

The Psychological and Physiological Effects of MDMA on Normal Volunteers†

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A member of the largest known family of hallucinogens, the substitution derivatives of mescaline phenylisopropylamine. 2-methylamino-1-(3,4-methylenedioxyphenyl)-propane (MDMA) is also referred to as 3,4-methylenedioxymethamphetamine. Quoting Shulgin (1981):

A number of hallucinogenic drugs are known with a methylenedioxy group located in place of two adjacent methoxyl groups. The simplest of these and one of the best studied is MDA It is unusual . . . in that it leads not to the usual mescaline-like state of visual and sensory distortion, but rather to a state of sensory amplification and enhancement without appreciable sympathomimetic stimulation. This property has led to extensive studies of this material in conjunction with psychotherapy, where there is usually seen an easy communication between subject and observer, or between subjects (Naranjo, Shulgin & Sargent 1967). This affective interaction is even more clearly evident in the N-methyl homolog of MDA, MDMA which is substantially free of perceptual distortion at effective dosages (75-150 mg) (Shulgin & Nichols 1978). The N-ethyl counterpart (MDE) is similar in action except that it is about 25% less potent.

This particular sequence of phenylisopropylamines was first synthesized and patented in Germany in 1914, reportedly with the purpose of using it for appetite control (Merck 1914). Lack of commercial interest led to the expiration of the patent and the entry of MDMA into the

public domain, effectively making the chemical valueless to the great pharmaceutical houses. During the period of 1953-54, MDMA was one of eight compounds studied in five animal species (i.e., mouse, rat, guinea pig, dog and monkey) by the Army Chemical Center. The toxicology study showed MDMA to be one of the more toxic of the drugs studied, in most animals, second only to MDA (Hardman, Haavik & Seevers 1973). These findings in animals are placed in perspective, as compared to therapeutic dosages in humans, in the most current summary of MDMA use and safety (Cotton 1986): "As reflected in the record (Braun, Shulgin & Braun 1980), MDMA has been administered to animals in a number of different studies. . . . the oral doses administered therapeutically are less than one percent of the LD₅₀, indicating a very high margin of safety. . . . the overwhelming weight of medical opinion evidence received in this proceeding concurred that sufficient information on MDMA existed to support a judgment by reputable physicians that MDMA was safe to use under medical supervision."

Having resynthesized the phenylisopropylamine series, Shulgin and Nichols (1978) first tested, analyzed and reported on MDMA. The concept of "affective interaction," "a state of sensory amplification and enhancement without appreciable sympathomimetic stimulation . . . an easy communication between subject and observer" that is characteristic of MDMA was introduced by Shulgin in 1981. The evident value of an affective enhancer—without perceptual distortion—for psychotherapy, business, indeed all interpersonal goal-centered activities led both to serious investigation and strong public media interest (Weil & Rosen 1983). Dec-

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ades of customary social exploration, followed by systematic investigation, were condensed into a few years of serious study, exemplified by Kueny's study (1980) on the feasibility of using MDMA to facilitate psychotherapy and Greer's pioneering description (1983) of the results of administering MDMA to 29 human subjects in a medical therapeutic setting. As no legal structure for controlling usage within a regulatory social institution yet existed, exponential growth of a user population took place concurrent with extensive media attention (Cohen 1985; Corwin 1985; Katz 1985; Klein 1985; Mandel 1985; Polman 1985; Unsigned 1981).

Although documented negative effects were minimal (Cotton 1986; Nichols & Glennon 1984), the very presence of an unknown unregulated drug with active, affective interaction qualities created a demand for controls. On July 1, 1986, the Department of Justice's Drug Enforcement Administration used emergency administrative powers to place MDMA in Schedule I: having no medical use, high abuse potential and dangerous to use. This placement in Schedule I, rather than Schedule III, was protested by a small group of physicians, therapists and researchers. The necessity for scheduling MDMA was endorsed, but the disagreement derived from placing present research and potential medical therapeutic prescription out of practical reach.

