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Psychiatric disorders in Ecstasy (MDMA) users: a literature review focusing on personal predisposition and drug history

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3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) has been implicated in the onset of a number of psychological disorders and associated with a number of psychiatric symptoms that have persisted after cessation of the drug. This paper is a review of the published psychiatric case studies from the last 10 years involving MDMA. Only 24% of patients had a previous psychiatric history and 34% had a psychiatric illness amongst first degree relatives. The percentage of patients not having had a personal or family history of psychiatric illness and the temporal relationship between MDMA ingestion and the experience of recurring symptoms strongly suggest a causal relationship between the drug and neuropsychiatric manifestations. Further supporting evidence comes from several studies using non-clinical samples. Ecstasy users that don't present themselves in healthcare settings as having clinical symptoms have significantly higher scores on certain subscales of the SCL-90 compared with Ecstasy-naive controls, with higher pathology scores in heavier Ecstasy users. The full-blown psychiatric cases may represent the broad end of this problematic spectrum.

KEY WORDS — Ecstasy; psychopathology; problematic; recreational; polydrug

INTRODUCTION

3,4-methylenedioxymethampethamine (MDMA or Ecstasy) is a popular recreational drug, due to the easily controllable emotional state it gives. MDMA has been associated with a number of psychological disorders and psychiatric symptoms, which often persist after cessation of the drug; these include panic attacks (Whitaker-Azmitia and Aronson, 1989), depression (Cohen, 1996), flashbacks (Creighton *et al.*, 1991), psychosis (Vaiva *et al.*, 2001), paranoid ideation (McGuire and Fahy, 1991) and suicidal ideation (Benazzi and Mazzoli, 1991). The fact that MDMA is a prominent feature in many reported adverse psychiatric cases suggests that MDMA's pharmacological properties play a role in the development of such disorders. The question arises whether there is a causal link between Ecstasy use and the development of psychiatric disorders or whether MDMA exacerbates a predisposed neurological condition in individuals. This paper attempts to address this question by reviewing all published psychiatric cases from the last 10 years where MDMA has been the prominent feature and looking at further new evidence of clinical symptoms in a non-psychiatric population.

PSYCHIATRIC CASES

Numerous case studies where psychiatric symptoms have developed where MDMA use has been a prominent feature are summarised in Table 1. The adverse symptoms, which vary in nature and intensity, are most in behavioural domains that are putatively influenced by brain serotonin. Of these cases 29% involve psychotic symptoms, 26% anxiety and panic attacks, 26% delusions, hallucinations or visual illusions and a further 16% involve some form of depression. The varying persistency of the psychiatric disorders suggests that Ecstasy can cause long-term neurotoxicity, with symptoms evident long after Ecstasy use has been

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Table 1. Summary of 38 case studies from a clinical sample in the last 10 years where Ecstasy appears to have been a prominent feature

