

MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients

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Abstract

The present study examined the characteristics and the possible psychopathological consequences of ecstasy (MDMA, 3,4-methylenedioxyamphetamine) use. One hundred and fifty consecutive patients, presenting to the Padova (Italy) Addiction Treatment Unit and who had taken ecstasy on at least one occasion, were examined and studied using a semi-structured interview. Ninety-five percent of the patients had experimented with another drug of abuse at least once in their lifetime. Ecstasy was mainly self-administered at disco clubs, and reported acute psychoactive effects confirmed previous reports. Fifty-three percent of the total sample were found to be affected by one or more psychopathological problems; the most frequent were depression, psychotic disorders, cognitive disturbances, bulimic episodes, impulse control disorders, panic disorders, social phobia. Those who were free from any psychopathological problem, compared to the others, had taken a smaller number of MDMA tablets in their lifetime, for a shorter duration and with a lower frequency. Again, they were less likely to have used alcohol together with ecstasy but more likely to have used opiates. Longer-term, larger dosage (acute or cumulative) MDMA consumers were found to be at high risk of developing psychopathological disturbances. The results are discussed, taking into account both the ecstasy suggested serotonin (5-hydroxytryptamine) neurotoxicity and the various methodological issues pertaining to this kind of large-scale clinical study describing people for whom MDMA is far from being the only drug of abuse. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

The amphetamine analog 3,4-methylenedioxyamphetamine (MDMA, 'ecstasy') is a drug of abuse that has both hallucinogenic and excitatory properties.

MDMA has become increasingly popular in the last years all around Europe (Grob et al., 1996), although its use has been associated, in animals, with some

neurotoxic sequelae (Steele et al., 1996) and in humans with lasting psychopathological disturbances (Pallanti and Mazzi, 1992, Solowij, 1993, Schifano and Magni, 1994, Henry, 1997). It has been suggested (Henry, 1997) that it will take many years to understand fully the real contribution of MDMA abuse to the onset of psychiatric disturbances. Most of the scientific papers pertaining to MDMA issue are made up by single case reports or case series; the number of large-scale surveys is scant, possibly because MDMA consumers are traditionally not used to attending Public Health Services. The reports characterized by large samples are made up

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of people administered anonymous questionnaires or interviewed in non-clinical settings (Peroutka, 1987, Solowij et al., 1992, Forsyth, 1996). However, with these methods, control is lost over who answers the questionnaires themselves, and the possibility of making a thorough clinical examination of the patient seems remote.

The present report describes a large-scale sample of polydrug (including MDMA) consumers consecutively attending a Public Health Addiction Treatment Unit (preliminary observations have been described elsewhere; Schifano, 1991, Schifano and Magni, 1994, Schifano, 1995), with the aim of better understanding both the characteristics and the possible psychopathological consequences of ecstasy abuse in the context of multiple drug consumption.

2. Materials and methods

In the period between July 1991 and June 1996, 150 ecstasy consumers (all who had taken ecstasy on at least one occasion, consecutively chosen between all those who had presented for various reasons to the Padova Addiction Treatment Unit in northern Italy for help and/or referral) were studied. All of the patients underwent complete medical and psychiatric history and examination. Additional information was obtained from relatives and friends. Urine analyses (which confirmed, on the whole, what the patients themselves reported in terms of use of other drugs) were also performed.

All of the 150 patients were studied by means of a semi-structured interview (Schifano et al., 1997) aimed at gathering information about sociodemographic data (age; sex; marital status; schooling level; occupational status; judiciary problems), characteristics of ecstasy consumption (age at first self-administration; possible use of the drug in the last 3 months; usual place of consumption; smallest, average and largest dosage of ecstasy self-administered on a typical occasion; estimated total number of tablets taken in lifetime; time elapsed between two different administrations; average price and place in which the drug was bought), perceived psychological post-drug effects and their duration. There were also questions about the lifetime consumption of drugs other than ecstasy itself and about the drugs taken together with ecstasy (on the same occasion). Lastly, all of the patients were specifically assessed for the possible (subsequent to MDMA use) presence of psychopathological syndromes at the level of those areas thought to be biologically related to serotonin (5-hydroxytryptamine, 5-HT) dysfunctions (McCann et al., 1994): namely, mood, anxiety, sleep, aggression, impulsivity, cognition and appetite. The formal psychiatric examination of the patients was car-

