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Neuropsychiatric consequences (atypical psychosis and complex-partial seizures) of ecstasy use: possible evidence for toxicity–vulnerability predictors and implications for preventative and clinical care

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Two case reports of ecstasy abuse and its serious neuropsychiatric complications are presented. The first patient developed a florid paranoid psychosis resembling schizophrenia after repeated long-term recreational ecstasy abuse, and significant alterations with intermittent paroxysmal discharges were found in his electroencephalogram. The second patient showed an atypical paranoid psychosis with Fregoli syndrome and a series of complex-partial epileptic seizures with secondary generalization after a first single ecstasy dose. Both subjects presented considerable vulnerability; the first a minimal brain dysfunction after perinatal asphyxia and a persisting attention deficit/hyperactivity disorder, the second a long-lasting opioid addiction. In vulnerable individuals, dose-independent ecstasy abuse can lead to unpredictable and potentially dangerous neuropsychiatric sequelae which require proper initial assessment and adequate treatment.

Key words: case report, complex-partial epilepsy, ecstasy, Fregoli syndrome, MDMA, 3,4-methylenedioxyamphetamine, paranoid psychosis, prevention, side-effects

Introduction

MDMA or ecstasy (3,4-methylenedioxymethamphetamine) is a synthetic amphetamine analogue stimulant, broadly used 'recreationally' (Franken, 2001). In Switzerland, life prevalence of ecstasy-consume is 5.3% (BAG, 1998). Biochemically, it depletes stocks and thus induces an acute increase in levels of the neurotransmitters serotonin (5-hydroxytryptamine, 5-HT) as well as dopamine (Rattray, 1991). The immediate psychological effects of its use include a sense of well being, elation, enhanced subjective arousal and reduction in social anxiety (Curran and Travill, 1997).

Adverse reactions were reported even after the ingestion of a single dose, and they may include symptoms of sympathomimetic toxicity, trismus and bruxism (Greer and Tolbert, 1986). MDMA has also been implicated with serious physical disturbances including rhabdomyolysis, disseminated intravascular coagulation, intracranial haemorrhage, coma, and even death in some cases (Henry *et al*., 1992). Serious mental disorders such as chronic paranoid psychosis, recurrent paranoid psychosis, panic attacks and depression with suicidal ideation have been described (Bailly, 1999).

The usual recreational oral dose is 1–2 tablets (each containing approximately 60–120 mg of MDMA) and the drug is typically used once fortnightly, or less, because of rapid tolerance development. The perceived relative safety of MDMA is at odds with evidence of MDMA destruction of serotonergic neurones in animals (Curran, 2000) and emerging evidence of neurotoxicity in humans (Boot *et al*., 2000). There are pronounced interindividual differences with regard to the sensitivity to the MDMA toxic effects. Life-threatening or lethal outcomes have been seen with concentrations between 0.11 and 7 mg/l (Theune *et al*., 1999).

We report two cases of MDMA abuse with unusual neuropsychiatric complications. In both cases, predisposing factors were identified. We discuss assessment in cases with unusual syndromes and consider implications for clinical practice.

Case reports

Case 1

The patient was a 24-year-old man who suffered perinatal asphyxia and there was a slight delay in his psychomotor development. At the age of 3–4 years, attention deficit/hyperactivity disorder (ADHD) became evident with ensuing school and relational difficulties persisting until adulthood. He succeeded in completing an apprenticeship as a salesclerk; however, he could not maintain his job because of uncontrollable behaviour problems. Since the age of 21 years, there was a history of recreational use of ecstasy and cannabis. After the additional intake of LSD at age 23 years, the patient suffered a 'horror trip' with symptoms of panic attack, including intense fears of dying. He abstained from further LSD use; however, he intensified his abuse of ecstasy and cannabis. Three months later, he was referred for psychiatric hospitalization

because of a psychotic condition: He was anxious, expressed ideas of reference and of persecution (unknown people would shoot him dead) and bizarre fears (his eyes would fall out of his eye-sockets). He had acoustic (voices conveying him different messages) and visual (birds that would devour him) hallucinations.

There were no abnormalities on general medical and neurological examination and all laboratory parameters were within normal limits. Brain computerized tomography (CT) was normal. An electroencephalogram (EEG) showed normal basic activity; however, intermittent paroxysmal discharges were registered in both temporal regions with a tendency towards generalization, without any clinical evidence of seizures. Following treatment with olanzapine up to 40 mg/day, a slow amelioration over 6 weeks was observed with stepwise regression of hallucinatory experiences and delusional ideas. He was given a diagnosis of probable paranoid schizophrenia.

After discharge, the patient stopped his medication and restarted sporadic ecstasy and cannabis abuse. Drug intake was frequently followed by a short-lasting condition of prepsychotic decompensation with increased impulsivity and hyperactivity, loosening of associations and volatile paranoid ideas. However, he always recovered after such episodes within 2–3 days without using antipsychotic medication. Unfortunately, the patient refused control EEG.

