

What is MDMA?

By Alexander T. Shulgin

(Dr. Alexander Shulgin is a chemist and pharmacologist who has been active in research in the area of psychotropic drugs for many years. This paper is to be presented at the summer meeting of the California Association of Toxicologists in Sacramento, California, August 3, 1985.)

MDMA has been thrust upon the public awareness as a largely unknown drug which to some is a medical miracle and to others a social devil. Many questions have been asked. It is sad that most of these questions have received answers which have been quite contradictory, and often untrue. I have had innumerable calls from reporters and magazine staff writers, most of whom have bemoaned the fact that they always seem to encounter one of two extreme positions. There have been the born-again protagonists who say that once you have tried it you will see the light and will defend it against any attack, and there have been the staunch antagonists who say that this is nothing but LSD revisited and it will certainly destroy our youth. There are many voices to be heard presenting the modest inventory of facts that are known, but there is no one who will answer questions in a way that can be heard by both camps. Let me distill several reporter interactions into a hypothetical interview which parallels the many telephone inquiries I have had to field in the last few months. The questions are typical. Some questions call for opinions, but many have factual answers which are documented.

What is MDMA?

MDMA is the abbreviation given to a chemical with the full name 3,4-methylenedioxymethamphetamine. It has also been called in recent literature N-methyl-2-(3,4-methylenedioxyphenyl)-isopropylamine and 2-methylamino-1-(3,4-methylenedioxyphenyl)-propane. In Beilstein it is called methyl-(beta-(3,4-methylenedioxyphenyl)-isopropyl)-amine; in the early Chemical Abstracts it is called N, alpha-dimethyl-homopiperonylamine, in the pre-1972 Chemical Abstracts it is known as N, alpha-dimethyl-3,4-methylenedioxyphenethylamine; and in the most recent Chemical Abstracts, it is N, alpha-dimethyl-1,3-benzodioxole-5-ethanamine. Although it has many names, to a chemist there is a single chemical structure represented.

What is Ecstasy (or MDM, or Adam, or XTC, or E, or Doctor)?

These are names of street drugs, which have proven

to be on many occasions the same as the MDMA as described above. There have been some misrepresentations.

Is MDMA related to MDA?

Yes, it is very closely related to MDA. MDA is the abbreviation for 3,4-methylenedioxyamphetamine, currently listed as a Schedule I drug, under the classification of "hallucinogenic substances." But this is a structural relationship, not a pharmacological relationship. A structural relationship invokes slight rearrangements of atomic features.

MDMA is related to MDA (a hallucinogen) by being its N-methyl analog. It is similarly related to N-methyl-3,4-methylenedioxy-phenethylamine (an antitussive) by being its alpha-methyl homolog. It is similarly related to methamphetamine (a stimulant) by being its 3,4-methylenedioxy-analog. However, pharmacologically, it bears little resemblance to any of these drugs.

Is MDMA a psychedelic drug?

Not in the sense of the popular definition of psychedelic drugs where one makes immediate association with drugs such as mescaline or LSD. There is neither the visual distortion nor the interpretive problems that have been reported with most psychedelic drugs.

How is MDMA made?

There are published procedures for its production. The earliest literature describes the use of safrole as an intermediate (1,2). More recently published procedures have employed piperonylacetone as a starting material (3,4). The optical isomers have been prepared by the reduction of the amides prepared by formulation of the enantiomers of MDA (5). In one analytical report, MDMA was prepared (with byproduct impurities) from MDA by reaction with methyl iodide (6).

Where can one get MDMA?

It appears to be readily available on the street. But most of the psychiatrists who have reported on its clinical utility have prepared it themselves, a procedure which in many states meets the legal requirements for drug manufacture. MDMA has recently been offered to researchers by NIDA (National Institute on Drug Abuse), Rockville, MD.

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Is MDMA toxic?

There are two interpretations of the word "toxic." In the strict medical sense, toxic means "Is the drug poisonous; i.e., is it lethal?" In the popular language, toxic means "Does the drug have poisonous effects; i.e., are there unwanted side-effects?"

