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Potential Human Neurotoxicity of MDMA ('Ecstasy'): Subjective Self-Reports, Evidence from an Italian Drug Addiction Centre and Clinical Case Studies

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MDMA · Ecstasy abuse · Psychopathological consequences · Epidemiology

Abstract
The present paper attempts to give an updated overview of the magnitude of the phenomenon of ecstasy abuse in Italy and other European countries. It gives an account of some clinical case studies and of a larger-scale report on polydrug (including MDMA) consumers attending our Public Health Addiction Treatment Unit in recent years, with a view to clarifying the characteristics and psychopathological consequences (mainly depression, psychotic disorders, cognitive disturbances, bulimic episodes, impulse control disorders, panic disorders, social phobia) of MDMA consumption. Longer-term, larger-dose (acute or cumulative) MDMA consumers were found to be at high risk of developing these psychopathological disturbances. A tentative description of certain personological dimensions of ecstasy consumers is also given (the novelty-seeking dimension was characteristic of those who occasionally experimented with the drug) while those who ingested larger quantities revealed low harm avoidance scores). Results are discussed in the light of the complex and different methodological issues arising from this kind of study, in which MDMA is far from being the only drug of abuse.

Introduction

In the past few years, the European (and Italian) drug misuse scene has shown an increase in the use of drugs with excitatory properties (cocaine, amphetamines and ecstasy [1]). Apart from concern with regard to 'new' and more powerful cocaine formulations (free-base, crack), there is also the problem that the use of the amphetamine analogue 3,4-methylenedioxymethamphetamine (MDMA, or ecstasy) has been associated, in animals and humans, with some neurotoxic sequelae [2]. In this respect, it has been suggested that it will take many years to fully understand the real contribution of MDMA abuse to the onset of psychiatric disturbances [3]. The literature on the possible psychopathological consequences of MDMA abuse is characterised by a scant number of large-scale clinical surveys, possibly because MDMA consumers are traditionally not used to attending Public Health Services. After examining some reports describing the magnitude

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of MDMA abuse in Italy and other European countries, this article gives an account of some clinical case studies and of a larger-scale report pertaining to polydrug (including MDMA) consumers attending our Public Health Addiction Treatment Unit (ATU) in recent years (the data will also be discussed in relation to certain other researchers' findings), with a view to gaining a better understanding of the characteristics and the psychopathological consequences of ecstasy abuse (albeit in the context of multiple drug consumption).

MDMA Abuse: Epidemiological Notes

Ecstasy use has been reported in virtually all European countries, though the chronology and the scale of its use vary greatly; the UK, Spain and the Netherlands have relatively long-standing populations of ecstasy users, and the prevalence of MDMA abuse in these countries is comparatively high [4]. In other areas (Scandinavia and Greece), ecstasy use appears to be a relatively new phenomenon. Data from the UK [5] suggest a lifetime prevalence of ecstasy use of 2% for the general population in 1994 (but this figure rose to 6% for the 16–29 age bracket). Ecstasy was almost exclusively reported to be used at clubs, parties and raves. Data on the general population in Germany suggest that the lifetime prevalence of ecstasy use in 1995 was 1.6% [6]. In Spain, it is estimated that between 5 and 10% of the 18- to 25-year-olds have used the drug [7]. As for surveys on MDMA use among school children, in Vienna [8] it was found that 6% of the 15- to 18-year-olds reported using the drug; in the UK, among a large representative sample of 15- to 16-year-olds collected in 1996, 9.2% of the boys and 7.3% of the girls reported having used ecstasy [5].

