently found higher depression scores in Ecstasy users, with mean scores ranging from 15 to 17. One study that recruited depressed patients required a score of at least 17 on the 21-item HAM-D (Bennie et al. 1988). This criterion seems to indicate that the Ecstasy users in these three studies displayed HAM-D scores typical for the lower end of clinical depression or close to it. However, the Ecstasy users in these three studies first contacted a center for drug addiction and then were admitted to a long-term rehabilitation program. Thus, motivation and the presence of drug addiction are likely to have influenced test scores. Finally, sample sizes were small (12 to 15 Ecstasy users per study), and one-third to one-half of the Ecstasy users in each study reported having family conflict.

Morgan and colleagues (2002) failed to find significantly higher SCL-90-R depression scores in former Ecstasy users in comparison to drug-naive and polydrug controls, but they did find significantly higher scores in current Ecstasy users. Mean depression scores were approximately 5 for drug-naive controls, 6 for polydrug controls, 14 for current Ecstasy users, and 12 for former Ecstasy users (roughly calculated from the psychopathology scores provided in Figure 1d). In comparison to these mean scores, Gotlib (1984) obtained mean depression scores of 12 for male college students and 14 for female college students. Both of these mean scores are close to those found for Ecstasy users. Furthermore, depression scores were not significantly higher in current Ecstasy users after treating cannabis use as a covariate. In relation to this and other findings, Morgan and colleagues (2002: 301) stated that "psychopathology in regular ecstasy users may be associated more with their polydrug use generally, rather than with their ecstasy use." One limitation of this study was small sample sizes (18 current heavy Ecstasy users, 15 former heavy Ecstasy users, 16 polydrug controls, and 15 drug-naive controls).

Thomasius and colleagues (2003) found significantly higher SCL-90-R depression scores in current and former Ecstasy users in comparison to drug-naive controls. Mean depression scores were approximately 5 for drug-naive controls, 9 for polydrug controls, 10 for current Ecstasy users, and 13 for former Ecstasy users (roughly calculated from the psychopathology scores provided in Figure 1b). Mean scores for Ecstasy users in this study were somewhat lower than those found in the study by Morgan and colleagues, so they stand up a bit less to the same standards of comparison as in the previous paragraph. Thomasius and colleagues noted that Ecstasy users had significantly higher depression scores than drug-naive controls, whereas polydrug controls did not have significantly higher depression scores. In reference to this finding, Thomasius and colleagues concluded, "elevated depression scores were reported by current and ex-ecstasy users but not by polydrug controls. Elevated depression may therefore be considered an ecstasy effect" (pp. 92-93). However, the depression scores reported by polydrug controls were somewhat elevated in comparison to drug-naive controls, although not significantly elevated (see the mean scores above). Given this information, it seems more accurate to say that the significantly elevated depression scores reported by Ecstasy users may be considered an Ecstasy + polydrug use effect, not just an Ecstasy effect (the term "effect" is meant in a statistical sense here, not in a causative sense). Furthermore, the Ecstasy users in this study did not have significantly higher depression scores than polydrug controls. This finding suggests that the average difference in depressive symptoms related specifically to Ecstasy use is not significant, although Ecstasy use together with other illicit drug use does seem to be related to higher levels of depressive symptoms.

MacInnes, Handley and Harding (2001) found that Ecstasy users scored significantly higher than drug-naive controls on the BDI. Mean BDI scores were 5.2 for drug-

naive controls and 9.2 for Ecstasy users. Although MacInnes and colleagues stated within their discussion that "Beck et al. (1961) suggest a score of 9 represents mild depression" (p. 184), a mean BDI score of 9 actually still falls within the nondepressed range according to the cut score guidelines given by Beck and colleagues (0-9 = nondepressed, 10-15 = mildly depressed, 16-23 = moderately depressed, and 24-63 = severely depressed). Furthermore, Beck and colleagues recommended these cut score guidelines for patients already diagnosed with a psychiatric disorder. Importantly, the cut score guidelines given by Beck and colleagues have been placed relatively low in order to increase the sensitivity for detecting depression in psychiatric patients. Doing so reduces the number of false negatives (individuals misdiagnosed as not being depressed) but at the same time raises the number of false positives (individuals misdiagnosed as being depressed). A similar criticism regarding a mean BDI score of 9 previously was raised by Cole and Sumnall (2002), to which MacInnes, Handley, and Harding (2002) replied that they should have referenced Beck and Steer (1987) instead of Beck and colleagues (1961). However, Beck and Steer (1987) suggested that a BDI score of 9 still falls within the range of normal depression (Robert A. Steer, personal communication, June 1, 2006), which means that MacInnes, Handley, and Harding's reply is subject to the same criticism as their original statement. In a review of the literature, Robinson, Berman and Neimeyer (1990) determined that the general population had a mean BDI score of 7, and mean BDI scores of 7 to 8 have been obtained for college students (Baron & Hanna 1990; Lightfoot & Oliver 1985; Gotlib 1984; Robbins & Tanck 1984; Dobson & Breiter 1983; Rizley 1978). Thus, the Ecstasy users in the MacInnes, Handley and Harding study were not much more depressed than college students and the general population. Finally, the results of this study were weakened by the lack of a polydrug control group.