MATERIALS AND METHODS

A pilot study of the effects of a single exposure to MDMA in 21 healthy volunteers was conducted to provide baseline data on cardiovascular, biochemical and neurobehavioral parameters. Informed consent for the use of this experimental material was met by limiting the volunteer subjects to persons who had already taken MDMA at least once and thus had a basis for anticipating their experiences. What bias was introduced by this previous experience factor cannot be readily estimated—other than a possible reduction in anxiety-produced psychophysiological responses due to absence of first-time uneasiness or the exclusion of subjects potentially prone to negative experiences, inasmuch as only persons with previously favorable experiences would volunteer.

All 21 subjects were personally known to a member of the research staff, stated they were in good health (with two exceptions) and were considered mentally stable, both by their own account and by the staff. The two health exceptions were both individuals with ocular problems, one with glaucoma and the other being legally blind from retinal degeneration.

SETTING

On October 20, 1984, the participants were asked to

meet at appointed gathering points in the San Francisco Bay Area to be taken by volunteer drivers to the ocean front private home where the study was conducted. This was to obviate the need for the subjects to drive home afterward. On arrival they were assigned to three different subgroups according to their personal characteristics and needs of the five interlocking studies. All 21 filled out an individual data sheet before the experience began. Fourteen (14) of 21 completed an MDMA experience report afterward, on which other data were based.

Blood chemistry for the entire group included a 25-item standard panel, including total protein, albumin, globulin, albumin/globulin ratio, bilirubin, total, direct and indirect serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, lactic dehydrogenase, blood urea nitrogen (BUN), creatinine, BUN/creatinine ratio, uric acid, calcium, phosphorus, cholesterol, triglycerides, glucose, sodium, potassium and chloride. A subsample determined metabolic breakdown pathways of MDMA over time and mutagenicity (Ames Test). This analysis is not yet available.

Physiological measures included pulse and blood pressure for all subjects as well as neurological and electrocardiograph tests for a subsample. The schedule included preingestion, 30 minutes, one-, two-, three-, four-, five-, six- and 24-hour cardiovascular data collection. The blood chemistry routine for all subjects included preingestion, six-hour, and where possible, 24-hour samples. Eleven (11) of the 21 subjects had all three basic samples drawn, five had two, and five only one.

Neurological examinations were carried out at regular intervals over a 24-hour period on 10 subjects. Electrocardiograms were taken on five subjects.

STRUCTURE

At the time of the experiment, the amount of the dose of MDMA to be administered was discussed by the staff with the participants. The staff's preference was for a straightforward one milligram per pound of body weight, in order to provide easy intrasample comparison of the independent parameters. This dosage was opposed by the MDMA-experienced volunteers who argued that their previous sessions had shown that an optimal body level was necessary to attain the desired psychic effect. As no overriding counterstatement could be found for this argument, participants were allowed to select their own dose, resulting in a range of 0.8 to 1.9 mg/lb, the mean being 1.14 mg/lb. No added dose was requested and no subject was dissatisfied with his/her subjective experience.

All participants had pulse, blood pressure and blood chemistry readings taken immediately prior to ingestion

of their measured dose of MDMA. All wore color-coded badges to correspond with their specific subsets of medical testing, making possible ready identification throughout the approximately seven hours of testing.

INDIVIDUAL DRUG EXPERIENCE QUESTIONNAIRE RESPONSES

The data requested aimed primarily at drug experience, both MDMA and other. Simple parameters related to the effects of drug usage were requested. All responses were the opinion of the respondent. No attempt was made to verify their accuracy.

Demographic Characteristics

Thirteen (13) of the 21 subjects were men and eight were women. Age ranged from 20 to 58, with a median of 39. Median education was four years of college.

Previous MDMA Experience

Regarding the subjects' previous MDMA experience, the time range was up to six years, with a median of 2.3 years. The number of previous MDMA experiences ranged from one to 15 (median 8.5). The reported frequency of use was from slightly less than once monthly to seven months, with the mean being 2.2 months.

Other Drug Use

Regarding other current drug use, 84 percent of the subjects used alcohol, 56 percent used marijuana and 49 percent used cocaine. Two persons used refined sugar. One person reported being "addicted" to marijuana, two to refined sugar. No other drug dependence was reported. One person used tobacco and none used opiates or other drugs, besides those previously mentioned.