Surveys of populations at risk suggest far higher levels of ecstasy consumption; a 1995 study on disco-goers in Amsterdam [9] reported a lifetime prevalence of 52% (41% in the preceding year). In Germany, Tossmann and Heckmann [10] assessed the prevalence of ecstasy use in 1,674 people from the techno-party scene in 1997: they found a lifetime prevalence of 48% in the 21- to 24-year-old age group (and 37% in the preceding month). In cases with a high social (proportion of personal friends belonging to the techno scene) and behavioural (frequency and duration of going to techno parties) involvement, an elevated prevalence (75%) of MDMA abuse in the preceding month was recorded. In Scotland, Forsyth [11] interviewed 135 people involved in the Glasgow dance scene, contacted using the snowballing technique. On the whole, people had used a lifetime mean number of 10.7 different kinds of drugs (and in no sense could this group be classified as users of MDMA alone). The lifetime prevalence of ecstasy use was 91.1% (and 87.4% had used it in the previous year). It clearly emerged from these results that ecstasy use was more closely associated with the dance scene than any other drug.

It has been calculated [12] that 3–4 million youths attend the 5,000 Italian discos during a typical week-end night. The 'trendy' clubs, where MDMA consumption is likely to be greatest, amount to 7–8% of the total number of clubs [Italian Syndicate of Disco-Club Owners, unpubl. data]. About 500–4,000 people attend disco-parties on a typical Saturday night. As a conservative estimate, at least 25% of the disco-goers are probably MDMA consumers, so the total number of MDMA consumers on a typical Saturday night could be somewhere between 50,000 and 85,000.

From December 1996 to January 1997, we [12] administered a self-rating questionnaire to 360 young people (69 were football fans contacted during a national match, and 291 were disco-goers in north-eastern Italy). The results showed that the lifetime prevalence of ecstasy consumption among the disco-goers ranged between 31 and 92% (mean 59.7%), whereas in the sample of football fans it was 46%. Among the disco-goers, age at first use ranged between 13 and 31 years old (mean 18.6 $\pm$ 3.1 years). On the whole, people took a mean of 2.2 $\pm$ 1.5 ecstasy tablets on each occasion. One third of the MDMA consumers took the drug several times a week. Disco-goers were found to be genuine polydrug abusers, since 75.3% of them took several other drugs at least once a week: i.e. cannabinols (75.3% of cases), alcohol (53%), LSD and other psychedelics (50.4%), cocaine (30%), opiates (11.1%). People bought the MDMA tablets, usually at the disco itself (73.6%), because they were seeking some pleasurable effects, e.g. euphoria, well-being, a better appreciation of the music, wakefulness, easier social relations. Sixty-five percent of them felt they had enough information about MDMA, and 85.5% thought that the drug can be dangerous to nerve cells. A large proportion (93.6%) of MDMA consumers reported the onset of some psychological problems since they began to use MDMA, e.g. cognitive disturbances (45.3%), depression (40.7%), craving for carbohydrates and/or chocolate (27.3%), flashbacks (18%).

Ariano [13] distributed 2,107 self-rating questionnaires to equal numbers of youths (male and female) in the 14–20 years age range attending high schools, a disco and a youth centre (in north-eastern Italy). About 7% of

the students stated that they had used ecstasy at least once in their lifetime. When asked their opinions on the drug, 31% of the sample did not think of ecstasy as a drug of abuse, and 33% emphasised its positive psychedelic effects. Opinions were gathered about its neurotoxicity, and 63% of consumers and 79.5% of non-consumers stated that ecstasy could be dangerous to nerve cells.

During 1997, 3,193 questionnaires were distributed to high-school students in an area near Milan [Minicuci and Schifano, unpubl. data]. The reported lifetime prevalence of ecstasy use was 8.7% and risk factors for the use of the drug were: attending discos (odds ratio, OR = 8.7); meeting people who use synthetic drugs (OR = 6.07) and attending less versus more academic secondary schools (OR = 2.89). Having good relationships with parents and teachers proved to be a protective factor (OR = 0.56).

