NEUROPSYCHOPHARMACOLOGY 1988—VOL. 1, NO. 4

Subjective Effects of 3, 4-Methylenedioxymethamphetamine in Recreational Users

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Received April 13, 1988; revised and accepted May 27, 1988.

3,4-Methylenedioxymethamphetamine (MDMA; Ecstasy) is a serotonergic neurotoxin in laboratory animals that has been *used for recreational purposes by humans. The subjective effects of this drug were determined in recreational users at a university campus. Of individuals who had admitted to using MDMA recreationally, 100 of 1143 agreed to complete a detailed questionnaire concerning the subjective effects of this Schedule I compound. The most common effect of MDMA was a heightened sense of "closeness" with other people (90% of subjects). Tachycardia, dry mouth, bruxism and/or trismus were reported by the majority of users. These effects probably result from the amphetaminelike properties of the drug. Visual hallucinations were reported by* 20% *of users. Untoward side effects were most common on the day following the use of MDMA, with complaints of muscle aches, fatiguability; depression, and difficulty concentrating noted by 21% to 36% of subjects. Sixty-seven percent of frequent users of the drug (six or more separate doses) reported that the "positive" effects of the drug decreased with successive doses while the "negative" effects increased. Although these observations should be considered preliminary, they represent the first documentation of the subjective effects of MDMA in recreational users and confirm previous reports obtained — from patients treated with this drug.*

KEY WORDS: *Serotonin: MDMA; Drug abuse; Neurotoxicity; MPTP; 5-hydroxytryptamine*

3, 4-Methylenedioxymethafliphetamine (MDMA; "Ecstasy") is a ring-substituted amphetamine that since the early 1970s has been advocated by certain therapists as an adjunct to psychotherapy (Shulgin 1986; Greer and Tolbert 1986; Downing 1986). The drug is chemically related to both hallucinogens and stimulants yet has been reported to induce a unique state of

euphoria and enhanced self-awareness without psychotic effects or visual distortions (Snyder 1986). However, MDMA was placed on Schedule I by the Food and Drug Administration in July 1985 due to reports of neurotoxicity in laboratory animals (Ricaurte et al. 1985; Schmidt et al. 1986; Schmidt 1987a,b; Stone et al. 1986, 1987; Battaglia et al. 1987; Commins et al. 1987).

During the past few years, the recreational use of MDMA has appeared to be increasing significantly at undergraduate campuses in the United States. Although no formal epidemiologic studies have been performed, a recent poll of undergraduate students at a major university found that 39% (143 of 369) of individuals reported taking at least one recreational dose of MDMA (Peroutka 1987). Significant recreational MDMA use at other universities has also been reported anecdotally.

To date, the subjective effects of MDMA in non-clinical settings have not been reported. Therefore, the present study attempted to determine the subjective sensations experienced by recreational users of MDMA. In addition, the propensity of the drug to induce any detectable long-term effects in the users was assessed.

SUBJECTS AND METHODS

Undergraduate students at a major university were anonymously polled concerning possible recreational use of MDMA between May 4 and June 3, 1987. Subjects were selected and interviewed (in approximately equal numbers) at the student union, an undergraduate library, and three dormitories containing all four classes of students. The subjects were asked whether they had ever taken “Ecstasy” or “MDMA.” A total of 369 subjects was interviewed, as previously reported in preliminary form (Peroutka 1987). If the subject admitted having used the drug, he or she was asked to complete a questionnaire concerning the subjective effects of the drug. The questionnaire was based on previous reports of subjective MDMA effects (Shulgin 1986; Greer and Tolbert 1986; Downing 1986). A copy of the questionnaire is available upon request.

The subjects were asked to report whether or not they experienced a variety of psychologic and physiologic effects on both the day of usage and the following day. Subjects were also asked whether the effects of the drug changed with successive doses and whether the drug was felt to produce any permanent change in their behavior or personality. The use of this questionnaire was formally reviewed and approved for use in the present study by the Human Subjects Committee at Stanford University.