In answer to the first meaning, yes, MDMA is toxic, as is every chemical known if sufficiently high levels are administered. In an extensive toxicity study (7) the lethality of MDMA was compared with seven other related phenethylamines (including MDA and mescaline) in five animal species. The comparative toxicity is given below for these three compounds, as their LD-50 values in mg/Kg:

	MDMA	MDA	Mescaline
Mouse	97	68	212
Rat	49	27	132
Guinea Pig	98	28	328
Dog	14	7	54
Monkey	22	6	130

The toxicity thus lies as less than that for MDA, and more than that for mescaline.

A second study of toxicity in isolated and aggregated mice (8) has reported the LD-50 (i.p.) to be 106 mg/Kg (and 30 mg/Kg in aggregated colonies). The LD-50s for MDA were given (again in mice, i.p.) as 90 mg/Kg and 45 mg/Kg (aggregate). These values are good agreement with the reference (7) data above. A typical human dosage of MDMA (120 mg) is about 1.5 mg/Kg.

As to the second meaning of toxicity (toxic side-effects) there are some side-effects that have been frequently reported. See the "side-effects" question below.

Have there been deaths ascribed to the use of MDMA?

Yes. There have been three deaths ascribed to the use of MDMA, but the role that MDMA might have played, or whether MDMA was even involved, is uncertain. Two DAWN reports imply association, one in San Francisco, and one in Seattle. The San Francisco report was mis-entered in the DAWN network, and has been verified as a death involving MDA and alcohol (9). The Seattle report contained evidence that the material present was similar to, but not the same as, MDA. It was assumed to be MDMA, but not verified as such. I have not been able to get any information on the third alleged death.

Is it true that the effective level is close to the toxic level?

As the toxic level in man is not known, this closeness cannot be determined. The term "therapeutic index" has been used as a measure of comparative safety; i.e., how far apart are the effective levels and the lethal levels? The toxicity in mammals following parenteral administration lies between 14 and 100 mg/Kg. Oral toxicity has never been reported. The orally effective dosage in man is about 1.5 mg/Kg so the effective safety factor is greater than ten-fold.

What does MDMA do in animals?

There have been two *in vivo* studies of MDMA in animals. The earlier of these was the toxicology study by Hardman *et al.* (7) wherein several behavioral studies were reported in several animal species. Comparisons of MDMA with seven other structurally related phenethylamines, in the areas of motor activity, autonomic activity, and CNS activity, showed that it was, in general, similar to the other related compounds. Behavioral effects were observed at levels that approached the toxic levels. No particular effect deserved special mention in the discussion section of this paper.

The latter study (10) has reported both stimulant and analgesic effects of MDMA, in comparison to MDA and several higher homologs and analogs. It proved to be among the most potent of all compounds studied. No extrapolation to human psychotropic response was made.

What does MDMA do in man?

It provides, at least within a therapeutic setting, a brief period of openness and freedom from fear and defensiveness that allows a trust to be established between a therapist and a patient. There is no amnesia and no loss of control. An excellent summing-up can be found in a quote from a recent report by an admitted proponent (11).

"The drug takes away all your neuroses. It takes away the fear response. There is an overwhelming feeling of peace; you're at peace with the world. You feel open, clear, loving. I can't imagine anyone being angry under its influence, or feeling selfish or mean, or even defensive. You have a lot of insights into yourself, *real* insights: that stay with you after the experience is over. It doesn't give you anything that isn't already there. It's not a trip. You don't lose touch with the world. You could pick up the phone, call your mother, and she'd never know."

Two clinical studies have been reported that emphasize the qualitative aspects of MDMA therapy. A pilot study by Kueny on nine subjects (12) and another by Greer on 29 subjects (13) have both shown therapeutic value.

What is the chronology of effects of MDMA in man?