ried out by a single, unblind to drug use, psychiatrist (F.S.); a diagnosis of a specific disorder was made if the patient met the corresponding criteria of DSM-III-R (American Psychiatric Association, 1987), except for cognitive impairment. For this area, the clinical assessment followed a careful examination of what was reported by the patients themselves and was corroborated, for a sub-sample of these patients ($N=10$), by the use of psychometric tests (Milani, 1997). These patients were compared, in a parallel group design, with 20 normal subjects who did not report any lifetime consumption of illegal drugs and whose age and schooling level were not different from those of the study group. Both groups had been administered a battery of tests assessing memory (Rivermead Behavioural Memory Battery; Wilson et al., 1990) and planning abilities (Tower of London Test; Shallice, 1982). We compared, with respect to the different parameters described, those patients who had been diagnosed with at least one psychopathological disorder and those who, on the basis of the psychiatric examination, were free from any problem.

The statistical differences were assessed using the chi-square test, the Student *t*-test and the non-parametric Mann–Whitney test. To determine the independent association of the consumption of ecstasy with the appearance of psychopathological disturbances, we calculated odds ratios from a single forward stepwise multiple logistic regression model. The presence of at least one psychopathological disorder was the dependent variable and the number of MDMA tablets in lifetime, alcohol and opiate consumption were the primary independent variables (adjusted for: age; sex; weight; frequency and duration of consumption of MDMA; use of benzodiazepines, cannabinoids, cocaine and other substances). All statistical analyses were conducted using the SAS Statistical Analysis Package.

3. Results

Most (83%) of the 150 patients were males and the mean age was 23.2 ± 4.5 years. Thirty-five percent of the sample had been attending the school for more than 8 years; 48% of the patients were employed, 31% were unemployed and 21% were students. Only 6% of the sample were married.

Most of the patients reported that they had taken ecstasy at disco clubs, where they mostly bought it at a mean price of about UK £18 for each tablet. Patients' median age at the time of the first consumption of ecstasy was 19 years. The whole sample had been taking a total estimated (median) number of 11 tablets for a 32.5 week median period, but about one in four subjects had taken larger amounts (more than 50) of tablets in their lifetime. Fifty percent of the people took

Table 1
Main psychopathological disturbances subsequent to MDMA use

	No.	% of the whole sample
Depression	48	32
Psychotic disorders	42	28
Cognitive impairment	41	27
Bulimia	36	24
Impulse control disorders	21	14
Panic attacks	18	12
Any of the above	79	53

no more than one tablet on each occasion. For almost all (95%) of the patients, MDMA was not the only drug of abuse that they had experimented with at least once in their lifetime. Fifty-eight percent of the people had ever used opiates, but in the sample were also well represented those who had ever used different stimulants and psychedelics. In the same evening, together with MDMA, people took other drugs, mostly alcohol (39%), tetrahydrocannabinols (THC; 31%), other stimulants and psychedelics (24%). The acute pleasurable psychoactive effects most frequently reported after MDMA ingestion were euphoria, sense of well-being, and increase in social contacts. Other reactions included visual and auditory hallucinations, impulsivity, insomnia, rise in body temperature. In the group of those who had been diagnosed with at least one psychopatho-

logical disturbance, compared to those who were free from any disorder, there was a significantly higher prevalence of sense of well-being (78.3 vs 56.7%; $P < 0.034$), of increase in social contacts (84.4 vs 52.4%; $P = 0.001$) and of visual hallucinations (96.0 vs 56.8%; $P < 0.001$). However, those who reported a sense of well-being, increase in social contacts and visual hallucinations had taken a higher median number of MDMA tablets (respectively: 37.5 vs 8, $P = 0.002$; 47.0 vs 8, $P = 0.001$; 85 vs 12, $P < 0.001$) compared to those who had not reported these reactions.

