MDMA REPRESENTS A NEW TYPE OF PHARMACOLOGIC AGENT AND CANNOT BE CONSIDERED TO BE EITHER AN HALLUCINOGENIC AGENT OR AN AMPHETAMINE-TYPE STIMULANT

PREFATORY REMARKS

Attached as an appendix is a summary of the training and professional experience that I consider relevant to the following discussion.

A critical issue to be addressed at the heart of these proceedings is whether MDMA may represent the prototype of a new therapeutic category. It is well known that nitrous oxide and diethyl ether, as prototypes of the general anesthetics, were first used in a recreational way. Had these been subject to scheduling, the era of painless surgery that these two particular substances ushered in might well have been needlessly delayed.

Similarly, because MDMA presents abuse potential as a recreational drug, is it prudent to schedule it so that it will be extremely difficult, if not impossible, to assess whether it does indeed represent a novel drug prototype that potentially may be a major advance in psychotherapy? The fact that only a few psychiatrists have had any experience with MDMA-assisted therapy does not negate the fact that MDMA may have such potential.

If MDMA does represent a novel drug prototype, then one should be able to demonstrate that it differs from currently recognized drugs in some significant way. In the present instance, can MDMA be shown to differ significantly from known drugs of abuse, particularly of the hallucinogen (psychedelic,

psychotomimetic) type?

Although MDA and other hallucinogens have been used experimentally as adjuncts to psychotherapy [1-5], there was controversy regarding their value. Thus, utility cannot be claimed for MDMA if it is simply another hallucinogenic agent. Rather, MDMA must be shown to offer a pharmacologic profile that sets it apart from presently known agents.

At the outset of this discussion, it must be pointed out that citations will be made to animal studies on MDA, MDMA, and other psychoactive substances. However, it must be clearly recognized that such approaches can be used only to **model** the ultimate situation; human studies. Therefore, whenever clinical descriptions are available for the effects of psychoactive drugs, these descriptions must of necessity supercede results from any animal studies. Although animal studies may be helpful in understanding how the drugs act, they cannot be used to substitute for first-hand clinical descriptions. This is particularly relevant in the case of hallucinogenic substances, or for drugs which produce subtle changes in perception in humans. Thus, in all cases where human descriptions of the drug are available, these must take priority over animal studies in terms of their use in describing the qualitative effects of behaviorally-active drugs.

SIGNIFICANT POINTS

In the following discussion, critical to the premise that MDMA is a new class of drug, the following points will be made:

1. **Although MDMA itself is a derivative of MDA, MDA has**

unique pharmacology and actually may be considered to be comprised of an equal mixture of two pharmacologically distinct components, the R-(-) isomer and the S-(+) isomer. While R-(-) MDA possesses hallucinogenic properties, S-(+) MDA has a qualitatively different action. This situation is unusual and is not known to occur with other hallucinogenic amphetamine derivatives.

2. No cross-tolerance occurs between MDA and MDMA.

3. N-methylation of MDA to give MDMA has the effect of abolishing or greatly attenuating the hallucinogenic activity that is possessed only by the R-(-) isomer. Thus, racemic MDMA can be functionally represented as being comprised of an essentially inactive R-(-) optical isomer, and the S-(+) biologically active isomer.

4. The pharmacology both of S-(+) MDA and S-(+) or racemic MDMA is not adequately described by current pharmacological definitions. Although studies in rats and dogs indicate that S-(+) MDA or S-(+) MDMA have similarity to amphetamine, human studies clearly show that the psychoactive properties of S-(+) MDMA (or its racemate, since the R-(-) isomer is essentially inactive) do not resemble at all those of amphetamine itself.

If these arguments are held to be valid, then MDMA represents a new type of drug, previously undescribed in the

literature. It then follows that the possibility that MDMA may be attractive for recreational use is superfluous to the central issue of whether MDMA deserves study for its value in therapy, since it would be a previously unknown type of agent. One therefore could not predict, a priori, whether it had therapeutic value, without adequate clinical trials. One could envision a hypothetical situation where MDMA represents a drug that in years to come might be hailed as a major breakthrough in the treatment of certain forms of emotional illness. On what basis, without benefit of studies that would demonstrate this utility, could one conclude that the possibility of recreational use warranted restriction of this material so that its clinical evaluation and study would be hindered or prevented? Therefore, can MDMA be said to represent a new type of drug?

First of all, if we consider MDMA to be a derivative of the "hallucinogenic" agent MDA, does MDA itself represent a typical drug of this type? It is appropriate to briefly review the characterization of MDA itself at this point.