In another study, Santi et al [14] administered a semi-structured interview to assess the use of entactogenic drugs [15] to 479 subjects attending discos in the Florence area. The interview aimed to evaluate the social and demographic features of the sample, the characteristics of their possible MDMA consumption and any perceived psychopathological consequences of ecstasy use. The mean age of the disco-goers was 20.2 years, and 70.7% of them were males. Forty percent of the sample reported having taken ecstasy at least once in their lifetime (but 70.5% of the sample had been offered the drug in the past). Consumers were more likely to be males (log linear analysis; $p < 0.05$), students ($p < 0.05$) and younger (under 18 years old; $p < 0.05$) than non-consumers. Most of the people took 1.5–3 tablets on each occasion (but the range was 0.25–21 tablets a night). In the same report, roughly half (47.2%) of the MDMA consumers reported the onset of some psychopathological problems after beginning to use ecstasy; they complained of cognitive disturbances (51.2%), depression (28.6%), a craving for carbohydrates and/or chocolate (14.3%), and panic attacks (13.1%). Those who reported these disturbances were more likely to have been using ecstasy for longer ($p < 0.05$), with a higher frequency ($p < 0.05$) and in association with other psychoactive drugs ($p < 0.05$), than those who reported no such symptoms.

In another report, D'Alessandro et al. [16] administered a semi-structured interview to 737 people (from northern and central parts of Italy) who had consumed ecstasy at least once in their lives. They were contacted at discos, pubs and other places of entertainment for young people. Their mean age was 22.5 years old, and 51.7% of them reported having taken ecstasy, usually at discos (62.3%), starting at an age between 15 and 18 years old. For most of these people (82.2%), their first dose was 0.5–1 tablet, but in 25% of them the dosage went up to more than 4 tablets on each occasion in subsequent years. There seemed to be an inverse relationship between lower schooling level and family income on the one hand and the tendency to take higher MDMA doses on the other. Most of the subjects were polydrug abusers: 65.9% of them had used cocaine at least once in their lifetime, and 87.1% reported having taken high doses of alcohol in the past. Lastly, it was found that the sample used condoms less frequently when intoxicated: while 64.4% of the subjects used them regularly, this figure dropped to 51.3% when they were under the effects of MDMA.

Psychopathological Issues

MDMA is being used increasingly all over Europe, but this drug has been associated with lasting adverse neuropsychiatric sequelae in humans who have taken repeated doses (and in one case even after a single dose [17]). Such adverse effects include anxiety, panic attacks, insomnia, flashbacks, chronic psychoses [18], recurrent acute paranoid psychosis, cognitive disturbances [19] and depression with suicidal behaviour [20–24]. Since 1991 [25], our group has tried to focus on different aspects of the behavioural and psychopathological consequences of MDMA abuse and the most notable findings are given below.

One of our first reports [26] illustrated the clinical pictures of 7 patients whose psychopathological disturbances included a craving for chocolate (a symptom which, at the time, had not been observed in MDMA abusers before). The psychopathological features observed (table 1) were generally consistent with the findings of other authors (for a review, see Henry [3]), but it is worth noting that all the patients showed striking changes in appetite and food preferences.

In another study, we described a large-scale sample of polydrug (including MDMA) consumers [27]. Between July 1991 and June 1996, 150 ecstasy abusers (who had all taken ecstasy at least once), consecutively chosen from among all those presenting for various reasons to the Padova ATU (north-east Italy) for help were studied. All patients underwent a clinical examination and a complete medical and psychiatric history was collected. All patients were studied by means of a semi-structured interview [15] to gather information on the characteristics of their ecstasy consumption. All patients were specifically assessed for any psychopathological syndromes (subsequent to MDMA use) on a level with the areas thought to be biolog-

Table 1. Psychopathological features (including chocolate craving) of 7 MDMA abusers

Case No.	Age/Sex years	Estimated cumulative number of MDMA tablets ingested	Psychopathological features
1	24/M	150	aggressive outbursts, atypical psychosis, chocolate craving
2	24/M	50	major depression, panic disorder, cognitive disturbances, chocolate craving
3	28/M	40	atypical psychosis, chocolate craving
4	28/M	65	atypical psychosis, cognitive disturbances, carbohydrate + chocolate craving
5	22/M	40	atypical psychosis, major depression, chocolate craving
6	20/F	45	major depression, 'fear of being ridiculed', cognitive disturbances, carbohydrate + chocolate craving
7	23/M	2,000	'fear of being ridiculed', tremor, flashbacks, carbohydrate + chocolate craving

