THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

The University of North Carolina at Chapel Hill
School of Medicine
Biological Sciences Research Center 220 H
Chapel Hill, N.C. 27514

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Mr. Richard Cotten
Dewey, Ballentine, Bushby, Palmer and Wood
1775 Pennsylvania Avenue N.W.
Washington, D.C. 20006

Dear Mr. Cotten:

I have gone over almost all of the material you sent me. This includes reprints of published material, preprints of material to be published, some correspondence, and finally, the position paper presented by the Drug Enforcement Agency and supported by Dr. Edward Brandt, the former Assistant Secretary for Health in the Department of Health and Human Services. These two statements attempt to justify scheduling methylenedioxymethamphetamine (MDMA) in Schedule I of the Controlled Substance Act (CSA). My conclusion, after reading all of this material is that MDMA is an extraordinarily interesting compound which deserves further investigation at both the basic science and clinical level. Scheduling it as Class I is probably an error and is certainly premature. It will inhibit research by making the federal review process more cumbersome for those who seek INDs for such work and it adds on the additional bureaucratic burden of special approval that several states require for Schedule I drugs. I would advocate that MDMA be a Schedule III drug, open to investigation by interested, responsible investigators in appropriate settings.

The DEA offers six arguments for using Schedule I. All of them have partial and superficial truth, but all of them are subject to different honest interpretation. Let me consider these one by one.

1. MDMA is an analog of 3,4 methylenedioxyamphetamine (MDA), a Schedule I substance. This statement is true, but chemical "analog" does not mean identity nor even necessarily great similarity in terms of biological action. We know many compounds where analogous chemical structures have quite different effects. Among the steroids, male and female sex hormones are analogous, but obviously yield different sexual differentiation. The glucocorticoids are analogous to the electrocorticoids, but the one controls glucose metabolism; the other electrolytes. Ritalin and

dextroamphetamine are analogous amphetamines and are approximately equally effective when used in the treatment of hyperactivity and attention deficit disorders in children. But, recent work shows that they effect catecholamine metabolism in directly opposite ways. In those cases in which chemical analogs have identical action, there is usually conversion of the one to the other in the body. Thus, imipramine and desmethylimipramine are chemically analogous and also pharmacologically analogous. It is because in the body one is converted to the other. In the case of MDMA compared to MDA, there is no evidence of conversion at this time. Indeed, this is an area of research which should be vigorously pursued. If the compounds are converted into each other in the body, the case for pharmacological similarity or even identity would be greatly strengthened. If they are not so converted, the compounds should be considered to be quite different regardless of their chemical similarity. There is some indirect evidence that the two compounds are biologically quite dissimilar. Clinically, MDMA has a shorter duration of action than MDA. Tolerance is reported to occur with the repeated use of either compound but there is no reported cross tolerance between them. A subject who has become tolerant to MDMA will still respond to MDA and vice versa. Finally, there is the matter of the isomers. The recemic mixture of R and S isomers typically prepared by the chemist can be separated into the R and S isomers. With MDMA the S isomer seems to be 4 times as active as the R isomer. In the case of MDA, the R isomer is more active than the S. This is an extraordinarily interesting finding that requires confirmation because it may imply that the central nervous system's receptors on which these compounds work are different in structure and in location within the brain. Thus, there is some evidence that MDA works primarily on dopamine receptor systems while MDMA may work on serotonin receptor systems. The point to this summary is that it is scientifically hazardous to extrapolate from a similarity in chemical structure to a presumed pharmacological identity. An N-methyl group can make a very big difference.

2. <u>The DEA states that MDMA has no legitimate medical use</u>. Superficially, this is true because the anecdotally reported usefulness of MDMA by several well trained and serious clinical investigators has not received the blessing of legitmacy. I am not at all sure how one goes about legitimizing a drug that is not patentable and hence which lacks the funds of the quantity that drug companies employ to put their drugs on the market. The fact remains that several clinicians have used MDMA and Dr. George Greer of New Mexico, has reported extensively on it. He has limited his work to the study of its effects on subjects who are physically healthy and who have no history of a socially or vocationally disabling psychological condition other than alcohol or drug intoxication. Thus all of his subjects were

either neurotic or had adjustment reactions which made them unhappy. In this group of 40 patients, he found that the drug enhanced communication between people involved in significant emotional relationships, it also enhanced introspection, frequently with the achievement of insight, it improved self image, and apparently, it facilitated psychotherapy. It should be granted that Dr. Greer's work remains anecdotal even though approximately 50 subjects have been treated. To this number may be added unpublished reports from approximately 6 other psychiatrists who have employed the drug in similar settings. It is also worth noting that Greer and others report that the immediate effects are shortlasting, that larger doses diminish the pleasurable effects and increase the distressing side effects, that repeated daily use leads to tolerance for the desirable psychological effects without effecting the undesirable side effects and that no one in their experience has elected to take MDMA more than once a week and usually much less because the psychological "glow" of the initial treatment is long lasting.

I think it important that MDMA be tested against other stimulants in a double blind fashion in order to eliminate or minimize the mystical and charismatic placebo effects. I would recommend double blind studies be conducted comparing MDMA not to an inactive placebo but rather to active placebos, like methylphenidate or fenfluramine.

