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CASE REPORT

MDMA (Ecstasy) Precipitation of Panic Disorder

Stefano Pallanti and Donatella Mazzi

The authors describe three patients whose panic disorder began during recreational use of MDMA (Ecstasy) and was subsequently complicated by agoraphobic avoidance that continued autonomously after cessation of the drug. Their panic disorder responded well to serotoninergic antidepressant drugs. Theoretical and practical implications are discussed.

Introduction

The use of 3,4-Methylenedioxymethamphetamine (MDMA, also known as "Ecstasy") is rarely associated with recurrent time-limited panic attacks that are closely related to the use of the drug (Greer and Strassman 1985; Barnes 1988; Whitaker-Azmitia and Aronson 1989).

Recent evidence suggests that MDMA may act as both an indirect dopamine agonist and as a potent serotonin releaser and serotonin receptor agonist (Lyon et al 1986; Schechter 1986), but its neurotoxic effects appear to be restricted to serotonergic neurons (Gold et al 1989). Clinical and experimental observations have not yet clarified the hypothetical relationship between serotonin function and the development of anxiety (Charney et al 1987; Kahn et al 1988a).

The specificity of MDMA, a synthetic drug, and its growing popularity with young people, could furnish an experimental model for the study of panic disorder (PD). Greer claimed in 1985 that MDMA-induced panic symptoms disappeared with psychotherapeutic treatment, but no information is available on pharmacologic treatment for MDMA-induced panic attacks.

We report three cases of MDMA-induced PD out of 36 patients with PD evaluated in our clinic over the last year. The subjects described their panic disorder as having been precipitated by recreational use of MDMA. Once they began, the attacks persisted autonomously, unprovoked by any stimuli or drug; subsequently, we observed a good response to serotoninergic antidepressant drug therapy.

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Case Reports

Case 1

Mr. N., a 27-year-old salesman, experienced subjective positive effects of MDMA on about 20 occasions during 10 months before the onset of PD. He had no family history of depression, school-phobia, PD, or phobic avoidance behavior. His first panic attack occurred 40–60 min after drinking two pints of beer and ingesting an MDMA dose (said to be 50 mg) similar to that taken by several friends, none of whom experienced adverse effects. His panic attacks were characterized by tenseness, cardiac palpitations, sweaty palms, vertigo, difficulty in breathing, and fear of dying. He was transported to a hospital and given a small unknown dose of diazepam PO and was released after 2 hr. He stopped taking drugs and drinking alcohol; however, panic attacks continued to occur twice a week. His symptoms were soon compounded by the development of avoidance behaviors (e.g., he avoided using elevators, taking the bus, and standing in lines).

He came to our clinic 2 months after the first attack and received a prescription for tranylcypramine, the only MAOI available in Italy (20 mg a day), taken for a period of 2 months before his symptoms disappeared. Tranylcypramine was used because we believed the patient would not tolerate the side effects of fluvoxamine, the drug we ordinarily use for PD. During the treatment period he did not receive any formal psychotherapy and he continued to avoid drugs and alcohol consumption. During a 4-month treatment period, his dosage of tranylcypramine was gradually diminished to zero without reappearance of his symptoms. During a 6-month period after tranylcypramine was stopped, he remained symptom free.

Case 2

Mr. R., a 21-year-old typographist, had used MDMA on three previous occasions in the last 6 months and had experienced positive effects. He had no family history of depression, PD, or phobic avoidance behavior. In the 3 months preceding the appearance of the disorder he was divorced and changed his residence. His first attack occurred at a New Year's Eve party; he was in London for a vacation and consumed two doses of MDMA (presumably 100 mg), about the amount taken by several of his friends, none of whom experienced adverse effects. His panic attacks began 90 min after consuming that dose, and were characterized by intense fear, tachycardia, feelings of numbness, profuse sweating, vertigo, shortness of breath, and chest pain. He received first aid and 1.0 mg of lorazepam from the medical staff at his hotel. On his return flight to Italy, he suffered another attack and an unknown dose of diazepam was administered by the airplane staff. He subsequently had episodic panic attacks, one to four per week, and developed phobic avoidance behavior (fear of airplanes, driving a car on the highway, etc.).

Four weeks after his panic symptoms began, he was referred to our clinic and described his disorder as well as mild depressive symptoms that did not meet DSM III criteria for major depression. He received fluvoxamine (100 mg daily) and amitriptyline (50 mg daily), and the frequency of panic attacks rapidly decreased to one per week. Amitriptyline was used to treat the patient's insomnia. After the first 6-week period, his panic symptoms were further reduced both in frequency and intensity to one mild attack per week. His attacks ceased after 3 months and in the subsequent 3-month period, antidepressant drugs were tapered to zero. During an 8-month follow-up period free from medication, he remained symptom free.