Table 2. Lifetime prevalence of use of different drugs in 150 polydrug (including MDMA) users

	n	%
BDZ[1]	6	4
Opiates	87	58
Cocaine	89	59
THC	107	71
Alcohol[2]	53	35
Others	66	44
Any of the above	143	95
Missing data	3	2

[1] Non-medical use.
[2] Only cases with a diagnosis of alcohol abuse or dependence.

Table 3. Main psychopathological disturbances subsequent to MDMA use in a sample of 150 polydrug consumers

	n	% (of 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

ically related to 5-HT dysfunctions [28], namely: mood, anxiety, sleep, aggression, impulsiveness, cognition and appetite. Concerning cognitive impairment, the clinical assessment followed a careful assessment of what the patients reported, supported – in a subsample of patients – by psychometric tests [29]. For the different parameters described, we compared patients who had been diagnosed as having at least one psychopathological disorder and those who had not. Most (83%) of the 150 patients were males, and their mean age was 23.2 ± 4.5 years. The patients' median age when they first used ecstasy was 19 years. The whole sample had been taking an estimated median total number of 11 tablets for a median 32.5 weeks, but about 1 in 4 subjects had taken larger amounts (more than 50) in their lifetime. Half the people tended to take no more than 1 tablet on each occasion. As shown in table 2, for almost all patients (95%) MDMA was not the only drug they had used at least once in their lives: 59% of them had used opiates, but those who had used different stimulants and psychedelics were also well represented in the sample. People took other drugs in combination with MDMA: this was mostly alcohol (39%), THC (31%), other stimulants and psychedelics (24%). Seventy-nine people (53% of the total sample) were diagnosed as having one or more psychopathological disorders (the patients specifically denied any such disturbances prior to using MDMA; table 3), which were usually depression and psychotic disorders. A cognitive impairment (memory and concentration problems) was found in 41 subjects (27%).

Table 4. Main characteristics and MDMA-related behaviour (in a sample of 150 polydrug users) of patients with at least one psychopathological disturbance as compared with those with no psychiatric diagnosis

	With psychiatric problems	Without psychiatric problems	Test	p
n	79	71		
Sex				
Male	50%	50%	χ^2	n.s.
Female	68%	32%		
Age, years	22.1 ± 3.6	23.7 ± 5.9	t test	0.046
Weight, kg	65.1 ± 17.0	69.9 ± 13.9	t test	n.s.
MDMA use				
Age at first use, years	19.1 ± 3.4	22.4 ± 5.3	t test	<0.001
Lifetime intake, tablets	47 (20–125)	3 (1–7.3)	M-W	<0.001
Frequency, tablets/week	1 (0.5–2)	0.4 (0.12–1)	M-W	<0.001
Period, weeks	52 (26–104)	14 (1–52)	M-W	<0.001
Largest single intake, tablets	3 (1.25–5)	1 (1–1)	M-W	<0.001

Figures are means ± SD and median with 1st to 3rd quartile in parentheses. M-W = Mann-Whitney.

Patients with at least one psychopathological disturbance 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 frequency (1 vs. 0.4 tablets/week; p < 0.001), for a longer time (52 vs. 14 weeks; p < 0.001) and a larger median number of tablets in the same evening (3 vs. 1; p < 0.001) than the others (table 4). They were also less likely to have used opiates (37 vs. 75%; p < 0.001), but more likely to have used alcohol (70 vs. 43%; p < 0.003) or other drugs (mostly nitrites and LSD; 68 vs. 40%; p < 0.001). By logistic regression analysis, it was found that only 3 variables were statistically related to the onset of psychopathological disorders: (1) those who had taken larger numbers of MDMA tablets in their lifetime had a higher risk of developing psychopathological disturbances (i.e. those who had taken 3 or more tablets had an OR of 8.9, while those who had taken more than 11 tablets had an OR of 17.4); (2) those who had drunk alcohol together with MDMA were at a 2.5 times higher risk of developing psychopathological disturbances than alcohol abstainers; (3) opiate consumers were significantly less likely than non-consumers to show any psychopathological disturbances (OR = 0.2); again, they had taken a smaller total number of MDMA tablets in their lifetime (6 vs. 27.5; p = 0.015) and were less likely to have used alcohol and MDMA during the same evening (27.6 vs. 48.3%; p = 0.016). Sex, age, weight and the use of other drugs were not statistically related to the onset of psychopathological disorders.