Case 2

The patient was a 23-year-old female who was referred for psychiatric emergency hospitalization. There was no history of psychotic disorder, epilepsy and organic brain disorder, but the patient had been heroin-dependent for several years and was currently under methadone substitution (45 mg/day). Also, there was a history of recreational use of cannabis and benzodiazepines. On admission, approximately 3 h after she had taken a single, probably high dose of ecstasy for the first time, the patient presented a wide range of sympathomimetic symptoms, including tachycardia, tremor, mydriasis and headache. She felt extremely anxious, was psychomotorically agitated, incoherent in thinking and disoriented in time and place. She experienced vivid visual and auditory hallucinations along with feelings of bodily change, alienation and strangeness. Furthermore, she expressed ideas of reference (people staring and ridiculing her) and considered the male interviewer to be her sister.

Except for slightly increased liver enzymes (history of hepatitis C), all laboratory parameters and electrocardiogram were within normal limits. Urine drug screening was positive for MDMA, benzodiazepines, cannabis and methadone, and it was negative for other substances of abuse. Blood screening for dextromethorphane and psilocine was negative. Brain CT showed no intracerebral anomalies. EEG revealed discrete general alteration with an increase of beta-waves and a significant irritative focus in the right temporal and parietal region, consistent with the diagnosis of temporal lobe epilepsy.

During the initial hours of her hospital stay, the patient presented with two series of four and five complex-partial epileptic seizures, two of them with secondary generalization (grand mal). Initial treatment consisted of valium 10 mg and phenobarbital 100 mg. After the second episode, she received clonazepam (1 mg i.m). Medication with phenobarbital (100 mg/day), clonazepam (3 mg/day) and valium (as needed to prevent seizure repetition) was continued. The seizures became clinically milder and gradually disappeared. During the following days, phenobarbital was stopped and clonazepam therapy continued. The EEG abnormalities disappeared, whereas individual psychotic symptoms persisted for several weeks in spite of the initiated neuroleptic treatment with haloperidol, 10 mg (later reduced to 5 mg/day).

Discussion

After ecstasy ingestion, both patients experienced a florid psychotic condition necessitating hospitalization. Even though paranoid schizophrenia was suspected in the first case, it had some features of toxic delirium (i.e. vivid perceptual disturbances). Subsequently, the patient experienced short-lasting prepsychotic decompensations after sporadic ecstasy and cannabis abuse. Moderate thought disorder has been observed after taking MDMA even in healthy volunteers (Vollenweider *et al*., 1998). In the second case, an atypical psychosis with high anxiety level and florid paranoid hallucinatory experiences was diagnosed, with Fregoli syndrome (identification of a familiar person in a stranger who is perceived to be physically different but psychologically identical to the familiar person), a variant of misidentification syndrome (Ellis *et al*., 1994), being a part of patient's psychopathology. In both patients, a diagnosis of acute exogenic psychotic reaction could have been given. Cases of acute and chronic exogenic psychosis and delirium after ecstasy intake are well known (Bailly, 1999) and toxic psychosis is a recognized complication of amphetamine abuse, where schizophrenia-like psychotic reactions are described (Bell, 1965).

Both patients also presented significant EEG-alterations with lower threshold neuronal activity. The first patient showed irritative foci in both temporal lobes without clinical signs of seizures. The second patient had an irritative temporo-pariental focus in EEG and presented clinically with several series of complex-partial epileptic seizures. Both clinical semiology and EEG findings were compatible with the diagnosis of temporal lobe epilepsy, which has been characterized, among others, by visceral sensations, derealization and panic feelings (Niedermeyer, 1984), and which may generalize to include tonic-clonic seizures. The occurrence of complex-partial seizures after ecstasy intake is exceptional and was not mentioned by Bailly (1999) in his survey of neuropsychiatric disturbances following ecstasy intake. To our knowledge, such a complex clinical picture including Fregoli syndrome, as observed in our second patient, has not been described in association with the use of MDMA before. A positive correlation between level of previous ecstasy use and EEG changes has been reported (Dafters *et al*., 1999).

In both patients, toxic reactions appeared for the first time after ingestion of ecstasy; in the first patient, after increased abuse and, in the second patient, after the first abuse. In the first case, there was repeated ecstasy abuse over several years until the toxic reaction appeared; in the second patient, it appeared after a single ecstasy dose. Whereas in the latter case, abuse could be substantiated by identification of MDMA in urine, we had to rely on the patient's statement in the first case and we cannot be sure that he really always took MDMA; the conception of ecstasy sometimes encompasses the whole group of amphetamine derivatives with enactogenic effects (Enderlin *et al*., 1999). Therefore, we cannot be sure that there is a

true causal relationship between the drug ingested and the toxic reactions observed. Admittedly, the time relationship between ecstasy intake and epileptic seizures in the second patients is appealing, but seizures due to a reduced level of benzodiazepines must be considered. Nevertheless, epileptic grand maux seizures in the first hours following ecstasy intake were described (Theune *et al*., 1999) and the seizures in our patient occurred within hours after drug ingestion and, in two of them, generalization was observed.

