Readers of the MAPS newsletter may have come across recent articles in the media claiming that new evidence shows that MDMA may cause permanent and potentially harmful brain changes even in typical recreational doses. As in most other news reports involving research about illegal drugs, the stories oversimplified the scientific findings, took data out of context, exaggerated the dangers, and ignored possible counter-balancing benefits. This article reviews the latest study from Dr. Ricaurte and associates at the Johns Hopkins Medical Institutes (Fischer et al. 1995)(1) as well as some earlier findings. The best available data regarding MDMA neurotoxicity reveals a picture that is neither as simple nor as frightening as these recent news reports would have you believe.

MDMA is no exception to the rule that every drug has serious side effects in some users. Reports indicate that a small number of the millions of people who have taken MDMA over the last several decades have suffered negative consequences. Some people may be predisposed to react unfavorably to typical amounts of MDMA while heavy users may be placing themselves at special risk. MDMA increases blood pressure, posing a risk to people with preexisting heart conditions. MDMA can also increase body temperature which, in combination with hot environments, exhausting physical exercise (prolonged dancing) and lack of fluids has been linked in very rare cases to death from heat exhaustion. MDMA's psychological effects have been occasionally associated with acute anxiety, panic and depression and are substantially context-dependent. Several cases of longer-lasting effects have been identified. While no causal link has been established connecting serotonin reductions to any negative consequences, the potential risks as well as the benefits of MDMA must be carefully weighed before any decisions can be made concerning appropriate uses.

We owe our gratitude to Dr. Ricaurte and associates for conducting this latest study and to the National Institute on Drug Abuse (NIDA) for funding it. Now that this new study is completed, each of us entitled to make our own risk assessment after a careful look at the data. Below is my risk assessment, made with what I hope is a healthy dose of common sense.

The Latest Scientific Study
In August 1995, the Journal of Neuroscience published a scientific study by Fischer et al. investigating the regrowth of rat and primate brain neurons previously exposed to extremely large doses of MDMA.

The study was designed to determine whether there was long-term restoration of normal levels of serotonin in those brain regions in which serotonin levels were previously reduced as a result of exposure to very large amounts of MDMA. Also examined was whether the regrowth of serotonin nerve terminals (reinnervation) restored the original brain structures.

The study concluded that "in some rats and most monkeys, there is a lasting reorganization of ascending 5-HT [serotonin] axon projections following severe MDMA injury. In particular, while some projections (e.g. those to the neocortex) fail to recover for up to 18 months after drug administration, others (e.g. projections to the basal forebrain) recover fully, sometimes in excess." The authors of the paper noted that the "aberrant serotonergic brain reinnervation" had no known functional consequences, but that "if 5-HT [serotonin] function declines with age, MDMA-exposed individuals could be at increased risk for developing age-related cognitive impairment."(2)

**The Media Coverage**

The results of the study were reported in newspapers all across the United States and Europe. The reports began with an article in the August 15, 1995 New York Times Science Section incorrectly stating that the animals were given "recreational doses of MDMA - the amounts taken by many young people." In terms of human use, Dr. Ricaurte was cited as stating that "people could probably take normal amounts of MDMA three or four times a year without noticing any neuropsychiatric problems but people who took seven or eight doses a night could be inviting problems."

Published at the same time, but with a decidedly more alarming spin, was a report by the Associated Press (AP) wire service in which Dr. Ricaurte was quoted (he feels misquoted) as stating simplistically that "Results suggest that people who have used (Ecstasy) in the past have some kind of (brain) damage." To emphasize the point, the article quoted Dr. Robert Daroff, chief of staff at University Hospitals in Cleveland and editor-in-chief of the journal Neurology, as saying that "It makes you feel good, but you are going to probably get hurt."
The only counterpoint to these reports that I'm aware of was a letter to the editor that I co-wrote with Neal Goldsmith, Ph.D., published in the August 24, 1995 New York Times. We pointed out that the doses used in Dr. Ricaurte's study were roughly 45 times larger than the typical human dose, and that MDMA had been used "in therapeutic, sacramental and recreational contexts for over 20 years by hundreds of thousands of people without evidence of harmful neurotoxic effects on appetite, sleep, mood, impulsiveness or other neurological functions." On August 31, 1995 another story about the study was published in the British New Scientist magazine, and the London branch of the Reuters News Service distributed a story that was widely disseminated on the Internet. In both these stories, Dr. Ricaurte was quoted as stating, "If there is a margin of safety, it is not a large margin."

On September 2, 1995, yet another letter to the editor was published in the New York Times, this one by Richard A. Friedman, MD, Assistant Professor of Psychiatry, NY Hospital-Cornell Medical Center. He accused Dr. Goldsmith and me of entertaining ideas that were "dangerously naive and without scientific merit." He went on to assert that reports that MDMA had therapeutic benefits were pure speculation because "there are no long-term scientific studies of the effects of MDMA in humans," and that "lack of evidence of MDMA's possible dangers is by no means proof of its safety." Of course, Dr. Friedman was correct to assert that MDMA has not been proven safe; such a proposition can never be proven, only disproven. Furthermore, Dr. Friedman makes the valuable observation that drugs sold as MDMA "on the street" risk being contaminated. This risk of contamination complicates the question of "MDMA neurotoxicity."