In our most recent study [30], we used two well-known methods – the Tridimensional Personality Questionnaire (TPQ) for evaluating three trait personological dimensions, i.e. novelty seeking, harm avoidance and reward dependence [31], and the Symptom Distress Check-List (SCL 90), a self-rating questionnaire covering a range of psychopathological factors, i.e. somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, sleep disorders [32] – to compare 43 previous MDMA abusers and 77 controls (31 had previously taken other drugs and 46 had always been drug free). All subjects had been recruited (mostly at discos) with the snowballing technique, and none of them had ever attended any ATU. Apart from gender (males were significantly more represented, p < 0.001, in the group of MDMA abusers than controls), ecstasy abusers and controls were comparable in terms of the social and demographic variables. The TPQ findings showed that ecstasy consumers reported significantly higher scores than controls (p < 0.001) in the novelty-seeking subscale, but not in the other two subscales (harm avoidance and reward dependence). The SCL-90 showed higher scores in MDMA abusers than in controls for obsession-compulsion (p = 0.004), phobic anxiety (p = 0.037), psychoticism (p = 0.005) and sleep disorders (p = 0.046). In the group of MDMA abusers, moreover, we compared those who reported a lower lifetime consumption of MDMA (≤ 25 tablets) with those who had taken larger quantities. The TPQ showed signifi-

cantly higher harm-avoidance scores (p = 0.029) in those who had taken smaller amounts of MDMA, whereas the SCL-90 results were similar in the two groups.

Discussion

From the results presented, it could be assumed that the typical Italian ecstasy consumer is about 20 years old and male; he is a student or worker and usually takes 1–3 MDMA tablets (in combination with alcohol and/or other drugs) together with friends, at week-end disco nights, and he thinks he knows about the risks of ecstasy. As time goes by, however, he begins to suffer from various psychopathological disorders (especially memory troubles and depression). The evidence presented here suggests that some personality dimensions (i.e. novelty seeking) are likely to be characteristic of ecstasy consumers, while those who ingest larger quantities would have low harm-avoidance scores.

In animals, including primates, MDMA causes initial release of 5-HT followed by degeneration of 5-HT projections; the fine axons of the dorsal raphe, associated with 5-HT2 receptors, are especially vulnerable [33]. The lowest effective dose of MDMA capable of causing a long-term depletion of cortical 5-HT in primates is 2.5 mg/kg [34] (a dosage of about 1–2 tablets). Other authors [35] have pointed out that long-term effects in animals require either a large single dose (10–20 mg/kg, i.e. 16 ecstasy tablets) or several lower doses. Solowij et al [36] also emphasised that the negative effects of MDMA in humans are dose related in that their severity correlates with the total number of doses consumed and the frequency of use. The concentration of 5-HIAA (the metabolite of 5-HT) in the lumbar cerebrospinal fluid (CSF) is substantially lower [37] and serum prolactin response to *L*-tryptophan challenge is blunted [38] in people with a history of MDMA use. McCann et al. [39] found that MDMA users reveal a lower global and regional brain 5-HT transporter binding than controls, and decreases in 5-HT transporter binding positively correlated with the severity of previous MDMA abuse. Reduced central 5-HT levels could explain the clinical pictures described. In fact, a decreased central 5-HT function may contribute to the onset or persistence of binge-eating episodes in patients with bulimia nervosa [40]. The ingestion of carbohydrates (especially chocolate [41]) has been shown to selectively increase tryptophan uptake by the brain and consequently raise CNS levels of 5-HT; it may be that eating chocolate is an attempt to increment brain 5-HT and is therefore a form of self-medication. One might wonder why these patients tend to show a specific preference for chocolate rather than for a wider range of high-carbohydrate binge foods, as might be expected with a central 5-HT deficiency. However, chocolate also contains phenylethylamine (one of the endogenous amines with amphetamine-like properties [42]) and theobromine (a caffeine-like substance), which might be useful to patients in counteracting their blunted affect.

