

Long term psychiatric and cognitive effects of MDMA use

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Abstract

Clinical case reports suggest that regular MDMA use can be associated with chronic psychiatric symptoms which persist after the cessation of drug use. Neuropsychological comparisons of regular MDMA users and controls also suggest that MDMA use may lead to memory deficits, with other cognitive processes relatively unaffected. This paper reviews these studies and discusses a number of methodological issues that impact on the interpretation of the findings. Methods for examining the biological effects of MDMA use in man are also outlined. Future research should clarify whether MDMA use has long term psychological effects, and if these are related to changes in central serotonergic function.

Keywords: Ecstasy; MDMA; Psychiatry; Neuropsychology

1. Introduction

The other presentations have covered the epidemiology, toxicology and acute effects of 3,4-methylenedioxymethamphetamine (MDMA). In this paper I will focus on the long term psychiatric and cognitive effects of MDMA use.

2. Psychiatric cases

The first data that indicated that MDMA use might lead to chronic psychiatric symptoms came from descriptive reports of patients who presented to clinicians. These patients had psychiatric complaints which appeared to have developed in the

context of MDMA use, and which persisted after they stopped taking the drug. In the UK, 'ecstasy' (MDMA) use became widespread in the late 1980s in conjunction with a dramatic growth in the popularity of new forms of dance music. Young adults attending dance events ('raves') often took MDMA to enhance their appreciation of the experience. A number of reports of individuals who had developed psychopathology in association with regular MDMA use appeared over the next few years, with most describing a psychotic syndrome (Creighton et al., 1991; McCann and Ricaurte, 1991; McGuire and Fahy, 1991; Schifano, 1991). However, subsequent reports and our own case series suggested that MDMA use could also be associated with other psychiatric symptoms, including panic disorder (Pallanti and Mazzi, 1992; McGuire et al., 1994a), depersonalisation (McGuire et al., 1994b), depression (Benazi

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and Mazzoli, 1991; McGuire et al., 1994a), 'flash-backs' (Creighton et al., 1991; McGuire and Fahy, 1991), visual distortions and hallucinations (McGuire et al., 1994a), and obsessive-compulsive symptoms (Cassidy and Ballard, 1994; Table 1).

These symptoms appeared to be distinct from the more common acute psychiatric effects of MDMA (Solowij, et al., 1992; Curran and Trivil, 1997), in that they were often not linked to the timing of each dose, and were chronic, persisting long after MDMA use had discontinued.

While the media and the relatives of cases can sometimes be quick to conclude a causal relationship between MDMA use and psychiatric disturbance, in practice it is difficult to determine whether the MDMA use actually triggers the symptoms. Patients who are already psychotic or depressed may be more inclined to experiment with psychoactive drugs, as may individuals with personality disorders. Moreover, the population in which MDMA use is most prevalent (young adults) is also the one in which psychiatric disorders are most likely to develop, independent of drug use. Additional grounds for caution in interpretation are the absence of means of verifying or quantifying previous MDMA use (although this may now be feasible with hair drug analysis), and the fact that most MDMA users also use other

psychoactive drugs such as cannabis, amphetamines, LSD and cocaine, which can themselves have psychiatric effects (Connell, 1958; Vardy and Kay, 1983; McGuire et al., 1994b).

If MDMA use does lead to chronic symptoms, this may be more likely in subjects who are already predisposed to psychiatric disorders. We found that around 50% of cases in a series of MDMA users with chronic psychiatric symptoms had a first degree relative with a psychiatric illness, and about 50% had previously experienced transient psychiatric symptoms following use of other illicit drugs (McGuire et al., 1994a). Moreover, in cases who developed psychosis, the psychopathology was similar to that in psychosis in substance-naïve patients suffering from schizophrenia or bipolar illness. These observations are consistent with MDMA triggering the onset of a psychiatric disorder in subjects with a pre-existing diathesis.

As the subjects described in these studies experienced symptoms that were troubling enough for them to seek clinical help, they may represent the severe end of a spectrum of psychiatric problems associated with MDMA use: there might be other users who experience milder psychiatric disturbances who do not contact health professionals. The latter would be consistent with the prevalence of transient depressive symptoms a few days after MDMA use, which do not usually lead users to seek psychiatric help (Solowij et al., 1992; Curran and Trivil, 1997).