The usual dosages of MDMA employed in clinical work lie between 100 mg and 150 mg of the amine as the hydrochloride salt. A typical dose would be 120 mg. The onset of transition occurs between 25 and 30 minutes following oral administration. The changes stabilize at or just before the one-hour point and the plateau of effects persists for about 40 additional minutes. If desired, the plateau can be extended for an additional hour with the use of a supplementary 40-50 mg at the 1:30 point of the session. Recovery to the pre-session baseline psychologically generally requires an additional three hours. The complete dispelling of physical residue (anorexia, for example) may take additional hours.

Can MDMA be abused?

Certainly. When it is used therapeutically, the medical environment precludes much of the abuse potential, but with indiscriminate availability on the "street" it can, and will, be overused and will inevitably be associated with abuse situations.

A related question (of a more legal kind) is, does MDMA have a *high* abuse potential. This is, of course, the crux of the proposed scheduling of MDMA as a high-abuse-potential drug without medical utility. The FDA has explicitly stated that the use of any drug not approved by them constitutes drug abuse. Their implicit stand is that any drug that can be pleasurable has a high abuse potential. The questions posed here lie outside of the pharmacologist's territory.

How would you classify MDMA clinically?

There is no existing clinical classification for MDMA. The research currently exploring the use of MDMA in psychotherapy more closely resembles a medical procedure such as hypnosis or acupuncture. There is no therapeutics classification for this drug although efforts have been made to define one (14). The existing classification of "anti-depressant" could be justified, remembering that the effects are relatively abrupt following a single application, rather than being gradual following chronic medication.

Is MDMA illegal?

At the moment, no. (Editor's Note: Dr. Shulgin prepared this article before the DEA's emergency scheduling became effective. As of July 1, MDMA is a Schedule I drug and its possession is potentially a felony.) It was proposed for scheduling in the Controlled Substances Act by notice in the Federal Register in 1984 (15). However, there were several petitions filed requesting hearings to determine the appropriate schedule for listing, and this process was agreed to by the DEA (16). A program for hearings

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MDMA Analyzed

A sample of alleged MDMA recently obtained from a recreational user attending the Drug Enforcement Administration hearings in Los Angeles was analyzed by PharmChem's Research and Development Laboratory. The tablet, weighing 398 mg., was alleged to contain 125 mg of MDMA. Qualitatively and quantitatively analyzed by gas chromatography, the sample contained MDMA without adulteration plus inert material as filler and binding agents.

Quantitative results:

26.3% MDMA Hydrochloride (105 mg)
22.1% MDMA Free Base (88 mg)

While the sample contained less MDMA by weight than alleged, the tablet contained MDMA as the only psychoactive ingredient.

This compares with a 50 percent validity rate for alleged MDMA samples submitted to PharmChem's Analysis Anonymous service for qualitative analysis between 1978 and 1983. Sixty samples were submitted as MDMA, MDM, Ecstasy, XTC, or Adam during the five year period, excluding 1979 because of incomplete data.

There is no way of knowing if clients submitting samples under street names such as "XTC" or "ADAM" actually understood what they were supposed to be. These street names have become popular synonyms for MDMA only since recent widespread publicity about the drug.

Half of the alleged MDMA samples analyzed by PharmChem contained only MDMA while 16, or 27 percent, were adulterated or diluted with other drugs or unidentified substances. Thirteen samples (22 percent) were drugs other than MDMA, mostly MDA, and only one alleged MDMA sample could not be identified.

Six alleged MDMA samples in 1980 contained MDE [2-Ethylamino-1-(3,4-methylenedioxyphenyl)propane], which some believe will become a legal substitute for MDMA. The MDE samples originated from Texas, Virginia, San Francisco, Boone, N.C., Cambridge, Mass., and San Diego.