Having found roughly half of the 150 patients interviewed to be affected by one or more psychopathological disturbances, one might wonder why MDMA users with psychological problems go largely undetected in the community. Most long-term MDMA users with such problems reported spontaneously to our unit, referring to symptoms that they perceived as being linked in some way to their chronic ecstasy use so, to some extent, this sample could be considered 'biased' by the severity of their disturbances. McCann and Ricaurte [43] have suggested that psychopathological consequences may manifest only in susceptible individuals. Neurotoxic effects may not be readily evident for most humans because of the 'redundancy' and robustness of neuronal systems (like the 5-HT one) serving major brain functions: extensive neurotoxicity must be sustained before it becomes clinically detectable. In this sense, it is understandable that longer-term, larger-dose (acute or cumulative) MDMA consumers should emerge in the present study as being at high risk. In cases in which individuals developed symptoms after using relatively low doses of MDMA on rare occasions, it is likely that a predisposition (or pre-existing vulnerability to psychiatric disorders) combined with the drug's interaction with brain 5-HT and catecholamine systems in inducing psychiatric problems. On the whole, other research groups have confirmed and extended our findings. Parrott et al [44] compared 12 heavy ecstasy users (who had taken MDMA 30–1,000 times), 16 occasional ecstasy users (taken 1–20 times) and 22 similar-aged controls (using three psychiatric and personality questionnaires in drug-free intervals). Heavy ecstasy users had significantly higher scores than controls for the following SCL-90 factors: paranoid ideation, psychoticism, somatization, obsession-compulsion, anxiety, hostility, phobic anxiety, altered appetite and restless sleep; they also showed greater impulsiveness. Light MDMA users produced intermediate scores. McGuire et al. [45] collected a series of 13 psychiatric cases (who had been MDMA-free for 1–26 weeks) who had all used MDMA for a period ranging from 1 to 156 weeks. They found that the most prominent feature was psychotic syndrome followed by panic attacks and depression. In their opinion,

the prevalence of a familial psychiatric morbidity among the patients examined was suggestive of a greater vulnerability to psychiatric illness, so MDMA could have triggered these disorders in predisposed individuals. Again, they suggested that MDMA users with a less overt psychopathology may go undetected (which could explain the predominance of psychosis in the existing case reports).

Looking more in depth at other clinical issues in the 150 patients in our study, two major findings were related to alcohol (the combined consumption of alcohol and MDMA increased the risk of developing psychopathological disturbances) and opiates (the use of which may well have masked any psychiatric symptoms in MDMA consumers). Depression and psychoses are the disorders most frequently observed, thus confirming previous reports. Both the high rate of cognitive problems reported by the patients themselves and the suggestions emerging from the data on the small subsample of MDMA patients who underwent psychometric tests are worrying. Similar results have been reported in the UK; Curran and Travill [19] used a parallel group design to compare 12 subjects who reported having taken MDMA with 12 subjects who reported having consumed only alcohol on a given night. The same participants were then re-assessed the following day and again mid-week. The MDMA group showed significant impairment on the attentional/working memory tasks by comparison with the alcohol users. Again, Parrott et al. [46] assessed the cognitive task performance in three groups of young people: 20 MDMA (10 regular and 10 novice) users and 10 control subjects. On immediate word recall and delayed word recall, both groups of MDMA users recalled significantly fewer words than controls. Morgan [47] investigated immediate and delayed recall in 25 polydrug users who had taken more than 20 tablets of ecstasy (MDMA group), 22 polydrug controls (who had never taken ecstasy) and 19 non-drug controls. Subjects in the MDMA group recalled significantly fewer ideas in both immediate and delayed recall conditions and the findings, according to the author, provided evidence that memory performance deficits in recreational ecstasy users (which was a long-lasting phenomenon, persisting for at least 6 months) are primarily associated with exposure to MDMA, rather than to other legal and illegal drugs consumed by these individuals. In the USA, Bolla et al. [48] compared 24 abstaining MDMA users and 24 controls on several standardised memory tests: here again, they explored correlations between changes in memory function and decreases in CSF 5-HIAA, serving as a marker of central 5-HT neural function. Greater use of MDMA was associated with greater impairment in immediate verbal memory and delayed visual memory. Lower concentrations of CSF 5-HIAA were associated with a worse memory performance.