Predisposing toxicity-vulnerability factors

The pathogenesis of ecstasy-induced neuropsychiatric complications in general, and of psychotic reactions and seizures in particular, still remains unclear. Because only a minority of MDMA abusing individuals suffer such complications, and because there is a lack of relationship between ecstasy dose and seriousness of the complications (Thomasius *et al*., 1997), individual vulnerability must play a role. There are different potential toxicity–vulnerability factors:

Genetic vulnerability has been suggested to precipitate serious mental disorders for psychotomimetic drugs (Bowers, 1977) and MDMA (Thomasius *et al*., 1997). In our patients, there was no evidence of a personal or family history of mental illness. However, genetic factors could influence the MDMA metabolism. MDMA is demethylenated by the polymorphic cytochrome P450 CYP2D6. Individuals possessing CYP2D6, 2, 17 and, particularly, 10 alleles may show reduced MDMA metabolism and, consequently, higher MDMA toxicity (Ramamoorthy *et al*., 2002).

A past history of neurodevelopmental disorder may have been of importance in the first patient. ADHA following perinatal hypoxia may have predisposed him to acute psychosis after increased ecstasy intake. Correspondingly, perinatal hypoxia is considered a vulnerability factor for schizophrenic disorder (Davies *et al*., 1998). Incidentally, ADHA patients tend to abuse selectively psychostimulants such as cocaine, perhaps as a form of self-medication (Carroll and Rounsaville, 1993).

Multiple substance abuse may end in higher pharmacodynamic and phamacokinetic vulnerability. Indeed, ecstasy abuse may not be the main and sole responsible factor for psychiatric manifestations (Bango *et al*., 1998), and some 70–100% of ecstasy users also consume other psychoactive substances (Bilke, 1998). Both our patients abused cannabis. In addition, the second patient had a long history of heroin abuse and she was under methadone substitution. It has been suggested that delta-9-tetrahydrocannabinol, the psychoactive principle of cannabis, facilitates mesolimbic dopamine neurotransmission (Sakurei Yamashita *et al*., 1989) and that the repeated use of cannabis may increase dopamine intrasynaptic levels, thus leading to agitation, delirium and convulsive states (Hollister, 1988). On the other hand, according to Vaiva *et al*. (2001), 13 cases of acute psychotic episode after ecstasy ingestion have been reported, three of them after a single ecstasy dose, and the serotonergic dysregulation due to ecstasy, which is independent of cannabis use (Croft *et al*., 2001), may also lead to mesolimbic hyperdopaminergic state. According to Solowij (1993), MDMA possesses not only stimulant, but also mild hallucinogenic properties.

Other accidental dispositional factors have been reported. For example, MDMA seizures can occur in the absence of any metabolic abnormality but, in other cases, they were precipitated by other ecstasy complications such as hyponatraemia and cerebral oedema (Holmes *et al*., 1999).

Implications for clinical care

Prevention

There is a need for integrated school- and community-based drug prevention programs that capture the full spectrum of patterns of use and levels of risk among those populations at risk (Poulin and Elliott, 1997). Because adolescence is associated with an increased risk of developing drug abuse/dependence, young people should be addressed. During adolescence, brain and hormonal systems are still undergoing crucial maturational rearrangements, which take place together with significant modifications in psychosocial development. Novelty-seeking, a personality trait that is typical of this age period, might substantially contribute to psychobiological vulnerability to drugs (Laviola *et al*., 2000).

Recognition in the acute phase

Drug intake is high among those referred for psychiatric assessment and hospitalization (Modestin *et al*., 1997) and it must always be considered, especially in the young. Good history taking is crucial but often hindered because of abnormal psychic states with cognitive impairment, and those claiming to have ingested ecstasy may actually have taken other agents. Prodromi often include sympathomimetic signs and complaints of restlessness, tremor and visual hallucinations. A quick determination of MDMA in urine or serum should be mandatory in all unclear cases of psychotic decompensation and epileptic seizures. Initial monitoring of liver and renal functions, complete blood count, electrolytes, etc., helps to rule out other potential organic causes.

Management

Seizures due to ecstasy intoxication generally need aggressive treatment with benzodiazepines whereas, in our experience, ecstasy-induced psychotic conditions respond to neuroleptics. MDMA releases serotonin and, to a lesser extent, dopamine and norepinephrine. The release of serotonin could be blocked by serotonin uptake inhibitors such as citalopram which should reduce all MDMA effects except for body temperature (Liechti and Vollenweider, 2000). However, the clinical evidence of its efficacy in this indication is lacking. Somatic emergencies must be addressed as needed. In the case of hyperthermia, active cooling, rehydratation and treatment of acidosis and other metabolic problems, and the use of a benzodiazepine in large doses, may form part of the initial intervention.

In summary, our case reports confirm that clinically important and unpredictable effects (such as complex-partial epileptic seizures) may occur after MDMA ingestion, possibly when combined with other drugs such as cannabis. They remind us of the potential danger associated with ecstasy and other ‘social drugs’ sold on the illicit market.

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