Seventy-nine people (53% of the total sample) were diagnosed as affected by one or more psychopathological disorders (the patients specifically denied the presence of these disturbances prior to the beginning of MDMA use; see Table 1). The most represented were depression, psychotic disorders and bulimic episodes (with craving for carbohydrates and/or chocolate). A cognitive impairment (memory and concentration problems) was reported by 41 subjects (27% of the sample). The MDMA patients, with respect to the 20 control subjects, showed significant impairment at the level of the memory tasks ($P < 0.001$) and of planning abilities ($P < 0.005$). Patients affected by at least one psychopathological disturbance, compared to the others (Table 2), were younger (22.1 ± 3.6 vs 23.7 ± 5.9 years; $P = 0.046$), had taken a larger cumulative median number of tablets (47 vs 3; $P < 0.001$), with a higher fre-

Table 2
Main characteristics, MDMA-related behaviours and rates of lifetime use of different drugs of patients affected by at least one psychopathological disturbance (problematic users) and of those who were free from any psychiatric diagnosis (non-problematic users)

	Problematic users	Non-problematic users	Test	P
No.	79	71		
Sex				
Male	50%	50%	χ^2	n.s.
Female	68%	32%		
Age (years)	22.1 ± 3.6^a	23.7 ± 5.9	<i>t</i> -Test	0.046
Weight (kg)	65.1 ± 17.0	69.9 ± 13.9	<i>t</i> -Test	n.s.
MDMA use				
Age at first use (yrs)	19.1 ± 3.4	22.4 ± 5.3	<i>t</i> -Test	< 0.001
Lifetime intake (cps)	47 (20–125) ^b	3 (1–7.3)	M-W	< 0.001
Frequency (cps/wk)	1 (0.5–2)	0.4 (0.12–1)	M-W	< 0.001
Period (wks)	52 (26–104)	14 (1–52)	M-W	< 0.001
Largest single intake	3 (1.25–5)	1 (1–1)	M-W	< 0.001
Different drugs' lifetime use				
Benzodiazepines ^c	6%	1%	χ^2	n.s.
Opiates	78%	41%	χ^2	< 0.001
Cocaine	63%	56%	χ^2	n.s.
THC	78%	66%	χ^2	n.s.
Alcohol ^d	23%	47%	χ^2	0.003
Others (nitrites, LSD)	30%	57%	χ^2	0.001
Any of the above	96%	95%	χ^2	n.s.

^a Mean \pm S.D.

^b Median (1st–3rd quartile).

^c Non-medical use.

^d Only cases in which there was a problematic use of alcohol were taken into account.

M-W, Mann–Whitney.

quency (1 cp/week vs 0.4 cp/week; $P < 0.001$), for a longer duration (52 vs 14 weeks; $P < 0.001$) and a larger median number of tablets in the same evening (3 vs 1; $P < 0.001$). Again, they were less likely to have used opiates (40.5% vs 77.5%; $P < 0.001$) but more likely to have used alcohol (46.8% vs 22.5%; $P < 0.003$) or other drugs (mostly nitrites and LSD; 57% vs 29.6%; $P < 0.001$). To study this last issue in more depth, a further analysis of other drugs users versus non-users was done. In the group of other drugs users, those who showed psychopathological disorders, compared to those who were free from any disturbance, had taken a higher number of MDMA tablets (50 vs 5; Mann–Whitney test, $P < 0.001$) and the same result was observed in the group of non-users of nitrites and LSD (40 vs 2; Mann–Whitney test, $P < 0.001$). Again, in the group of people diagnosed with a psychopathological disorder, there was not any difference, in terms of number of MDMA tablets taken in lifetime, between other drugs users versus non-users (50 vs 40; Mann–Whitney test, n.s.). Lastly, the users of other drugs had taken a larger number of MDMA tablets in their lifetime compared to non-users (27.5 vs 6; Mann–Whitney test, $P < 0.001$).

With the logistic regression analysis it was found that only three variables were statistically related to the appearance of psychopathological disorders: (1) Those who had taken a larger number of MDMA tablets in their lifetime had a higher risk of eventual development of psychopathological disturbances (i.e. those who had taken three or more tablets had an odds ratio of 8.9); this ratio increased in people who had taken even larger number of tablets (i.e. those who had taken more than 11 tablets had an odds ratio of 17.4). (2) Those who had drunk alcohol together with MDMA had a risk 2.5 times higher, with respect to alcohol abstainers, of eventual development of psychopathological disturbances. (3) Lastly, opiate consumers were significantly less likely, with respect to opiate non-consumers, to show eventual psychopathological disturbances (odds ratio 0.2). To study this issue in depth, a further analysis of the opiate versus non-opiate users was done. Opiate users, compared to opiate non-users, were significantly older (respectively, 23.6 ± 5.5 vs 21.8 ± 3.7 years; $P = 0.026$), had consumed MDMA for the first time at an older age (21.4 ± 5.4 vs 19.4 ± 3.1 years; $P = 0.018$), had taken a smaller cumulative number of MDMA tablets in their lifetime (6 vs 27.5; $P = 0.015$) and were less likely to have consumed alcohol together with MDMA in the same evening (27.6 vs 48.3%; $P = 0.016$). Sex, age, weight, and use of the different other drugs (nitrites and LSD) were not statistically related to the appearance of psychopathological disorders.