There are several possible limitations in the studies presented. First, virtually all of the people involved had used other drugs during their lifetime and/or together with MDMA itself. Due to the recruitment methods, moreover, heroin abusers were over-represented in the ATU sample, and this population seems to differ considerably from the one going to high-risk venues (discos, rave parties). Second, in the study on 150 patients there were no control groups of age- and sex- matched people who had never used drugs and who had used drugs other than MDMA. Third, the real content of MDMA in the ecstasy tablets is open to doubt. Fourth, one could wonder as to the contribution of our studies to supporting the existing literature data on the neurotoxic potential of MDMA.

To answer the first possible objection, we should remember how difficult it is in clinical practice to find people who have only ever consumed ecstasy. From the data presented here, it is clear that MDMA consumption alone is likely to be a pure abstraction, at least at discos and other juvenile venues targeted in the quoted reports. All the ATUs, in Italy and other Mediterranean countries at least, are attended by heroin abusers, and this may have influenced some of the results of our 150-patient study. On the other hand, proper large-scale clinical studies are easier to perform in formal settings (e.g. the ATUs) than at the disco. Though the lack of proper control groups may restrict the validity of the 150-patient study findings, the statistical methods extracted a putative role for MDMA alone in its potential causal relationship with the psychopathological disturbances. Prospective studies are substantially lacking in the specific field of MDMA use and abuse due to ethical and legal constraints.

As for the content of the ecstasy tablets, sources [49] from local forensic toxicological laboratories (which have examined at least 20,000 ecstasy tablets in the last 5 years) suggest that about 85–90% of ecstasy tablets seized in the north-east of Italy contain MDMA as their active ingredient, in doses of 100–150 mg per tablet, thus confirming other reports [36]. Methylenedioxyamphetamine and methylenedioxyethamphetamine, drugs with effects similar to those of MDMA, are usually found in the remaining tablets. Phenylbutanamine has occasionally been found, and the rate of dummy tablets has been about 1% of the material examined. Toxic impurities have not been found in ecstasy tablets.

Although patients reported that the psychopathological disturbances had occurred after they began to use

MDMA, the possibility of pre-existing psychopathological abnormalities, maybe contributing to the onset of drug use, cannot be ruled out. Here again, even if the abnormalities are associated with the use of ecstasy, they may not necessarily be related to the neurotoxicity of the drug. Other drugs of abuse which have no recognised serotonergic neurotoxic potential (i.e. ketamine [50]) have also been associated with psychiatric sequelae and cognitive disturbances. On the other hand, for drugs with a demonstrated serotonergic toxic potential, in animals at least [51], e.g. fenfluramine, withdrawal from the European market was due to its causing primary pulmonary hypertension, and not to any psychopathological sequelae of which there are no reports [52]. So the issue remains somewhat controversial, also because the data that we have reported do not justify any direct and straightforward conclusions as to the neurotoxicity of ecstasy. Nonetheless, we feel that our data may help in interpreting the possible existence of a relationship between psychiatric disturbances and MDMA neurotoxic potential in humans.

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

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