RESULTS

Frequency of Use

Of the 369 subjects interviewed initially, 143 (39%) reported that they had used MDMA at least once. A total of 100 individuals (70% of positive responders) agreed to complete a

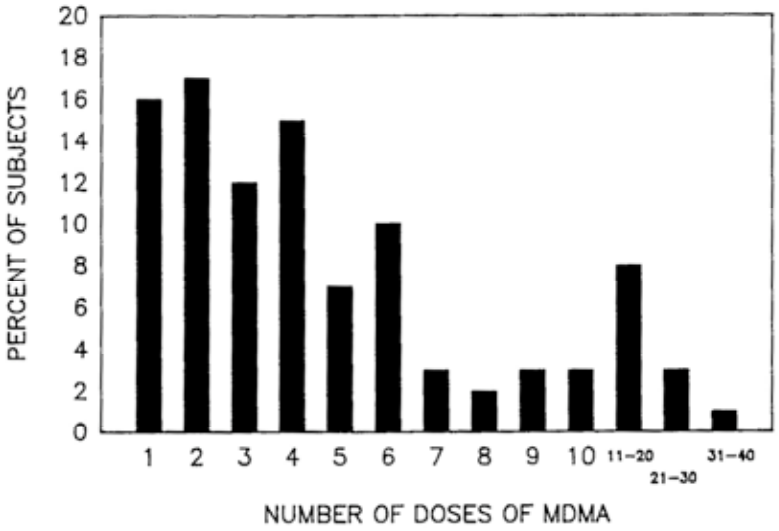

Figure 1. Frequency of MDMA use by recreational users (n = 100).

questionnaire concerning their subjective experiences while using the drug. The age of the respondents ranged from 18 to 25. The frequency of use by the subjects ranged from 1 to 38 doses of the drug (Fig. 1).

Acute Effects of MDMA

A total of 90% of the individuals reported that they had an increased sense of "closeness" with other people in the first few hours after taking MDMA. The subjects thought that they were more verbal during this time and were able to interact better with other people. In addition, a variety of physiologic effects were reported that were indicative of the sympathomimetic effects of the drugs. Tachycardia (72%), dry mouth (61%), tremor (42%), palpitations (41%), diaphoresis (38%), and parasthesias (35%) were the most frequently reported sympathomimetic effects. Trismus (tight jaw muscles) and bruxism (grinding of the teeth) were reported by 75% and 65% of the subjects, respectively. Similar sympathomimetic effects were observed with high-dose amphetamine use (Khantzian et al. 1979). Although increased alertness was reported by 50% of the subjects, 38% reported that they had difficulty concentrating during the acute phase of MDMA effects.

Visual hallucinations were noted by 20% of the respondents. Of note is the fact that these visual sensations rarely consisted of well-formed hallucinations. Rather, the subjects reported sensing that a flash of light or an object was in their peripheral visual field. However, when looking in that direction, they saw no objects. There were no reports of auditory hallucinations. A summary of the acute effects of MDMA in recreational users is given in Table 1.

Table 1. Acute Effects of MDMA[a]

Subjective sensation	Number of subjects with effect
Sense of "closeness" with other people	90
Trismus	75
Tachycardia	72
Bruxism	65
Dry mouth	61
Increased alertness	50
Luminescence of objects	42
Tremor	42
Palpitations	41
Diaphoresis	38
Difficulty concentrating	38
Paresthesias	35
Insomnia	33
Hot or cold flashes	31
Increased sensitivity to cold	27
Dizziness or vertigo	24
Visual hallucinations	20
Blurred vision	20

[a] Total number tested was 100.

Effects of MDMA 24 Hours After Ingestion

The subjects were also asked to report any residual effects of MDMA that were experienced on the day following the ingestion of the drug (Table 2). The most commonly reported effect was

Table 2. Subacute Effects of MDMA[a]

Subjective sensation	Number of subjects with effect
Drowsiness	36
Muscle aches or fatiguability	32
Sense of "closeness" with other people	22
Depression	21
Tight jaw muscles	21
Difficulty concentrating	21
Headache	17
Dry mouth	14
Anxiety, worry or fear	12
Irritability	12

[a] Total number tested was 100.

drowsiness (36%), which was frequently attributed to the acute insomnia that was reported by 33% of the respondents. Diffuse muscle aches and general fatiguability were reported by 32% of the subjects. Depression (21%), difficulty concentrating (21%), and headache (17%) were considered to be "negative" aspects of MDMA use occurring on the day after ingestion. Both the

sense of “closeness” with other people and trismus continued into the second day for 22% and 21%, respectively, of the respondents. Finally, a general sense of anxiety, worry, or fear as well as irritability were reported by 12% of the subjects on the day following MDMA use. Because of these frequent “negative” side effects, the respondents tended to prefer to use the drug on either a Friday or Saturday evening so that these drugs effects would not interfere with their school and/or work performance.