Table 1

Persistent psychiatric symptoms that have been associated with MDMA use

Symptom/disorder	Reference
Psychosis	McGuire and Fahy, 1991; Schifano, 1991; Creighton et al., 1991; McCann and Ricaurte, 1991; McGuire et al., 1994a
Panic attacks	Pallanti and Mazzi, 1992 McGuire et al., 1994a
Depersonalisation	McGuire et al., 1994a
Depression	Benazi and Mazzoli, 1991; McGuire et al., 1994a
Flashbacks	Creighton et al., 1991; McGuire and Fahy, 1992
Visual distortions and hallucinations	McGuire et al., 1994a
Obsessive-compulsive symptoms	Cassidy and Ballard, 1994

3. Comparisons of users and non-users

An alternative to studying subjects who present with frank psychopathology is to survey MDMA users in the community and compare them with non-users. This approach has the advantage that it is likely to sample subjects who are a more representative group of the total population of MDMA users. Studies of this type have usually incorporated a neuropsychological assessment which permits the identification of cognitive deficits which the subject may be unaware of. Most have found few differences in psychiatric morbidity between MDMA users and non-users,

Table 2
Studies reporting impaired memory function in MDMA users

Study	Tests of memory	Control group(s)
Krystal and Price, 1992	Initial and delayed paragraph tests of Weschler memory scale	None
Morgan, 1998	Immediate and delayed recall of Rivermead behavioural memory test	Other drug users and drug-naive subjects
Parrot et al., 1998	Immediate and delayed word recall	Novice MDMA users and MDMA-naive subjects
Bolla et al., 1998	Immediate verbal and delayed visual recall	Drug-naive subjects

but several have reported impaired performance on memory tests (Krystal and Price, 1992; Bolla et al., 1998; Parrot et al., 1998; Morgan, 1999; Table 2). Different studies have employed different means of assessing memory, and the number of subjects examined has generally been modest. Nevertheless, most have found memory deficits despite normal performance on tasks that engage other cognitive processes, suggesting that there may be a selective impairment of memory in MDMA users. In some studies, MDMA users have been contrasted with subjects who have never used illicit drugs: as MDMA users typically use multiple drugs, any differences on testing might thus be related to these substances rather than MDMA. However, memory deficits also appear to be evident in MDMA users relative to other drug users (Morgan, 1999). Moreover, these deficits do not seem to be an acute effect of MDMA, as they are evident in abstinent ex-users (Bolla et al., 1998). Larger studies explicitly focused on mnemonic processing should confirm whether there is indeed a selective cognitive impairment, and clarify if this is specific to a particular component or form of memory. Increased impulsivity has also been reported in MDMA users (Morgan, 1998), although an earlier study described the opposite finding, albeit using a different instrument (McCann et al., 1994).

4. Biological investigations

The main measure of brain dysfunction that has been used in MDMA users is the neuroendocrine response to serotonergic probes. Some

studies have reported a blunting of prolactin release in response to L-tryptophan (Price et al., 1988) or D-fenfluramine (Gerra et al., 1998) in MDMA users relative to controls, but others have not (McCann et al., 1994). Functional neuroimaging offers a more direct means of investigating central serotonergic processing. One approach is to use single photon or positron emission tomography (SPET or PET) to examine the distribution of radio-ligands that bind to 5HT receptors or the 5HT transporter. A recent PET study of McN-5652, which is thought to bind to the 5HT transporter, suggested that its binding was reduced in MDMA users (McCann et al., 1998). However the number of subjects was modest, individuals with personality disorders were not excluded, and it is unclear whether the controls had used substances other than MDMA. Nevertheless, this first investigation indicates that neuroimaging can be used to assess whether MDMA use damages brain serotonergic function *in vivo*, and further studies of this type are likely to follow. An alternative approach is to use neuroimaging to examine the effects of experimentally manipulating serotonergic function on brain activation during cognitive tasks. This method involves comparison of activation following acute administration of a serotonergic probe (such as D-fenfluramine) and placebo, and has previously been used to study the modulatory effects of 5HT on normal cognitive processing (Grasby et al., 1992). We are currently using functional magnetic resonance imaging (fMRI) to study the effects of serotonergic probes in MDMA users and controls (Reed et al., 1999).

5. Conclusions

Clinical case reports suggest that regular MDMA use can be associated with chronic psychiatric symptoms which persist after the cessation of drug use. However, it is difficult to determine whether MDMA use is directly responsible, triggers symptoms in subjects predisposed to mental illness, or is incidental. In any event, severe long term psychiatric disturbances following MDMA use seem uncommon relative to the large numbers of people who use MDMA. Neuropsychological comparisons of regular MDMA users and controls suggest that MDMA may be associated with memory deficits, with other cognitive processes unaffected, although there have been only a limited number of studies, each using different methods of assessment. It is assumed that these putative clinical and cognitive sequelae are secondary to an effect of MDMA on brain serotonergic function, but the relationship between psychological and biological changes in MDMA users has yet to be determined. Future research, involving detailed psychiatric and psychological assessments combined with functional neuroimaging, should define this relationship and clarify whether MDMA use leads to long term neurocognitive deficits in man.

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