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across the country was agreed upon, and arguments and rebuttals were filed. This judicial process was aborted by an evocation of the Emergency Act (S-5656) on May 31, 1985 (17), which proclaimed MDMA as being an "imminent hazard to public safety" thus demanding that it be immediately scheduled as a Schedule I drug, such action to be effective in 30 days. As of the moment, it must be assumed that MDMA will be illegal on July 1, 1985. Apparently, the public hearings will still be held, and judicial recommendations will be made as a result of those hearings.

What will be the eventual fate of MDMA?

This is conjecture into untested legal area. The emergency scheduling will place MDMA into Schedule I for a full year, with an allowed six-month extension. Many states automatically parrot the federal drug laws in the rewriting of their own statutes, and it must be assumed that several states will amend their narcotics laws to include MDMA as a Schedule I drug. Action in this direction has already been initiated in Texas. Although hearings must be allowed at the end of a year (federal law), the current hearings will have been concluded by then and some decision will have been made regarding a more modest scheduling. However, there are no legal precedents at hand that permit the reevaluation of state law to reflect reconsiderations of federal assignment. It must be assumed that MDMA will remain a Schedule I drug in many states regardless of any modification of federal stand.

How does MDMA act?

The current consensus is that MDMA acts through some effect on the serotonergic nervous system. A number of animal models have been studied to both explain its mechanism of action, and to compare it to structurally related analogs. A major focus in all of these studies has been the fact that the optically active isomer of all the psychedelic drugs (LSD, MDA, DOM, DOET, and DOB) is the "R" (or *levo*) isomer, and the optically active isomer of MDMA (and several stimulants such as amphetamine) is the "S" (or *dextro*) isomer (5). This isomeric difference between MDMA and MDA has been shown to be true in the release of serotonin from rat-brain synaptosomes (18). In rat discrimination studies (train a rat to respond differently to drug A or no drug, and then challenge with drug B). In rats trained to distinguish DOM from

saline, MDMA did not look like DOM (19). However, in rats trained to distinguish MDA from saline, or dextroamphetamine from saline, MDMA in both cases was distinguished from saline (20).

Can MDMA cause brain damage?

The answer is not known. No one has reported any study that addresses this question. One of the major arguments presented supporting the emergency scheduling of MDMA as an imminent hazard (17) was an unpublished study (by Ricaurte et al., ref. 21) on MDA in rats. Here the exposure of rats, acutely, to MDA led to the observation of degeneration of nerve terminals (possibly serotonergic) in the hippocampus and the striatum. No dopaminergic problems were observed although these were reported earlier (22) for amphetamine and methamphetamine. From these observations, it has been extrapolated that MDMA (a different drug than MDA or amphetamine) is likely to cause brain damage in man (a different species than rat).

Are there other drugs with actions similar to MDMA?

None are known at the present time. Several drugs are being studied that have some properties in common, but often there is either the absence of the benign "freedom from fear" property, or the presence of some disturbing "psychedelic" side-effects. As of the moment, MDMA remains unique.

What are the side effects of MDMA?

A number of side-effects have been reported with some regularity as a corollary to MDMA usage. In an extensive clinical study involving some score subjects (23) there was a consistent pressor response resulting in a blood pressure increase of some 15 or so mm Hg observed at the onset of action, although this disappeared shortly thereafter. There were some complaints of bruxism (teeth clenching) and nystagmus (eye twitching). Some subjects reported a lethargy and headache the following day. These were held by most subjects as being minor problems.

How can one tell if one has valid MDMA?

The record of analytical sophistication relating to the verification of a sample as being MDMA has not been good. Tools such as gas chromatography (GC) or gas chromatography/mass spectrometry (GCMS), and infra-red are excellent, but they have been rarely employed. The earliest report of analysis of seized material (24) showed color tests and U.V. to be inadequate, but reported that infra-red spectroscopy

and GC retention times to be satisfactory for identification. TLC properties suggest that MDA can be effectively distinguished from MDMA (6). Some mis-identifications have been reported, both as to compound

nomenclature (MDMA vs. MDEA; ref 25) and as to precursor identification (piperonylacetone vs. piperonylmethyl ketone, ref 26).

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