In another study, de Win and colleagues (2004) administered the BDI to moderate Ecstasy users, heavy Ecstasy users, former heavy Ecstasy users, and polydrug controls. The researchers failed to find significantly higher BDI scores in moderate or heavy Ecstasy users in comparison to polydrug controls, but they did find higher scores in former heavy Ecstasy users. Median BDI scores were 5.5 for former heavy Ecstasy users and 1.0 for polydrug controls (no means reported). Besides the fact that the median BDI score reported for polydrug controls was very low in this study, the median BDI score reported for former heavy Ecstasy users was far from being extraordinary. Finally, this study had small sample sizes (15 polydrug controls, 15 moderate Ecstasy users, 15 heavy Ecstasy users, and 16 former heavy Ecstasy users).

Roiser and Sahakian (2004) compared current and former Ecstasy users to drug-naive and polydrug controls. The researchers found that both current and former Ecstasy users scored significantly higher than drug-naive controls on the BDI. Mean scores were 3.8 for drug-naive controls, 6.0 for polydrug controls, 7.9 for current Ecstasy users, and 12.6 for former Ecstasy users. The mean BDI score of 8 found for current Ecstasy users is just one point higher than the mean score for the general population (Robinson, Berman & Neimeyer 1990), and it is within the range of mean BDI scores that has been obtained for college students (Baron & Hanna 1990; Lightfoot & Oliver 1985; Gotlib 1984; Robbins & Tanck 1984; Dobson & Breiter 1983; Rizley 1978). On the other hand, the mean BDI score of 13 found for former Ecstasy users is noticeably higher than a mean score of 8. However, neither current nor former Ecstasy users were shown to have significantly higher BDI scores than polydrug controls. In reference to this finding, Roiser and Sahakian (2004: 417) concluded, "These data do not suggest that ecstasy use alone can account for increased levels of self-reported depression in MDMA-using groups."

McCardle and colleagues (2004) found that Ecstasy users scored significantly higher than mostly drug-naïve controls on the BDI-II. They reported mean BDI-II scores of 5.5 for mostly drug-naive controls and 12.4 for Ecstasy users, and concluded, "Of particular concern is that the feelings of depression reported by MDMA users in the present study approached clinical levels of depression" (p. 438). The researchers must have been comparing a mean BDI-II score of 12 with that of the cut score guidelines given by Beck, Steer and Brown (1996), which state that 0 to 13 represent minimal depression, 14 to 19 represent mild depression, 20 to 28 represent moderate depression, and 29 to 63 represent severe depression. However, Beck, Steer and Brown stated just above these cut score guidelines that "the cut score guidelines below are suggested for total scores of patients diagnosed with depression" (p.11). Importantly, these cut score guidelines have been placed relatively low in order to increase the sensitivity for detecting depression in patients already diagnosed with major depression, and they were not intended for use in a nonclinical sample. In relation to nonclinical samples, Beck, Steer and Brown stated that "for research studies in which it is important to obtain as pure a group of persons with depression as possible with regard to symptomology, the cut score guidelines should be raised to reduce the number of false positives" (p. 11). For example, mean BDI-II scores of 8 to 13 have been obtained for college students (Storch, Roberti & Roth 2004; Dozois 2003; Al-Musawi & Nu'man 2001; Whisman & Perez 2000; Steer & Clark 1997; Beck, Steer & Brown 1996), and a mean BDI score of 12 falls within this range. Similarly, Guillot and Greenway (2006) found mean BDI-II scores of 10 both for Ecstasy users and college students. In contrast to what McCardle and colleagues concluded, it is apparent that the Ecstasy users in their study did not report symptoms of depression that are near clinical levels of depression. Finally, this study was limited by small sample sizes (15 Ecstasy users and 17 mostly drug-naive controls) and the lack of a polydrug control group.