Reference	Symptom or disorder	Age, Sex	Psychiatric history	Psychiatric illness among first degree relatives	Duration of MDMA use
Teggin (1992)	Hysterical dissociative state followed by mild expressive aphasia	32, F	?	?	1 occasion
Cohen & Cocores (1997)	Perpetual neuropsychotic symptomatology	17, M	None	?	1 occasion
Cohen (1996)	Adverse symptomatology incl. persistent depressive episodes	22, F	None	?	6 years
McGuire and Fahy (1991)	Paranoid symptoms	28, M	Amphetamine psychosis	Schizophrenia	2–10 per night for 18 months
	Paranoid delusions	22, M	None	Unknown (adopted)	2 years
Cassidy and Ballard (1994)	Paranoid psychosis	21, M	None	None	1–2 per week for 6 months
Series *et al.* (1994)	Paranoid psychosis	24, M	None	None	2 in 1 month
Keenan *et al.* (1993)	Paranoid psychosis	17, M	None	None	1–2 per week for 5 months
Bone *et al.* (2000)	Paranoid psychosis	24, M	Bad manners & violent conduct	?	5 every weekend
Williams *et al.* (1993)	Psychosis	18, M	None	Psychotic depression & paranoid delusions	1/4 tablet on occasions
Creighton *et al.* (1991)	Psychosis	22, M	None	None	4–7 per week for 4 months
Vaiva *et al.* (2001)	Acute psychosis	26, M	Moderate anxiety disorder	?	1 tablet
Schifano (1991)	Chronic atypical psychosis	24, M	None	None	150 over 4 years
Milas (2000)	Acute psychosis with aggressive behaviour	26, ?	?	?	?
Spatt *et al.* (1997)	Psychotic episode with ongoing pure amnesic syndrome	20, F	None	None	1/2 tablet
Cassidy & Ballard (1994)	Hallucinogenic delusional disorder	17, M	None	None	2–3 per week for 4–6 months
McGuire *et al.* (1994)	Depersonalisation/hallucinations	19, M	Cannabis & LSD-induced hallucinations	Drug abuse	Less than 1 week
	Delusions/hallucinations	26, M	None	Alcohol abuse	2 years
	Delusions	24, M	Paranoid ideation	None	7 months
	Delusions	30, M	None	Personality disorder & drug abuse	13 months
	Delusions/illusions	21, M	Transient paranoid psychosis	Depression	1 year
	Delusions/hallucinations	20, M	Paranoid ideation	None	2 years
	Illusions/hallucinations	18, F	None	None	6 months
Creighton *et al.* (1991)	Flashbacks & anxiety symptoms	22, F	None	None	2 in 1 week
	Flashbacks & anxiety symptoms	17, M	None	None	
McGuire *et al.* (1994)	Delusions/panic attacks	32, M	Paranoid ideation	Depression	3 months
	Panic attacks/flashbacks	18, F	None	None	4 months
	Panic attacks/depersonalisation	22, F	None	Panic disorder	3 years
Pallanti & Mazzi (1992)	Panic disorder & agoraphobic avoidance	27, M	None	None	20 in 10 months
	Panic disorder & agoraphobic avoidance	21, M	None	None	3 in 6 months
	Panic disorder & agoraphobic avoidance	28, M	None	None	1 per 2 months for 2 years
McCann & Ricaurte (1992)	Panic disorder	23, M	None	None	?
Windhaber *et al.* (1998)	Panic disorder	23, M	None	None	?
Series *et al.* (1994)	Anxiety & depression	23, F	None	Depression	1–2 for 2 months
Teggin (1992)	Major depressive disorder	48, M	?	?	6 occasions
McGuire *et al.* (1994)	Depression	38, M	None	Depression & drug and alcohol abuse	1 year
Benazzi & Mazzoli (1991)	Depression with suicidal ideation	23, M	None	None	1 on 4 occasions
Cohen (1996)	Depression & suicide	17, M	?	?	1 tablet

discontinued (Cohen, 1996; McCann and Ricaurte, 1992; Schifano, 1991; Windhaber, *et al.*, 1998).

It is difficult to draw any conclusions comparing Ecstasy use amongst these individuals, due to lack of documentation, but the amounts recorded vary greatly from 0.25 tablets (Williams *et al.*, 1993) up to 10 tablets per night (McGuire and Fahy, 1991). The duration of usage also varies extensively, from just the one occasion (Cohen, 1996; Teggin, 1992; Cohen and Cocores 1997; Vaiva *et al.*, 2001; Spatt *et al.*, 1997) to 6 years (McGuire and Fahy, 1991). The majority of patients appear to be male (75%), yet this may reflect the general pattern of drug usage.

Attention should be drawn to the interpretative difficulties of these case studies. The anecdotal nature of case reports makes it difficult to determine the risk to the average recreational user. There is the suggestion that the basis of the disorder already existed before Ecstasy use occurred, since poor premorbid adjustment is associated with increased drug use. The mean age of the sample (24 years) is in the age range when the first episode of psychiatric illness is likely to occur. It could also be possible that a genetic predisposition for a neuropsychiatric illness may exist in these individuals or that a personal history of psychiatric problems increases their likelihood of the development of Ecstasy-induced disorders. A review of 13 case reports by McGuire *et al.* (1994) reported that a psychiatric illness had occurred among first-degree relatives of approximately 50% of patients. However, the current review found that only 24% of patients had a previously diagnosed psychiatric illness and that only 34% had a family psychiatric history.