4. Discussion

The present paper represents, to the best of our knowledge, the largest sample-size clinical contribution to the understanding of the characteristics of MDMA consumption, although in a context of polydrug abuse.

The results of this study confirm several of the findings pointed out by Solowij et al. (1992) and Forsyth (1996) in their samples. In particular, it is here emphasized that 'ecstasy' is almost exclusively consumed in dance clubs, during the weekend, to have 'fun'. Most 'ecstasy' consumers appear to have administered themselves only with moderate dosages and this may be due to the fact that 'positive' or pleasurable effects of drugs (which, in the present study, were more frequent in those who had taken larger number of tablets) decrease with continuous, frequent use. However, a non-negligible proportion of the sample showed a clearly dysfunctional use of the drug, consuming up to 13 tablets on one single occasion and an estimated lifetime cumulative number of 2000 tablets. The reported acute psychoactive effects of MDMA and the high rates of consumption of drugs with excitatory and/or hallucinogenic properties found can be interpreted in the light of choosing drugs that are suitable for the enjoyment of a night.

Two major findings have been related to alcohol (whose consumption, together with MDMA, increased the risk of eventual development of psychopathological disturbances) and opiates. We are convinced that the fact that opiate consumers showed a smaller psychopathological risk, with respect to the others, needs to be seen in terms of the population (polydrug abusers). In fact, we have found that opiate users reported a smaller cumulative number of MDMA tablets taken in their lifetime and a less frequent use of alcohol together with ecstasy with respect to non-opiate users, parameters which, per se, influenced the risk of eventual development of psychopathological disturbances. Again, the use of opiates may well have masked the possible presentation of the psychiatric symptomatology of the MDMA consumers.

In animals, including primates, MDMA causes initial release of serotonin (5-HT) followed by degeneration of 5-HT projections; the fine axons of dorsal raphe, associated with 5-HT₂ receptors, are especially vulnerable (Stone et al., 1988). The lowest effective dose of MDMA capable of producing a long-term depletion of cortical 5-HT in primates is 2.5 mg/kg (Finnegan and Schuster, 1989) (a dosage of about one to two tablets). Others (Green and Goodwin, 1996) have pointed out, in animals, that long-term effects require either a large single dose (10–20 mg/kg, i.e. 16 'ecstasy' tablets) or several lower doses. Also Solowij et al. (1992) emphasized that, in humans, the negative effects of MDMA are dose-related, in that their severity correlates with

both the total number of doses ever consumed and with frequency of use. The concentration of 5-HIAA (the metabolite of 5-HT) in lumbar cerebrospinal fluid (CSF) is substantially lower (Ricaurte et al., 1990) and serum prolactin response to L-tryptophan challenge is blunted (Price et al., 1989) in people with a history of MDMA use.

One could wonder why, if we have found roughly half of the patients interviewed (some of these clinical vignettes have been reported elsewhere; Schifano, 1991, Schifano and Magni, 1994, Schifano, 1995, Milani, 1997) affected by one or more psychopathological disturbances, problematic MDMA users are largely undetected in the community. Most of the problematic long-term MDMA users spontaneously self-referred to our Unit with problems that they perceived to be linked in some way to their chronic 'ecstasy' use; thus, to some extent, this sample could be considered 'biased' by the severity of disturbances. McCann and Ricaurte (1991) have suggested that psychopathological consequences may manifest only in susceptible individuals. Neurotoxic effects might not be readily evident for the most humans because of the 'redundance' and the robustness of neuronal systems (like the 5-HT one) subserving major brain functions: extensive neurotoxicity must be sustained before it becomes clinically detectable. In this sense, one can understand why longer-term, larger dosage (acute or cumulative) MDMA consumers were found, in the present study, to be at high risk. In those cases in which individuals developed symptoms after relatively small doses of MDMA used on rare occasions it is likely that a predisposition (or a pre-existing vulnerability to psychiatric disturbance) in combination with a drug that interacts with brain serotonin and catecholamine systems resulted in psychiatric difficulties.