**Implications for human use**

To evaluate what implications the Fischer et al. study has for humans using MDMA therapeutically, sacramentally and recreationally, the following questions must be addressed:

- How does the amount of MDMA administered to the animals relate to human use patterns?
- What are the consequences of MDMA-caused serotonin reductions in animals?
- What evidence is there that MDMA causes serotonin reductions in humans?
- If there are MDMA-caused serotonin reductions in humans, what are the consequences?

**Animal vs Human Doses**
The Fischer et al. study was designed to investigate whether the regrowth of serotonin nerve terminals (reinnervation) restored the original brain structures in the rats and primates in this study. Therefore, it was necessary to cause large initial reductions in serotonin levels in multiple brain regions so that regrowth would have an opportunity to occur.

The study was not designed to evaluate the effect of the typical human dose of MDMA, which is about 1.7 milligrams of MDMA for each kilogram of body weight (mg/kg) taken orally. Typical human doses do not cause neurotoxicity in primates. Dr. Ricaurte has previously determined in primates that 2.5 mg/kg given orally once every two weeks for four months caused no significant reductions in serotonin levels. He did find that significant reductions in serotonin levels in primates first occur with a single oral dose of 5 mg/kg, an amount of MDMA that some recreational users do self-administer. This dose produced no reductions in most brain regions tested two weeks after administration, but there was a 21% reduction in serotonin in the thalamus and a 16% reduction in the hypothalamus. Thus, the "no-effect" level in primates for serotonin reductions is somewhere between an oral dose of 2.5 mg/kg and 5.0 mg/kg. Whether there is a direct linkage between these initial reductions in serotonin levels and structural damage (neurotoxicity) has been questioned. In addition, no associated functional or behavioral consequences have been noted either from these minor and localized reductions or from the larger reductions caused by the higher doses administered to the primates in this experiment.

In order to cause substantial serotonin reductions in multiple primate brain regions, it was necessary to administer subcutaneous injections of 5 mg/kg twice daily, four days in a row, for a total of eight injections. The relevance of the data from this study to the human therapeutic or recreational use of MDMA is not clear. Virtually all human use of MDMA involves oral administration, not injection. In addition, it is almost unheard of for someone to use MDMA for four days in a row because a tolerance to the desired effects develops that cannot be overcome by increasing the amount consumed, distinguishing MDMA from drugs such as cocaine or heroin.

The 5 mg/kg dose of MDMA injected in the primates is about 3 times larger than the typical human dose of 1.7 mg/kg. Dr. Ricaurte has previously shown that subcutaneous injection of MDMA is roughly twice as toxic as oral administration (this varies somewhat depending on brain region), and that repeated dosing is more toxic than single administration. Therefore, each injection received by the primate is equivalent to slightly less than 6 times the typical oral human dose. Since there were 8 injections, each primate received the rough equivalent of 45 times the amount of MDMA that a human would self-administer in a typical MDMA session. This is a very rough estimate since it multiplies dose, frequency and route-of-administration effects, even though there may not be a linear relationship between these factors and serotonin reductions. In addition, the typical human dose varies from person to person. The smaller figure of 25 times
the typical dose is used by Dr. O'Callaghan to estimate the relationship between the doses
given to the primates in this study and the typical human dose.

Data from this study can be used to generate hypotheses about the effects of MDMA in
humans, but no clear conclusions can be drawn because there are dramatic species-dependent
differences in response to the administration of drugs. For example, rats respond differently to
MDMA than mice in some studies. In this study, the rats responded differently than the primates
in that most rats but only some primates reestablished normal serotonin levels. Primate data is
most useful in estimating the effect of a drug in humans, but even primate data needs to be
confirmed by human studies. Neither the relative safety nor risk of MDMA can be determined
conclusively without human studies.

Consequences of serotonin reductions in animals

The long-term functional or behavioral consequences in animals who have been administered
large amounts of MDMA is still unknown. No obvious impairments have been noted. According
to Fischer et al., "Hyperinnervation of the hypothalamus may lead to neuroendocrine
abnormalities, but this has yet to be documented. Hyperinnervation of other limbic structures
(e.g. amygdala) might be anticipated to produce changes in emotion, motivation, learning or
memory (Aggleton, 1992), but, again, few such changes have been documented (for review,
see Steele et al. 1994)." Evidence demonstrating that serotonergic denervation leads to
problems is also lacking. If there are consequences of MDMA-caused serotonin changes in
animals, they are very subtle.