General Health

Concerning their health, all persons considered themselves healthy. Two had severe eye conditions. The woman with glaucoma had used MDMA 13 times, without worsening her visual problems. The other person had used MDMA 10 times, also without complications. MDMA had no effect on health according to 70 percent ($N = 10$), while the remainder did not answer. Asked a second question as to whether MDMA was good or bad for their own health (in their opinion), five said good, one bad, two undecided and six did not answer.

Negative Effects

Regarding specific bodily symptoms during either the present experience or past experiences, 80 percent reported jaw clenching, 60 percent headaches, and 20 percent eyelid twitches. No one objected to these effects.

Reported mental deficits either during or after the MDMA experience were minimal and difficult to interpret. Seemingly these phenomena, if present, are transient, minimal and inconclusive.

Possible Effect on Social Adjustment

Since taking MDMA is there any evidence of either gain or loss in life adjustment, either social or interpersonal? Six persons (30%) reported major life changes since first taking MDMA, two specified marriage and two divorce. No social conflict was reported, two had received traffic tickets and none were unemployed. Three had found better jobs. The available evidence does not suggest any interpersonal or social effect, either positive or negative.

Based on this and previous experiences, the volunteers joined in recommending MDMA to others, both to their own intimates and their social contacts. In addition, 90 percent were favorable to the idea of allowing cancer patients to have MDMA.

Would these persons want to continue using MDMA? All signified yes. All felt that they had benefited, with 90 percent stating their relationships were "better" and none stating "worse."

Preferred Frequency of Use and Recommended Legal Status for MDMA

When asked their preferred frequency of use, the range was one to four months, the mean being 2.2 months. Regarding preferred dosage, the range was 75-200 mg, the mean being 158 mg. This mean is near the average the participants actually chose for the present study, 165 mg.

The final opinion requested of the group was their recommendation concerning the legal status of MDMA. No categories were given, yet the 11 answers fit into three categories: (1) therapists and spiritual leaders only; (2) medical prescription; and (3) over-the-counter. Eight (70%) recommended legal controls, while three recommended over-the-counter availability. Three indicated "prescription only," one "therapist only" and four both.

CARDIOVASCULAR RESPONSE

All subjects experienced an elevation of blood pressure and pulse rate; the hypertensive effect of MDMA peaks within one hour of ingestion. Approximately one half (10) peaked at 30 minutes, nine persons at one hour, one person at two hours and one person at three hours.

Four subjects peaked at a diastolic pressure over 100 mm Hg. The highest single peak of 200/120 occurred in a 58-year-old woman who had taken 1.00 mg/lb, slightly under the group average. The woman taking the highest per pound dosage (1.9 mg/lb) had the greatest car-

diovascular response; her pulse going from 72 per minute to 148 within 30 minutes after MDMA ingestion and to 128 at two hours. She had no particular discomfort or awareness of her heart activity.

By the sixth hour, 60 percent (nine of 14 persons) were below their predose blood pressure levels. Of the 12 subjects available for the taking of 24-hour blood pressures the next day, five were clearly below their preingestion pressures, but well within normal limits. Comparing maximum cardiac workload, as determined by beginning flow compared to maximum flow volume, against milligram per pound of MDMA, there was no correlation either by age or dosage.

BIOCHEMICAL RESPONSE

Turning to the 49 blood chemistry panel samples taken from these 21 subjects, 11 subjects had three chemistry panels, six had two panels, and four gave blood only once. For this reason, the actual data are suggestive rather than definitive in certain areas.

Nothing positive stands out in the blood chemistry. The thyroid, renal, serum amylase and creatine phosphokinase tests were entirely within the normal range in all samples. Variations outside the normal range were all slight, being only a few points above the laboratory maximums and none approaching statistical significance. Blood glucose was elevated in six samples, but as there were no controls on eating or drinking, the significance cannot be assessed. Potassium, calcium and phosphorus were slightly above the normal range in five persons each. Albumin was elevated in seven samples, five being pre-drug tests. The albumin/globulin ratio was above normal in nine samples, with six of the nine being two persons who presented a stable finding throughout their course from before drug testing up to and including the 24-hour sample.

NEUROBEHAVIORAL STUDY

At preingestion, one to two hours postingestion and four to five hours postingestion, 10 subjects were examined. In addition, six subjects were examined at approximately 24 hours after ingestion.