Lamers and colleagues (2006) found that Ecstasy/marijuana users scored significantly higher on the BDI-II than marijuana users and mostly drug-naïve controls after controlling for alcohol and marijuana use. The authors reported mean BDI-II scores of 2.5 for mostly drug-naïve controls, 4.4 for marijuana users, and 9.8 for Ecstasy/marijuana users. Once again, mean BDI-II scores of 8 to 13 have been obtained for college students (Storch, Roberti & Roth 2004; Dozois 2003; Al-Musawi & Nu'man 2001; Whisman & Perez 2000; Steer & Clark 1997; Beck, Steer & Brown 1996). Guillot and Greenway (2006) directly compared Ecstasy users and college students and found a mean BDI-II score of 10 for both groups. In the context of this information, the comparison groups used in the Lamers and colleagues study seem to be exceptionally healthy, which makes obtaining a significant result more likely. In addition, this study had small sample sizes (15 mostly drug-naïve controls, 15 marijuana users, and 11 Ecstasy/marijuana users), a fact that limits any conclusions drawn from the results.

CLARIFICATIONS AND RECOMMENDATIONS

Based on the literature, recreational Ecstasy users who confine their illicit drug use to Ecstasy seem to be very rare. However, several studies examined above have not employed a group of control participants who used illicit drugs besides Ecstasy at a level similar to that of Ecstasy users, which allows for the possibility that other drugs are responsible for any differences seen. This possibility is especially relevant for cannabis use, which has been shown to be associated with the psychopathological symptoms found in Ecstasy users in several studies (Daumann et al. 2004, 2001; Morgan et al. 2002). Therefore, Ecstasy use studies should strive to control adequately for drug use other than Ecstasy. In regard to this sentiment, Sumnall and Cole (2005) recently conducted a meta-analysis of studies that measured the levels of depressive symptoms in Ecstasy users. Although Sumnall and Cole found a small but significant association between Ecstasy use and higher levels of depressive symptoms, they also "highlighted the methodological inadequacy of the research base" (p. 95) and acknowledged the possibility that this association was more a reflection of polysubstance use in general.

One point worth mentioning is that even if drug use besides Ecstasy is adequately controlled, then this still does not mean necessarily that differences in depressive symptoms are due to Ecstasy use alone. Of course, there may be preexisting differences in the levels of depressive symptoms in recreational Ecstasy users. Several studies have concluded that mental disorders were more likely to precede the initial use of Ecstasy in users who had received a psychiatric diagnosis, with percentages of previously diagnosed Ecstasy users ranging from approximately 50% to 90% (Falck et al. 2006; Guillot & Greenway 2006; de Win et al. 2004; Lieb et al. 2002). Although many studies have excluded participants with a current or past psychiatric diagnosis in an attempt to factor out such preexisting differences, the possibility remains that undiagnosed individuals with higher levels of depressive symptoms might be more inclined to use Ecstasy than undiagnosed individuals with lower levels of depressive symptoms. For example, Huizink and colleagues (2006) conducted a large-scale prospective study and found an increased risk for Ecstasy use in adults who had scored high on a measure of depression as a child or adolescent.

Another possibility is that samples may not be representative of typical Ecstasy users, which could bias results in the expected direction. In the current review, I have pointed out three studies that used a method of recruitment not likely to provide representative samples (Gerra et al. 2002, 2000, 1998). In addition, eight out of eleven studies that obtained significant results employed samples of less than 20 participants (de Win et al. 2004; McCardle et al. 2004; Gerra et al. 2002, 2000, 1998; Morgan et al. 2002; Gamma et al. 2001). Some researchers may emphasize that differences obtained in smaller samples at a certain significance level (e.g., $p < .05$, $p < .01$, $p < .001$) are greater than differences obtained in larger samples at the same significance level, which is a fact that can make significant results look more impressive in studies with smaller sample sizes (Keppel 1991: 64). However, assuming that sampling procedures are sound in the first place, a larger sample of participants will be more representative of the target population than a smaller sample (Hopkins, Hopkins & Glass 1996: 145). In light of these considerations, it is important that researchers attempt to minimize bias in recruitment techniques at the same time as gathering samples that are as large as possible. Notably, Sumnall and Cole (2005) reported that the strength of the association between Ecstasy use and higher levels of depressive symptoms tended to decrease as sample sizes increased. Furthermore, none of the studies that have employed samples of 20 or more participants have found significantly higher depression scores in Ecstasy users in comparison to cannabis or polydrug controls (de Almeida & Silva, 2005; Milani et al. 2004; Roiser & Sahakian 2004; Thomasius et al. 2003; Daumann et al. 2001; Dughiero, Schifano, & Forza, 2001; Parrott et al. 2001).