CHARACTERIZATION OF MDA

From the outset, it has been clear that MDA does not present the profile characteristic of typical hallucinogenic agents such as LSD, psilocybin, or DOM. Not only does it not produce severe sensory disruption and hallucinations, at moderate doses, but it was popularly marketed as the "love drug", since it has a unique effect on empathy and emotion [6].

Early attempts to classify MDA within the confines of known pharmacologic classifications were described by Martin et al.,

[7]. These workers studied MDA in the chronic spinal dog and reported that MDA had effects resembling both LSD and amphetamine. It has been shown that in drug discrimination studies in rats, MDA has properties similar to LSD [8,9] and to DOM [10]. Studies by Glennon et al. [11,12] have shown MDA to also have amphetamine-like effects in rats. However, Shannon [13] reported that MDA could not be classified as an amphetamine-like drug. Shannon further concluded that "...the majority of evidence, including the present findings, suggests that MDA may...represent a unique class of drugs."

Glennon and Young [9] have also shown that MDA has stimulus properties in rats characteristic of both amphetamine and LSD, reinforcing the conclusions of Martin et al. [7]. These workers reported that the R-(-) isomer of MDA possessed properties similar to the hallucinogenic agent DOM, while the S-(+) isomer of MDA possessed amphetamine-like stimulant properties in rats. Their results suggest that MDA possesses a rather complex mechanism of action.

Clinical studies carried out by Shulgin have also demonstrated that it is the R-(-) isomer of MDA that possesses the hallucinogenic properties elicited by racemic MDA, while the S-(+) isomer of MDA does not possess hallucinogenic properties, but rather was characterized as "more benign and peaceful", when compared with racemic or R-(-)-MDA [14]. This may partially parallel the rat studies, in which R-(-) MDA has been shown to possess stimulus properties similar to DOM or to LSD. However S-(+)-MDA, while it may have general sympathomimetic qualities, is

distinctly different from the central stimulant, amphetamine. Thus, rat studies that indicate the effects of S-(+) MDA to be similar to amphetamine [12] are shown to be erroneous when S-(+) MDA and amphetamine are compared in man.

Furthermore, the R-(-) and S-(+) isomers of MDA have similar clinical potency, a situation quite different from that observed with other hallucinogenic amphetamines, where the R-(-) isomer invariably has substantially greater biological activity.

Thus, it is my opinion, and that of many other scientists, that it is appropriate to consider that racemic MDA is a unique psychoactive compound, actually comprised of two separate and distinct drugs, the R-(-) isomer, which has effects similar to known hallucinogens such as DOM or LSD, and the S-(+) isomer, which has a unique pharmacology that is not adequately described by current pharmacological definitions. To say that the S-(+) isomer is a stimulant, or has sympathomimetic properties, is, in my opinion, completely inadequate as a description.

CHARACTERIZATION OF MDMA - EFFECT OF N-METHYLATION

MDMA is the N-methyl derivative of MDA. Since MDA is more properly considered to be comprised of two optical isomers with distinct pharmacological properties, one must consider what effect the N-methyl will have on each of the optical isomers of MDMA.

It is known that N-methylation abolishes or greatly attenuates the biological activity of all hallucinogenic amphetamines that have so far been studied [15,16]. This applies both in animal models and in humans. For example, Glennon et al.

[17] have shown that in drug discrimination studies in rats trained to discriminate saline from DOM, the N-methyl derivative of DOM is more than ten-fold less active than the non-methylated parent. It is known that it is the R-(-) isomer of DOM that possesses the hallucinogenic properties of the racemic material [15,16]. Therefore, N-methyl addition greatly attenuates, or abolishes the hallucinogenic activity of the R-(-) isomers of substituted amphetamines.

In studies of the effect of the isomers of MDA and MDMA on release of serotonin from rat brain synaptosomes, we have found that the addition of the N-methyl had no appreciable effect on the activity of the S-(+) isomer, but attenuated the activity of the R-(-) isomer [18]. Similarly, in man it is the S-(+) isomer of MDMA that is active [19]. The R-(-) isomer is substantially without activity, consistent with the argument that the N-methyl greatly attenuates the hallucinogenic quality of the R-(-) isomer. In this latter study, it was also found that racemic MDMA has qualitatively different effects from those produced by racemic MDA [19]. Indeed, as Glennon et al. [10] point out, based on drug discrimination studies in rats, "within the context of the discrimination paradigm, it is evident that the structural requirements necessary for the MDA molecule to produce DOM-like effects are quite limited, and appear to be optimized in R-(-) MDA." MDMA produces few physical indicators of intoxication, and psychological sequelae are virtually non-existent. Qualitatively, the drug appears to evoke an easily controlled altered state of consciousness with emotional and sensual

overtones [20].

