PRELIMINARY FINDINGS FROM PRIMATE STUDIES

Two studies to which MAPS contributed have been completed. The following report is based on preliminary findings and is not to be quoted for attribution or cited in any report or media article. Publication of scientific papers about the findings are pending.

The Neurotoxic Threshold

Previous primate research funded in part by MAPS demonstrated that a single oral dose of 5 mg/kg of MDMA (about 3X larger than average human doses) caused some neurotoxicity in some brain regions though a single oral dose of 2.5 mg/kg (about 1.5X larger than average human doses) did not. To determine if a dose of 2.5 mg/kg was actually below the neurotoxic threshold, MAPS contributed to a primate study at Johns Hopkins in which 2.5 mg/kg was administered orally every two weeks for four months for a total of eight exposures.

Preliminary data suggests that multiple exposures to 2.5 mg/kg of MDMA had no neurotoxic effect in all brain regions studied except one, the thalamus.

This news is somewhat discouraging. If a primate no-effect level for MDMA neurotoxicity had been established at the 2.5 mg/kg dose, securing FDA permission for human studies using less than that dose might have been possible. The finding that eight doses of 2.5 mg/kg of MDMA seem to produce a small neurotoxic effect in one brain region calls into question the assumption that one dose of 2.5 mg/kg is without neurotoxic risk, however slight. However, since so few animals were studied, the effect in the thalamus may be a statistical aberration. More research is needed.(See p. 10!)

Without a clear primate no-effect level, the case for human exposure to doses less than 2.5 mg/kg remains complicated by the concern over neurotoxicity. This data suggests, however, that the neurotoxic threshold is very close to 2.5 mg/kg.

The Extent of Recovery

Previous studies in rats have shown that serotonin levels decreased by 90% return to normal after 12 months. In previous primate studies, serotonin reductions of 90% climbed to 50% of normal levels after only 4 months, recovering more rapidly than the rat. To test the assumption that primates would show complete recovery, MAPS contributed to another Johns Hopkins primate study which examined primates with 90% reductions after 12 and 18 months.

Preliminary data yielded unexpected results, and suggest that total recovery may not occur after severe neurotoxicity. Persistent reductions of serotonin of about 70% were seen after 18 months, indicating that the process of recovery noticed at 4 months had halted and even reversed itself. Whether total recovery occurs after more moderate toxicity needs to be explored (See page 10!).

Most surprising are indications that other neurotransmitter systems may be increasing in number, possibly acting to counteract the loss of serotonin neurons.

When considering the implications of this new data, it is important to keep in mind that MDMA has been used for almost twenty years in the United States without a single case in the scientific literature suggesting that anyone, user or abuser, suffers from MDMA-related brain damage. Fenfluramine, an FDA-approved prescription drug for over twenty years, has recently been discovered to cause serotonin neurotoxicity more readily than MDMA, yet it too has failed to result in a single case of fenfluramine-related brain damage being reported in the literature.

DR. NICHOLS CONFIRMS THAT PROZAC BLOCKS MDMA NEUROTOXICITY

At Purdue University's School of Medicinal Chemistry, Dr. David Nichols replicated an experiment conducted by Dr. Schmidt in which rats were given both MDMA and Prozac (fluoxetine), a new drug for the treatment of clinical depression. Prozac is extremely popular, returning sales of about $400 million a year and growing to Eli Lilly. Prozac stimulates the serotonin system in a manner somewhat similar to MDMA but to a lesser degree and without neurotoxicity.

The simultaneous administration of Prozac and MDMA completely blocked the neurotoxic properties of MDMA. This finding may be the key to unlocking the door to FDA-approved human studies with MDMA, since it seems possible that the MDMA neurotoxicity risk, difficult to estimate, can instead be entirely eliminated.

It may be that both the dopamine neurotransmitter itself, released by the MDMA, and MDMA metabolites are neurotoxic, not the MDMA itself. Several hours after Prozac and MDMA are administered, the brain has broken MDMA down into its metabolites and released extra dopamine. These compounds, which usually would be absorbed by the serotonin nerve terminal re-uptake sites, are blocked from doing so by Prozac molecules which have filled the re-uptake sites. Neurotoxicity is prevented and the dopamine and MDMA metabolites are eventually reabsorbed or broken down into their harmless components, without having caused any damage.

Two basic questions remain, 1) Can Prozac's prophylactic effect in rats be replicated in primates or man? (See p. 10!) and 2) Does Prozac change the subjective experience of MDMA, and if so how.

REQUESTED: SUBJECTIVE REPORTS OF THE PROZAC/MDMA COMBINATION

Determining if there is a method of eliminating MDMA's neurotoxicity without diminishing its valuable subjective, therapeutic effects would provide important information to MDMA users and could play a major role in the initiation of FDA-approved human studies. Several people who have tried a combination of Prozac and MDMA report the MDMA experience to be essentially unchanged. Others feel there is some effect. Reports from experimenters in the field (that hopefully means some of the intrepid readers of this newsletter) are the only sources of information on this matter.

MAPS requests people who have tried an MDMA/Prozac combination to send in written reports on their subjective experiences. The combination of most interest is a standard dose of Prozac (20mg) with 75-100 mg of MDMA, taken simultaneously.

If the reports suggest the MDMA experience remains unchanged, a small study to determine if Prozac blocks neurotoxicity in primates would follow (See p. 10!). If successful, an application for an FDA-approved study to investigate therapeutic uses of the combination would be submitted.