Another potential confound that cannot be removed by controlling for use of drugs besides Ecstasy is that the concomitant use of Ecstasy and other drugs may affect MDMA-induced neurotoxicity. Large scale studies have reported that heavy Ecstasy users also commonly use other illicit drugs heavily, such as LSD (lysergic acid diethylamide) and amphetamine (Scholey et al. 2004; Parrott et al. 2001). Importantly, when Ecstasy is taken in combination with other illicit drugs, its adverse effects may worsen. First, the co-use of MDMA and amphetamine may enhance MDMA-induced serotonergic deficits (Gouzoulis-Mayfrank & Daumann 2006; Cole & Sumnall 2003). Second, experimental studies in rats have indicated that the activation of

5-HT_2 receptors is in part responsible for MDMA-induced serotonergic deficits (Gudelsky, Yamamoto & Nash 1994; Nash, Meltzer & Gudelsky 1990; Schmidt et al. 1990). Since LSD is a 5-HT_2 receptor agonist, the combined use of LSD and MDMA also may increase MDMA's adverse effects (Gudelsky, Yamamoto & Nash 1994). Given all of this information, it may be useful to question participants about the use of Ecstasy and other drugs within the same time frame and then probe for an association between those co-occurrences and depressive symptoms. Coincidentally, in three studies which included two different groups of Ecstasy users (current and former Ecstasy users), the Ecstasy user group in each study that had the highest level of LSD and amphetamine use also had the highest mean depression score (Roiser & Sahakian 2004; Thomasius et al. 2003; Morgan et al. 2002).

A few studies that misinterpreted results from tests of depression already have been discussed (McCardle et al. 2004; MacInnes, Handley & Harding 2001). Additionally, de Win and colleagues (2004) compared the BDI to the Composite International Diagnostic Interview and stated, "BDI, on the other hand, is more sensitive because of its gradual scale including both sub-clinical and clinical scores. BDI scores from 0 to 9 are considered to be within the normal range." In fact, Beck and colleagues (1961) did not differentiate between subclinical and clinical scores with the cut score guidelines given for the BDI. They merely suggested that scores from 0 to 9 represent the nondepressed range in patients already diagnosed with a psychiatric disorder, and they did not address what these scores represent in relation to a nonclinical sample. In a review of over two decades of research with the BDI, Beck, Steer and Garbin (1988: 78) stated that "the correlations of the BDI with other symptom measures in nonclinical subjects are sufficiently high to warrant caution in interpreting findings as indicative of depression in such populations." For example, BDI scores have been shown to be positively correlated with lower levels of education, adjustment difficulties, social undesirability, loneliness, vocational disappointment, anxiety, and stress (Beck, Steer & Garbin 1988). Similar to the BDI, Beck, Steer and Brown (1996: 6) stated in reference to the BDI-II that the test "was developed as an indicator of the presence and degree of depressive symptoms consistent with the DSM-IV, not as an instrument for specifying a clinical diagnosis." Thus, it would be inappropriate to classify nonclinical samples qualitatively according to cut score guidelines that were recommended for quantitatively measuring levels of depression in clinically diagnosed patients. The mistakes mentioned above highlight the need for researchers to be cautious in their interpretation of test results.

CONCLUSIONS

MDMA is likely to cause serotonergic deficits in humans at some dose level, and this may have a long-term negative impact on mood. Eleven out of 22 studies have reported significantly higher depression scores in Ecstasy users in comparison to control participants. However, only three studies ultimately have revealed significantly higher depression scores in Ecstasy users in comparison to cannabis or polydrug controls. Furthermore, most studies have suffered from methodological flaws, possibly including small sample sizes and comparison groups that did not control adequately for illicit drug use besides Ecstasy. Finally, the levels of depressive symptoms that have been found in Ecstasy users generally have not been shown to be much higher than those found in normative groups such as college students and the general population.

In conclusion, the evidence for an association specifically between recreational Ecstasy use and higher levels of depressive symptoms is thus far weak and unconvincing. Currently, the most that can be said with confidence is that the frequent concomitant use of Ecstasy and other illicit drugs has been shown to be associated with higher levels of depressive symptoms. Possible causes of this association include polydrug use in general, MDMA-induced serotonergic deficits, individual effects of illicit drugs besides Ecstasy, combined effects of MDMA and other illicit drugs, and preexisting differences in the levels of depressive symptoms in Ecstasy users. These potential causes are not mutually exclusive, and it is possible that they all contribute to higher levels of depressive symptoms in Ecstasy users. Regardless of the causative factors involved, however, frequent Ecstasy users are at particular risk for the development of higher levels of depressive symptoms, given the fact that they typically use other illicit drugs frequently as well.

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