Additional evidence suggesting a relationship between Ecstasy use per se and psychiatric problems are the studies by Series *et al.* (1994), McGuire *et al.* (1994) and Milas (2000). They present cases where a reoccurrence of symptoms occurred after further Ecstasy use. In addition, Creighton *et al.* (1991) reported a patient who was free of psychiatric symptoms for 8 months, but after taking a further 4 doses of Ecstasy the psychological symptoms returned. The individual reported by Cassidy and Ballard (1994) stated that there was a close relationship between symptom improvement and Ecstasy cessation. Additional support comes from a large-scale clinical survey (Schifano *et al.*, 1998), where the longer-term polydrug users, who had consumed an average of 43 Ecstasy tablets, were found to be at a considerably higher risk of developing a psychopathological disorder than the patients who took smaller amounts (average = 3). Most importantly, these patients specifically denied the presence of these psychiatric disturbances prior to MDMA use. The high percentage of patients who do not have a personal and family history of mental illness and the temporal relationship between MDMA ingestion and the experience of recurring symptoms after additional Ecstasy consumption strongly suggest a cause and effect relation in most of the reported cases.

NON-PSYCHIATRIC CASES

Ecstasy-related psychopathology has not only been shown in a clinical population. Recent research suggests that there may be other Ecstasy users who experience milder psychiatric disturbances but who do not contact health professionals. There is a growing body of evidence for this in studies of recreational users who don't present themselves to clinicians, general practitioners or drug services with clinical symptoms, yet who have significantly higher scores on a revised version of the SCL-90 (self-rating clinical symptom questionnaire) than Ecstasy-naive controls. The revised version of the SCL-90 includes 30 extra questions on various positive moods and life experiences, together with an 'Ecstasy side effects' factor.

Parrott *et al.* (2000b) surveyed a group of young people from a small town near Cork, Ireland. All volunteers completed a questionnaire on past drug use and the SCL-90. Heavy Ecstasy users reported significantly higher scores on several dimensions of the SCL-90 than the non-Ecstasy users. These included somatisation, obsessionality, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and appetite. Similar results were found in a large-scale survey of 768 volunteers from Italy and the UK (Parrott *et al.*, 2000a). Using the UEL drug questionnaire, the researchers placed participants in one of six groups, depending on their past drug use: non-drug users; alcohol and tobacco users; cannabis, alcohol and tobacco users; illicit polydrug users, but not of Ecstasy; light Ecstasy polydrug users; and heavy Ecstasy (20 + tablets) polydrug users. All participants completed the modified version of the SCL-90. There were significant differences between non-drug users and Ecstacy polydrug users on the somatisation, obsessive-compulsive, anxiety, anger/hostility, phobic anxiety, psychoticism and MDMA side effect scales. The highest pathology scores were found in the heavy Ecstasy polydrug users and to a lesser extent in the light Ecstasy polydrug users.

It should be emphasised that in these studies polydrug use was a general characteristic of Ecstasy use. The heavier the Ecstasy use, the heavier the polydrug use. Symptom profiles were similar among the