State of consciousness was measured by alertness and lucidity of thought. No subjects were found to have impairment of consciousness in these respects at any time. Subjects reported feelings of euphoria as well as an increase in physical and emotional energy, and there was no evidence for depression/crash at 24 hours. Two subjects reported an increase in quantity of sleep above their usual duration. There was no evidence of confused thinking at any point. Visual and auditory hallucinations were absent in all subjects except one who reported some visual im-

agery of a nonhallucinatory nature prior to ingestion. All subjects reported that their attention was focused on the here and now rather than future or past. Euphoria and time focus diminished by three hours with a return to baseline in the bulk of the group. Several subjects reported mild to moderate enhancement of mood at 24 hours.

All subjects were assessed for short-term memory function and digit repetition. There was no change from baseline. Difficulty with multiplication was seen in three of the 10 subjects at peak drug levels. This appeared to be due, at least in part, to difficulties in focusing on the task. Judgment was impaired in four of 10 subjects at one to two hours, with idiosyncratic responses given to the hypothetical problems requiring decision making. This suggests that important decision making should be postponed or reevaluated after the MDMA experience has concluded.

Dilation of pupils was seen in all subjects, except for the individual who was blind. He reported an enhanced sense of light. Light reflex was maintained in all subjects. Nystagmus was present in eight subjects at one to two hours, with three subjects manifesting nystagmus in all directions including rotary nystagmus. By four hours, nystagmus had ceased in five of the eight subjects. At 24 hours, two subjects demonstrated an equivocal nystagmoid movement.

Six of 10 subjects had evident jaw clench and an increase in the jaw reflex. By four hours, the jaw clench had diminished in all subjects and persisted mildly in only one at the 24-hour examination. Deep tendon reflexes were significantly enhanced in eight of 10 subjects. There was a return to baseline at four to five hours in all subjects. One subject had an equivocal plantar reflex and no other pathological reflexes were demonstrated. Finger-to-nose testing was impaired in two subjects at one to two hours. Gait was affected in seven of the subjects with varying degrees of instability and incoordination. These results suggest that tasks requiring significant coordination and concentration should not be performed while under the influence of MDMA, especially operating motor vehicles.

All subjects reported heightened sensual awareness, with three reporting sexual arousal. There was an increase above usual frequency for sexual contact within the 24-hour period.

One subject reported nausea and vomiting at three hours. No difficulties with urination or defecation were reported. Headaches were absent as was insomnia.

Inasmuch as the study began in the morning hours, this study did not provide a valid measure of sleep distortion. In addition, electrocardiograms were normal in all five subjects tested. Moreover, appetite was suppressed for the 24-hour period in all individuals, with no food

consumption in the initial five-hour period. In conclusion, this study indicates no significant immediate or subsequent neurobehavioral consequences from the use of MDMA within the parameters examined.

SUMMARY

The experimental subjects were older than the average general population, more educated and considerably experienced in drug use. They considered themselves to have benefited by their MDMA experience, with no evidence of harm.

There were moderate, consistent biochemical, cardiovascular and neurobehavioral changes within normal limits that peaked between one and two hours following ingestion, returning to predrug levels within 24 hours. This experimental situation produced no observed or reported psychological or physiological damage, either during the 24-hour study period or during the three-month follow-up period.

While the subjects are not typical of the general population, the findings support the general impression among knowledgeable professionals that MDMA is reasonably safe, produces positive mood changes in users, does not cause negative problems (if used sparingly and episodically) and is without evidence of abuse.

Certainly, any drug that causes ataxia, elevates blood pressure and pulse is potentially unsafe. One can say little about safety when effects and side effects are studied for only 24 hours and then a blood cytology is obtained after three months. In this study, safety must exclude long-term toxicity. Not enough is known about MDMA's long-range effects other than information from random anecdotal evidence supplied by a few clinicians plus self-reports by unselected and unsupervised users.

From the information presented here, one can only say that MDMA, at the doses tested, has remarkably consistent and predictable psychological effects that are transient and free of clinically apparent major toxicity. The experimental subjects believed that MDMA is both safe and beneficial, but there is insufficient evidence to accurately judge either the drug's potential harm or benefit.

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