In addition, Anderson et al. [19] noted that cross tolerance was not produced between MDA and MDMA. Cross-tolerance has been shown to occur between hallucinogenic drugs of diverse chemical structure, and has generally been accepted as evidence that all hallucinogenic drugs have a common or similar mode of action. The lack of cross-tolerance between MDA and MDMA further indicates that the two are acting in different ways to produce different effects.

Based on these, and a variety of studies reported in the literature, it is my opinion that the addition of the N-methyl group to MDA, that results in the compound MDMA, has the effect of abolishing the hallucinogenic activity that resides in the R-(-) isomer, while allowing activity of the S-(+) isomer to be retained. However, although such activity may differ qualitatively from S-(+) MDA, in my opinion studies have not been carried out that adequately compare the effects of S-(+) MDA to S-(+) MDMA.

Thus, in my opinion it is justified to say that MDMA lacks the hallucinogenic activity characteristic of MDA and other substituted amphetamines such as DOM, as a result of the effect of the addition of the N-methyl group. Activity for the S-(+) isomer is retained, but in my opinion is not characterizable by present pharmacological categories or descriptions. While S-(+) MDMA possesses certain sympathomimetic properties, and perhaps has some general similarity to CNS stimulants, it is my firm opinion that these descriptions are inadequate to describe the psychoactive properties of MDMA.

CHARACTERIZATION OF MDMA - STEREOCHEMISTRY

The second point that illustrates the difference between MDMA and commonly known hallucinogenic agents such as DOM concerns the stereochemical requirement for activity. For DOM and for every other substituted amphetamine type hallucinogenic agent so far tested, it is the R-(-) isomer that is active. There is no indication in the literature that the S-(+) isomers of any hallucinogenic amphetamines possess similar qualitative effects in man, even at higher dosages. MDA and MDMA are unique at the present time. For MDMA it is the S-(+) isomer that is most active. At the most basic and fundamental level of pharmacologic understanding, involving the essential principle of three-point attachment of drugs to receptors, one must conclude that R-(-) DOM, R-(-) MDA, or any other R-(-) hallucinogenic substituted amphetamine derivative interact with a different receptor type than does S-(+) MDMA. The stereochemistry for these two types of isomers is completely reversed; they are mirror images of each other. Therefore, it is my firmly-held opinion that the action of S-(+)-MDMA, at the level of the neuronal receptor within the CNS, must involve different substrates than does DOM or R-(-) MDA. Hence, irrespective of any qualitative or subjective similarity between S-(+) MDMA and other psychoactive substituted amphetamines, the essential mechanism of action must differ. Further, the attenuation of the activity of the R-(-) isomer of MDMA by virtue of the presence of the N-methyl substituent, leads me to the conclusion that the

action of racemic MDMA may be considered to be primarily due to the action of the S-(+) isomer.

CONCLUSION

It is my firmly-held opinion that MDMA has unique pharmacology, not properly described either as hallucinogenic or amphetamine-like. In my opinion, it represents a new pharmacological class that has not been properly characterized. It is my opinion that it is premature to conclude that it has no therapeutic value simply because large-scale rigorous clinical evaluations have not yet been carried out. Furthermore, in my opinion the action of MDMA is not so similar to MDA that it can be concluded that they are the same, or that they have similar pharmacology or toxicology. This is especially true if one compares the racemic materials, the forms that are actually available for use. In this respect, reports from human studies must be weighted more heavily than results from animal studies. MDA has both a hallucinogenic component, embodied in the R-(-) isomer, and a "sympathomimetic" component embodied in the S-(+) isomer. Furthermore, it is possible, and even likely, that the pharmacology and toxicology of racemic MDA is the result of a synergistic interaction between the effects of R-(-) MDA and S-(+) MDA. If this should be the case, the intensity of effects, and the toxicity of MDA could be dramatically enhanced over that embodied in MDMA. The latter apparently has its biological activity in the S-(+) isomer, and lacks the hallucinogenic activity of the R-(-) isomer. Thus, the possibility of a potentiation of the toxicity of one isomer by the action of the

other is less likely. This points out one of the dangers in attempting to extrapolate from the toxicity of MDA to that of MDMA.

Based on the foregoing discussion, there would seem to be little justification for scheduling MDMA, other than the fact that it may have some appeal as a recreational drug. Its potential as an adjunct to psychotherapy, as well as the fact that it probably represents a new pharmacological class of drug, would seem to provide strong arguments aginst placing MDMA in schedule I. Such scheduling would, in my opinion, severely restrict further clinical studies with MDMA that would be essential to clearly establish its utility as an adjunct to psychotherapy. I want to clearly point out that I do believe that MDMA should be scheduled, so as to allow prosecution of operators of clandestine laboratories, and to restrict access to MDMA by the general public. However, I believe that MDMA should be placed in a schedule less restrictive than Schedule I.