The subjects were also asked whether the beneficial effects of MDMA decreased with usage. In the 43 subjects who had taken two to five separate doses of the drugs, 21 (49%) reported that the effects of the drug decreased with subsequent doses. In subjects who had taken six or more doses of MDMA, 67% reported a decrease in beneficial effects over time. In general, the subjects reported that the “positive” effects of the drug decreased while the “negative” effects increased with successive doses. An increase in the size of a single dose of MDMA was found to increase the “negative” effects of the drug while decreasing the “positive” effects.

Long-Term Effects of Recreational MDMA Use

Only 2 of 100 subjects reported any long-term effect of the drug. One claimed a tendency to clench his teeth when anxious for a period of months following two separate doses of MDMA. A second subject attributed increased emotionality to the effects of three separate doses of MDMA.

DISCUSSION

The major finding of the present study is that MDMA induces a sense of “closeness” with other individuals that is distinct from the psychoactive effects of either stimulants or hallucinogens. Although this report does not constitute a formal epidemiologic study, it represents the first analysis of the subjective effects of MDMA in recreational users. Over the past year, unconfirmed reports from various campuses have suggested that the recreational use of this compound has rapidly gained popularity. As previously reported (Peroutka 1987), 39% of randomly selected undergraduates at a major university campus reported taking at least one dose of this compound. The median amount of MDMA usage was four doses, while the mean number of doses taken was 5.4. The amount of drug taken in a single dosage ranged from 60 to 250 mg (approximately 1 to 4 mg/kg).

By contrast, previous descriptions of MDMA effects have focused on patients who used the drug as an adjunct to psychotherapy. For example, Greer and Tolbert (1986) analyzed a group of 29 people who were given MDMA in a clinical setting. Fourteen of these patients were reported to have psycho-logic problems. The patients ranged in age from 18 to 54 years. As in the present study, jaw tension (22 of 29 patients) and insomnia (11 of 29) were frequent side effects of the drug. Similar results were also described by Downing (1986), who analyzed the subjective and physiologic effects of MDMA in a group of experienced users of the drug.

These observations are of significance since MDMA has been shown to produce neurotoxicity in animals. Ricaurte et al. (1985) showed that a structural analogue of MDMA,

methylenedioxyamphetamine, destroyed as many as 80% of serotonergic nerve terminals in the rat. A similar toxicity exists for MDMA and can occur after a single injection of the drug (Schmidt et al. 1986; Schmidt 1987a,b; Stone et aI. 1986, 1987; Battaglia et al. 1987; Commins et al. 1987). A single 5 mg/kg dose of MDMA in the rat decreases brain serotonin levels by 60% at 3 hours. Significant depletion of brain serotonin levels is observed as long as 7 days after a single 10 mg/kg dose of MDMA (Schmidt et al. 1986). Histopathologically, MDMA destroys fine serotonergic terminals, whereas larger serotonergic axon terminals with spherical varicosities appear to survive (O'Hearn et al. 1986). The mechanism of action by which MDMA produces neurotoxicity in laboratory animals remains unknown.

MDMA has also been associated with toxicity in human users. To date, there have been five deaths attributed to the recreational use of MDMA and its structural analogue, 3,4-methylenedioxyethamphetamine (MDE; "Eve") (Dowling et al. 1987). Three of the five cases apparently died from induced arrhythmias, one from an accidental fall, and the fifth from unknown acute causes. In addition, a case of presumed MDMA-induced toxic psychosis has been reported (Hayner and McKinney 1986).

By contrast, no serious acute reactions to MDMA were reported by the 100 subjects in the present study. Moreover, only two subjects reported any long-term effects of the drug. These effects were limited to a tendency to clench the jaw when anxious and a perceived increase in emotionality. However, the majority of multiple users did report that the "positive" effects of the drug decreased with frequent usage of MDMA. Similarly, Greer and Tolbert (1986) found that frequent or high doses of MDMA diminished the pleasurable effects of the drug while increasing the side effects. Conceivably, this finding may suggest subtle long-term effects of the drug on the human central nervous system since the primary psychoactive effects of MDMA last only 3 to 5 hours (Shulgin 1986).

The major question that remains unanswered is whether MDMA produces neurotoxicity in human users of the drug. An analogy between MDMA and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) may be appropriate. MPTP is a selective neurotoxin to the substantia nigra that was sold as "synthetic heroin" to recreational drug users (Davis et al. 1979; Langston et aI. 1983, 1984; Snyder 1984). Approximately 400 people in the San Jose, California, area are known to have been exposed to MPTP. Importantly, only seven of these patients currently have clinical evidence of Parkinson's Syndrome (Langston et al. 1983, 1984). However, positron emission tomography on four of the clinically normal patients has documented significant depletions of dopamine (Caine et al. 1985). These studies demonstrate that significant dopaminergic toxicity due to recreational MPTP use can exist in the absence of clinical deficits.