Although one should research this drug very cautiously, its reported mechanism of action suggests that it might have clinical utility in several other serious psychiatric conditions for which treatment is currently not very effective. Thus, in schizophrenia the so-called positive symptoms (things which are there but shouldn't be) like hallucinations and delusions respond very well to the traditional antipsychotics, but the negative symptoms (things which are not there but should be) like autistic behavior, inability to communicate and to feel affect or empathy, do not respond to the typical neuroleptics. Recent work involves giving two drugs simultaneously, one to reduce the positive symptoms and the other the negative symptoms. MDMA in a controlled clinical trial warrants testing for the treatment of negative symptoms in such patients. Childhood autism is an essentially untreatable condition in which the child is unable to relate to significant people in his environment. MDMA might be tried on such children, partly because this distressing illness is otherwise untreatable and partly because the reported effects of enhancing communication among adults might be helpful in autism. Posttraumatic stress disorder is another condition that might warrant a trial. In World War II abreaction with barbiturates was used effectively to free the inhibited terror of soldiers following severe stress. There is some evidence that in posttraumatic stress disorder abreaction in

a congenial environment might be helpful. MDMA as a communication enhancer might be worth a trial. I have mentioned previously that the treatment of choice today for hyperactivity and learning disability is methylphenidate or dextoamphetamine. MDMA, it could be argued, has properties sufficiently similar to those compounds to warrant a trial. Fenfluramine has been introduced and is an accepted treatment for obesity. A recent report suggests that it may also be useful in the treatment of childhood autism. Some similarity between the actions of fenfluramine and MDMA might warrant trials of the use of MDMA in eating disorders and in childhood autism. Finally, as far back as Freud and many times in the intervening 70 years, agents have appeared which it was proposed would enhance insight oriented psychotherapy. In principle, there is no reason why such drugs should not exist. In practice, LSD, mescaline, and similar drugs have failed to be consistently useful. The search for such drugs should go on and someday they will be found. MDMA might be such a drug. I should close this section by noting that cocaine abuse has become a major national health problem with tremendous economic implications. A legitimate synthetic substitute for cocaine is badly needed. At least one verbal report states that a daily cocaine user who experienced MDMA stopped cocaine and took MDMA at two-weekly intervals instead. If this is true, and can be confirmed, MDMA would have enormous value for cocaine abuse. Let me close this section by agreeing that today MDMA has no "legitimate" use but there are many reports from reliable clinicians that it is a useful drug and further study might legitimatize it. I suggest that it deserves thorough investigation for the claimed uses today and for the potential future uses that I have outlined above.

3. The DEA states that MDMA produces stimulant and psychotomimetic effects similar to those produced by MDA but at slightly higher doses. This is, again, a partial truth. There seems to be no doubt that MDMA has stimulant effects like all other amphetamines. The psychotomimetic effects are not similar either quantitatively or qualitatively. Indeed, there is some question whether MDMA produces any psychotomimetic effects. To the best of my knowledge, active hallucinations have not been noted with MDMA. MDA has been reported to occasionally produce hallucinations in large doses but even MDA is a much weaker hallucinogen than mescaline to which it is closely related in chemical structure. This again emphasizes the difficulties in projecting human clinical effects from comparisons of chemical structure or from testing in lower animals. Human tests, under rigorously controlled conditions, are necessary.

4. MDMA is easy to synthesize clandestinally. I agree and I suspect that given its recent publicity in magazines and

television, it will continue to be produced. The seductiveness of the mystique of its benefits cannot be overemphasized. I have had phone calls from psychiatrists, psychologists, attorneys, educators, and biomedical scientists who recommend it or who wish to try it. Rather than make research difficult, I think it imperative to conduct research that will give an honest evaluation of its risks and benefits.

5.& 6. MDMA has been found in illicit traffic throughout the United States. I agree. It has also been reported to be associated with medical emergencies and one death reported by Dawn. I can only comment that the gas chromatographic, high pressure liquid chromatographic and mass spectrometric methods for the detection and measurement of MDMA require sophisticated laboratories and analytical chemists. Since clandestine laboratories rarely make pure material, it would be simple to misidentify MDMA or for that matter to miss it when it is present in tissue fluids. The case of death reported by Dawn in Seattle has been questioned legitimately by Shulgin. I would remain somewhat suspicious of the other reports on toxicity or for that matter of the nature of the materials found on seizure. I should say in passing that if MDMA is as widely produced and distributed as the DEA implies and if its abuse is as great as that which the DEA implies, it is most surprising that only one death has been reported and this one is questionable. It remains possible that many more deaths have occurred that have not been identified, but it is equally possible that MDMA is singularly nontoxic nor subject to abuse. These are research questions.

I wish to emphasize that I am not an advocate of MDMA nor an opponent. From what I have read, it is an interesting compound which deserves further rigorous controlled study. I would hope that the FDA and the DEA will take actions to expedite such research rather than to inhibit it. I think this is best done by making it a Schedule III drug.

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 24, 1985.

Morris A. Lipton

Morris A. Lipton, Ph.D., M.D.
Sarah Graham Kenan Professor of Psychiatry
Professor of Biochemistry
Director, Biological Sciences Research Center