BIBLIOGRAPHY

1. W.N. Pahnke, A.A. Kurland, S. Unger, C. Savage, S. Grof, The Experimental Use of Psychedelic (LSD) Psychotherapy, J. Amer. Med. Assn., 212: 1856-1863, 1970.

2. E. Brandrup, T. Vanggaard, LSD Treatment in a Severe Case of Compulsive Neurosis, Acta. Psychiat.Scand. 55: 127-141,1977.

3. O.L. McCabe, C. Savage, A. Kurland, S. Unger, Psychedelic (LSD) Therapy of Neurotic Disorders; Short Term Effects, J. Psychedelic Drugs, 5: 18-28, 1972.

4. C. Naranjo, The Healing Journey, Ballantine Books, New York, 1975.

5. R. Yensen, F.B. DiLeo, J.C. Rhead, W.A. Richards, R.A. Soskin, B. Turek, A.A. Kurland, MDA-Assisted Psychotherapy with Neurotic Outpatients: A Pilot Study, J. Nerv. Ment. Dis., 163: 233-245.

6. A. Weil, The Love Drug, J. Psychedelic Drugs, 8: 335-337, 1976.

7. W.R. Martin, D.B. Vaupel, J.W. Sloan, J.A. Bell, M. Nozaki, L.D. Bright, The Mode of Action of LSD-like Hallucinogens and Their Identification, in The Psychopharmacology of Hallucinogens, R.C. Stillman and R.E. Willette, eds., Permagon Press, New York, 1978, pp. 118-125.

8. D.E. Nichols and R.A. Oberlender, unpublished results.

9. R.A. Glennon, R. Young, MDA: An Agent That Produces Stimulus Effects Similar to Those of 3,4-DMA, LSD and Cocaine, Eur. J. Pharmacol., 99: 249-250, 1984.

10. R.A. Glennon, R. Young, J.A. Rosecrans, G.M. Anderson, Discriminative Stimulus Properties of MDA Analogs, Biol. Psychiatry, 17: 807-814, 1982.

11. R.A. Glennon, R. Young, MDA: A Psychoactive Agent With Dual Stimulus Effects, Life Sci., 34: 379-383, 1984.

12. R.A. Glennon, R. Young, Further Investigations of the Discriminative Stimulus Properties of MDA, Pharmacol. Biochem. Behav., 20: 501-505, 1984.

13. H.E. Shannon, MDA and DOM: Substituted Amphetamines That Do Not Produce Amphetamine-like Discriminative Stimuli in the Rat, Psychopharmacol., 67: 311-312, 1980.

14. Communication from Dr. A.T. Shulgin to Dr. George Greer, April 5, 1985.

15. D.E. Nichols, Structure - Activity Relationships of Phenethylamine Hallucinogens, J.Pharm.Sci.,70: 839-849, 1981.

16. D.E. Nichols, R.A. Glennon, Medicinal Chemistry and Structure-Activity Relationships of Hallucinogens, in Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives, B.L. Jacobs, ed., Raven Press, New York, 1984, pp. 95-142.

17. R.A. Glennon, R. Young, J.M. Jacyno, Indolealkylamine and Phenylalkylamine Hallucinogens: Effects of o-Methyl and N-Methyl Substituents on Behavioral Activity, Biochem. Pharmacol., 32: 1267-1273, 1983.

18. D.E. Nichols, D.H. Lloyd, A.J. Hoffman, M.B. Nichols, G.K.W. Yim, Effects of Certain Hallucinogenic Amphetamine Analogues on the Release of [3H] Serotonin from Rat Brain Synaptosomes,

J. Med. Chem., 25: 530-535, 1982.

19. G.M. Anderson, III, G. Braun, U. Braun, D.E. Nichols, A.T. Shulgin, Absolute Configuration and Psychotomimetic Activity, NIDA Research Monograph 22: 1978, pp. 8-15.

20. A.T. Shulgin, D.E. Nichols, Characterization of Three New Psychotomimetics, in, The Psychopharmacology of Hallucinogens, R.C. Stillman and R.E. Willette, eds., Pergamon Press, New York, 1978, pp. 74-83.

The above discussion does, to the best of my knowledge, accurately reflect my professional opinion and basic understanding of the drug 3,4-methylenedioxymethamphetamine (MDMA), and its pharmacological and structural relationship to MDA and other hallucinogenic and related psychoactive agents.

I declare, under penalty of perjury under the laws of the United States of America, that the foregoing is true and correct.

Executed on April 22, 1985

David E. Nichols

David E. Nichols, Ph.D.
Professor of Medicinal Chemistry