polydrug users who hadn't taken Ecstasy, thus the high pathology scores for the heavy Ecstasy users could simply be a profile of polydrug use in general. Support for this comes from a study by Fox *et al.* (2001), which reported that psychological symptoms in such individuals were unrelated to Ecstasy use. This study examined the differences between 'self-reported problem' (psychological, emotional and somatic problems) and 'non-problem' Ecstasy users in relation to both consumption and premorbid life adjustment variables. The problem Ecstasy group had significantly higher scores on all scales of the SCL-90, yet their self-perceived problematic use was related not to their drug use but to negative interpersonal relationships prior to taking the drug and less socially orientated motivations for using the drug. However, this study used a relatively small sample of Ecstasy users. Milani *et al.* (2000) showed there was a significant positive correlation between the amount of Ecstasy pills consumed by polydrug users and their scores on the anxiety, phobic anxiety and psychoticism scales. Furthermore, in a study by Milani *et al.* (2001) of 234 Ecstasy polydrug users, 'problematic' users had higher pathology scores on several subscales of the SCL-90, compared with the 'non-problematic' users. But their perceived problems were related to the greater lifetime consumption of Ecstasy and the number of pills taken in a single occasion. This suggests that there may certainly be an association between Ecstasy use and psychopathological symptoms. What needs to be addressed is whether the SCL-90 scores of these individuals lie within the clinical range.

Caution should be taken when interpreting the results of these studies, because a number of methodological issues need to be addressed. These include inadequate sampling techniques through self-referral. The different sample sizes of the studies also leads to inconsistencies, with small sample sizes having lesser statistical power, which is the case in most MDMA-related research. Data were reliant on subjective reports in both the drug use and SCL-90 responses, which may contain inaccuracies. There is also the uncertainty of the pharmacological constituents of the Ecstasy tablets: numerous reports suggest varying levels of MDMA or related compounds in Ecstasy tablets, with some tablets containing other active ingredients (caffeine, amphetamine) and some containing none at all (Curran, 2000). Chemical analysis of street Ecstasy has shown that tablets are unlikely to be pure MDMA. Baggott *et al.* (2000) identified the most common drug other than MDMA in street-bought Ecstasy tablets as the antitussive dextromethorpan (DXM), which in high doses can cause serious adverse reactions, including phencyclidine-like psychosis (Dodds and Reval, 1967). Finally, as already mentioned, it is difficult to determine which, if any, of the previously used drugs are responsible for the manifestation of the symptoms, since Ecstasy users are almost always polydrug users.

Despite the discrepancies in the research non-clinical populations, there is still evidence that MDMA use is significantly related to psychiatric symptoms. Many of the reported symptoms are parallel to the disorders presented in the case studies. It may be that in the individual clinical cases the patients' symptoms developed to such an extent that they sought professional help, and thus they are at the broad end of the problematic spectrum.

CONCLUSION

Given that the total number of people in Britain who have tried Ecstasy is approximately 5 million, if Ecstasy were directly responsible for causing psychiatric symptoms a greater number of reported psychiatric cases would be expected. With adverse individual cases it is more likely that the individual has a pre-existing vulnerability to psychiatric disturbances or low serotonin levels prior to Ecstasy consumption. However, this review shows that there is some evidence that MDMA may cause psychopathology in recreational users. This evidence comes from the reports of psychiatric disorders among individuals who have consumed large quantities of Ecstasy (McGuire and Fahy, 1991; Creighton *et al.*, 1991) and from reports of psychological symptoms in Ecstasy users that have not manifested to such a degree that they seek professional help.

The suggestion that the intensity of dosing of Ecstasy is crucial in the development of psychopathology has also been made. Individuals who have taken a larger number of MDMA tablets have a higher risk of developing psychiatric disorders (Milani *et al.*, 2000; Schifano *et al.*, 1998) and are more likely to report having been inpatients (Hammersley *et al.*, 1999).

Attention should be drawn to the fact that more often than not recreational Ecstasy users take other drugs, such as cannabis, psychostimulants and hallucinogens. Polydrug use itself may lead to different types of psychobiological problems. Milani *et al.* (2000) found a correlation between other drug use and pathology scores, and Parrott *et al.* (2000a) showed that heavy Ecstasy polydrug users have the highest pathology scores. Because of these constraints it may be beneficial to assess the consequences of

Ecstasy use within the wider context of recreational drug use as a whole.

Ideally a prospective study should be done that combines detailed psychiatric and psychological assessments with functional neuroimaging techniques, to clarify the relationship between the intensity of Ecstasy dosing and the resulting psychological effects. However, the illegality of Ecstasy use and ethical constraints mean that such a study is unlikely.

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