In the present study, no unequivocal evidence of toxicity could be detected in recreational users of MDMA through the use of this screening questionnaire. However, more thorough clinical evaluations are necessary to determine if any human neurotoxicity from this drug exists. Indeed, the data derived from MPTP users suggests that the lack of overt clinical toxicity in recreational users of MDMA does not rule out mild to moderate neurotoxicity to human Serotonergic pathways. Moreover, the clinical sequelae of neurotoxicity to human serotonergic neurons is unknown. Whether any long-term clinical effects will occur in the recreational users of MDMA is a critical question that will be answered in the years ahead.

REFERENCES

Battaglia G, Yeh SY, O'Hearn E, Molliver ME, Kuhar Mi, De Souza EB (1987): 3,4-methylenedioxymethamphet amine and 3,4-methylenedioxyamphetamine destroy serotonin terminals in rat brain: Quantification of neurodegeneration by measurement of [^{3}H]paroxetine-labeled serotonin uptake sites. J Pharmacol Exp Ther 242:911-916

Caine DB, Langston JW, Martin WRW, et al. (1985): Positron emission tomography after MPTP: observations relating to the cause of Parkinson's disease. Nature 317:246-248

Commins DL, Vosmer C, Virus RM, Woolverton WL, Schuster CR, Seiden LS (1987): Biochemical and histological evidence that MDMA is toxic to neurons in the rat brain. J Pharmacol Exp Ther 241:338-345

Davis GC, Williams AC, Markey SP, et al. (1979): Chronic Parkinsonism secondary to intravenous injection of meperidine analogues. Psychiat Res 1:249-254

Dowling GP, McDonough ET, Bost RO (1986): "Eve" and "Ecstacy": A report of five deaths associated with the use of MDEA and MDMA. JAMA 257:1615-1617

Downing J (1986): The psychological and physiological effects of MDMA on normal volunteers. J Psychoactive Drugs 18:335-340

Greer C, Tolbert R (1986): Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs 18:319-328

Hayner GN, McKinney H (1986): MDMA: The dark side of ecstacy. J Psychoactive Drugs 18:341-347

Khantzian EJ, McKenna MD (1979): Acute toxic and withdrawal reactions associated with drug use and abuse. Ann Int Med 90:361-372

Langston JW, Ballard P, Tetrud JW, Irwin 1(1983): Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science 219:979-980

Langston JW, Ballard P (1984): Parkinsonism induced by l-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): Implications for treatment and pathogenesis of Parkinson's disease. Can J Neurol Sci 11:160-165

O'Hearn E, Battaglia C, DeSouza EB, Kuhar MJ, Molliver ME (1986): Systemic MDA and MDMA, psychotropic substituted amphetamines, produce serotonin neurotoxicity. Soc Neurosci (Abs) 11:1233

Peroutka SJ (1987) Incidence of recreational use of 3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy") on an undergraduate campus. New Engl J Med 317:1542-1543

Ricaurte C, Bryan C, Strauss L, Seiden L, Schuster C (1985): Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. Science 229:986-988

Schmidt CJ (1987a): MDMA: Acute administration of methylenedioxymethamphetamine: Comparison with the neurochemical effects of its N-desmethyl and N-ethyl analogs. Eur J Pharmacol 6:81-88

Schmidt CJ (198Th): Neurotoxicity of the psychedelic amphetamine, MDMA. J Pharmacol Exp Ther 240:1-7

Schmidt CJ, Wu L, Lovenberg W (1986): Methylenedimethoxymethamphetamine: A potentially

neurotoxic amphetamine analog. Eur I Pharmacol 124:175-78
Shulgin AT. The background and chemistry of MDMA (1986): **J** Psychoactive Drugs 18:291-304
Snyder SH (1984): Clues to aetiology from a toxin. Nature 311:514
Snyder SH (1986): Enlightenment in a pill. In Drugs and the Brain. New York, W.H. Freeman, pp 179-205
Stone DM, Stahl DC, Hanson CR, Gibb JW (1986): The effects of 3,4-methylenedioxymethamphetamine (MDMA) on monoaminergic systems in the rat brain. Eur J Pharmacol 128:41-48
Stone DM, Johnson M, Hanson CR, Gibb JW (1987): A comparison of the neurotoxic potential of methylenedioxyamphetamine (MDA) and its N-methylated and N-ethylated derivatives. Eur J Pharmacol 4:245-248