Case 3

Mr. M., a 28-year-old married businessman, had used cocaine and Ecstasy recreationally, once every 2 months, in the previous 2 years and had always experienced subjectively positive effects. He had no family history of PD or depression; in the 3-month period preceding the disorder, he experienced marked stress related to changes in his work. During a stay in Columbia, he experienced a panic attack 60 to 90 min after consuming a dose of MDMA. The attack was characterized by fear of imminent death, depersonalization, derealization, sweating, difficulty in breathing, and tachycardia. He was transported to a first aid station, where he received an unknown dose of diazepam. The symptoms resolved, but after this episode panic attacks recurred, unprovoked by the consumption of any drug, and were associated with the appearance of mild avoidance behaviors (e.g., he avoided traffic-congested streets and crowded theaters or sporting events).

He arrived at our clinic 8 weeks after the first episode and received fluvoxamine (150 mg daily) for 2 months before the symptoms diminished. Panic symptoms soon improved and gradually his avoidance behaviors disappeared. During the following 3-month period, the fluvoxamine dosage was gradually diminished to 50 mg daily and then to zero. During the 6-month follow-up period, he remained symptom free.

Discussion

In these three cases, sporadic MDMA consumption provoked not merely a panic attack, but the development of a panic disorder with agoraphobia, rarely seen after use of cocaine and LSD (Geracioti and Post 1991; Aronson and Craig 1986). Only these three patients suffered panic disorder, whereas their friends who ingested MDMA with them had no unpleasant effects. This seems to suggest that the onset of panic disorder was due to a subjective vulnerability of the patients and not to a contaminated mixture of MDMA and other substances, However, in Case 1, the concomitant consumption of alcohol may have played a role. Although these subjectively positive effects, which have made this drug so popular, are generally known, MDMA's negative actions express themselves only after repeated, even sporadic, consumption.

In laboratory animals, the neurotoxic action of MDMA seems to cause selective degeneration of brain serotonin neurons (Schmidt et al 1986; Schmidt 1986; Battaglia et al 1988; Ricaurte et al 1988; Gold et al 1989); this appears to be a function of both the dose administered as well as the number of times the drug is given (Battaglia et al 1988). Toxic effects appear more evident in the higher phylogenetic classes; in fact, primates, when compared with rodents, have been found to be approximately four to eight times more sensitive to the toxic effects of MDMA (Ricaurte et al 1988). We may thus hypothesize a lower threshold to MDMA toxic action in humans compared with lower mammalian orders.

Other evidence supports the hypothesis that behavioral effects of 5HT potentiators depend on the condition of the 5HT receptor system. Where hypersensitivity exists, as has been postulated for panic disorders, these potentiators may increase anxiety (Kahn et al 1988b). As a result, we hypothesize that susceptibility to the PD-inducing effect of MDMA probably depends on a subjective temporary stress-related state of susceptibility more than on a stable vulnerability trait. This possibility seems confirmed by a recent study on rats (Wright et al 1991) suggesting supersensitivity of postsynaptic 5-HT1A and

5-HT2 receptors induced by stressful situations. In support of this hypothesis, we did not find a past history of psychiatric disorders in any of our three cases, but we did find significant stressful life events in the 6 months preceding the first panic episode in Cases 2 and 3.

The efficacy of drugs that activate the 5HT system in MDMA-induced PD support the hypothesis that this system is involved in the pathophysiology of PD (Westenberg et al 1987, 1989). On the other hand, the ability of nonserotonergic drugs (e.g., cocaine, caffeine) to induce PD, and the poor response to a tricyclic antidepressant that was recently described in PD induced by cocaine (Geracioti and Post 1991) suggests that there may be several different pathophysiological and genetic subgroups in PD. If our patients' PD had been the consequence of toxic destruction of 5 HT neurons, their symptoms should not have improved with treatment or, at least, would have required chronic therapy. Instead, the symptoms did not reappear when drug treatment was stopped. This observation, therefore, seems to support the hypothesis that occasional use of MDMA produces a dysfunction, rather than a destruction, of neurons within the 5HT system. Although more data are needed to determine if sporadic usage of MDMA is capable of triggering a full blown, self-sustaining panic disorder with agoraphobia, our cases suggest that Ecstasy can be considered among the exogenous factors capable of precipitating true PD.

Panic disorder provoked by a 5HT toxic substance (MDMA) and corrected by 5HT-active drugs (fluvoxamine, amitryptyline, and tranyclypramine) is an interesting model that supports the hypothesis of the role of the 5HT system in at least some cases of PD (Westenberg and Den Boer 1989; Kahn et al 1988a).

The widespread popularity of illicit drugs (cocaine, LSD, Ecstasy), unfortunately provides a naturalistic experiment in "pharmacological dissection." With further observations, this naturalistic experiment could help to distinguish different subgroups of PD patients or identify substances that could be used as predictors of treatment response. Such cases could provide more specific models than sodium lactate infusion or CO_2 challenges.

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