Depression and psychoses are the disorders that we have most frequently observed, thus confirming the results of the large-scale study of Peroutka et al. (1988), who found depression to be one of the most frequent subacute symptoms after MDMA use. Both the high rate of cognitive problems self-reported by the patients in the present study and the suggestions derived from the data of the small sub-sample of MDMA patients administered the psychometric tests (a specific large-scale study aimed at the evaluation of the issue is going to be completed in our Unit) are worrying. It is worth noting that Krystal (1992) found, in a series of nine individuals with lengthy histories of MDMA abuse, poor performances on tasks assessing cognition, and this was found in patients who were not aware of their difficulties. Similar results have been replicated very recently in the UK; Curran and Travill (1997) used a parallel group design to compare 12 subjects who reported having taken MDMA with 12 subjects who reported having consumed only alcohol on the relevant

night. The same participants were then re-assessed the following day and again mid-week. The MDMA group showed significant impairments on the attentional/working memory tasks, compared with alcohol users. Again, Parrott et al. (1998) assessed the cognitive task performance in three groups of young people: 20 MDMA (ten regular and ten novice) users and ten control subjects. On immediate word recall and delayed word recall both groups of MDMA users recalled significantly fewer words than controls. We have commented elsewhere (Schifano and Magni, 1994) about the possible interpretation of anxiety disturbances and food preferences observed in these patients.

There are several possible limitations of the present study. First, virtually all of the people had used other drugs during their lifetime and/or together with MDMA itself. Again, due to the characteristics of recruitment, heroin abusers were overrepresented in the sample, and this population seems quite different from the one that attends the at-risk (disco clubs, rave parties) venues. Second, in the present study, there is not any 'control' group (i.e. one constituted by age- and sex-matched people who had never used drugs in their lifetimes and the other one given by people who had used drugs different from MDMA itself). Third, the data are retrospective and collected by a professional unblind to drug use and for these reasons subject to possible biases. Fourth, one could argue about the real content of MDMA in the 'ecstasy' tablets.

To the first possible criticism one could answer that it is really difficult, in clinical practice, to find people who had ever consumed, in their lifetime, only ecstasy. Even between those interviewed in the disco clubs, most of the subjects report to take, in the same evening, at least another psychoactive drug together with MDMA itself (Forsyth, 1996). Our group has recently administered a questionnaire (aimed at the evaluation of the lifetime consumption of different drugs) to 3200 students (14–19 years old) attending different high schools. We have found that about 10% of the people interviewed reported having taken MDMA at least once in their lifetime, but for none of the pupils had MDMA been the only illicit drug of abuse experimented with (manuscript in preparation). All of the addiction treatment units, at least in our (and in other Mediterranean) country, are attended by heroin abusers and this may have influenced some of the results of the present study. On the other hand, correct large-scale clinical studies are easier to be performed in formal settings (like the addiction treatment units) compared to what it is possible to do in the disco clubs. If the lack of proper 'control' groups may limit the validity of the present results, with the statistical methods used the putative role of the sole MDMA in its possible association with the psychopathological disturbances has been extracted. Prospective studies are, in the specific field of MDMA

use and abuse, substantially lacking, due to ethical and legal constraints. However, Grob et al. (1996) have administered six people (with previous experiences with the same drug) with two different dosages of MDMA (roughly equivalent to one-fourth to one-half of an ecstasy tablet) and an inactive placebo using a randomized double-blind design. Although results from this kind of studies are much less difficult to interpret and are less biased, nonetheless only very small samples of subjects (administered with very low dosages) can be studied. Lastly, looking at the content of the 'ecstasy' tablets, sources (CBFT, 1995) from local forensic toxicological laboratories (which have examined, in the last 5 years, at least 20000 'ecstasy' tablets) suggest that about 85–90% of 'ecstasy' tablets, seized in this area of Italy, contain MDMA as the active ingredient, at a dosage of 100–150 mg per tablet, thus confirming other reports (Solowij et al., 1992). Methylenedioxyamphetamine (MDA) and methylenedioxyethamphetamine (MDEA), drugs with effects similar to those of MDMA, are usually found in the remaining tablets. Lastly, MBDB (phenylbutanamine) has occasionally been observed and the rate of dummy tablets found has been about 1% of the material examined. Toxic impurities have not been found in the 'ecstasy' tablets.

Further studies pertaining to the epidemiological, preventative, clinical and therapeutic issues of MDMA abuse in Europe are clearly needed.

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