Evidence for serotonin reductions in humans

There is no conclusive evidence demonstrating that MDMA causes serotonin reductions in
humans. Studies using spinal taps and/or brains scans to evaluate people before and after
administration of MDMA will be needed to determine definitively whether MDMA causes
serotonin reductions in humans. Dr. Ricaurte is currently conducting valuable studies using PET
scans to investigate brain structure in heavy MDMA users, though he is not administering
MDMA to human subjects. If any readers have a prior history of extensive MDMA use, and wish
to spend about a week in Johns Hopkins Hospital volunteering to be a research subject, contact
Dr. Ricaurte at (410) 550-0993.
The best indirect evidence for MDMA neurotoxicity comes from a study by Drs. McCann and Ricaurte that is the most comprehensive and controlled research project to date investigating the long-term effects of MDMA on experienced MDMA users. The study showed that a group of MDMA users (average exposure of 95 times) had roughly 32% less serotonin metabolite in their spinal fluid on average than a group of controls. To put this finding in context, it is important to note that the normal range of serotonin metabolites in spinal fluid is quite large. Some people naturally have twice as much or more than others. A difference of 32% between groups, although statistically significant, is a relatively small shift within the normal range of serotonin metabolite levels.

Whether the 32% difference can be attributed to MDMA use is uncertain, primarily because the serotonin metabolite levels of the MDMA users were not measured before they began to use MDMA. This study used a matched control group design instead of pre- and post-measures on the same subjects. Therefore, the difference in serotonin levels could be due to uncontrolled factors resulting from an imprecise matching process. For example, some personality factors such as risk-taking behavior (i.e. illegal drug use) have been linked to lower serotonin metabolite levels. In addition, the volunteers in this study had extensive exposure to other drugs as well as MDMA, while the control group was relatively drug naive. Furthermore, MDMA sold illegally is often impure. Serotonin reductions, if they occurred as a result of drug use, could be due to impurities and not to MDMA itself.

Anecdotal evidence raises the question of whether a long-term neurochemical process is at work. Some MDMA users report that the quality of the MDMA experience eventually begins to decline as the number of MDMA experiences increases. While this may be due to a long-term neurochemical process, it could also be due to the loss of novelty of the experience or some kind of learning-based tolerance. Whether such changes are harmful or beneficial is an open question. This frequent loss of quality of the experience over time serves as a kind of built-in antidote to long-term compulsive use, as does the increase in the ratio of unwanted side effects to desired effects that accompanies the attempt to take increasingly larger doses.

**Consequences of serotonin reductions in humans**

While Drs. McCann and Ricaurte found lower serotonin metabolite levels in MDMA users compared to controls, they found no harmful functional or behavioral differences between the subjects in the MDMA and control groups. In fact, the MDMA users exhibited less hostile and impulsive personality traits, and greater constraint and control than the members of the control group. This finding is especially surprising since it runs counter to previous research that has associated low levels of serotonin with increased violent and impulsive behavior. Furthermore, a
reduction in hostile and impulsive behaviors sounds more like a benefit than evidence of "brain damage." Perhaps this finding is due to MDMA's psychological effect rather than any long-term change in serotonin.

Sleep EEG data from this study indicated that the MDMA group averaged 19 minutes less total sleep per night than members of the control group.(8) MDMA users had about 37 minutes less of Stage 2 non-REM sleep, generally considered to be of lesser importance than other stages of sleep in terms of restorative function. MDMA users actually spent about 18 minutes more than controls in the stages of sleep considered essential for physical and biological restoration, Stages 3 and 4 non-REM sleep, and REM sleep. The sleep patterns of the MDMA users could conceivably be considered more efficient and more restorative than those of the control group because they went more quickly into deep sleep. This finding also sounds more like a benefit than evidence of "brain damage," especially since there was no evidence of increased sleep problems in the MDMA subjects as compared to the control group.

At present, there is no evidence for harmful neurotoxic effects in the current population of MDMA-experienced people. However, Fischer et al. speculate that there may be sufficient neural reserve to forestall problems under usual circumstances, but "if 5-HT [serotonin] function declines with age, MDMA-exposed individuals could be at increased risk for developing age-related cognitive impairment." Only time will determine if this delayed-damage theory is accurate. I have my doubts, in part because 5-HT may not decline with age. More salient to me is that there are numerous MDMA users in their 60's and 70's who have taken MDMA many times, seemingly without developing age-related cognitive impairment at a different rate than non-MDMA users. If there is such an age-related cognitive impairment, it is subtle and has yet to be reported.

*Tentative Conclusion*

As with any substance, some people are likely to be particularly sensitive to relatively small amounts of MDMA. Other people take unusually large amounts, especially in recreational contexts. It would therefore not be surprising if some people took enough MDMA to cause long-term reductions in their levels of serotonin in some brain regions. What would be surprising is if these serotonin reductions are eventually shown to have significant harmful functional or behavioral effects. Such changes, if they do occur, could as easily be beneficial as harmful, especially considering the fact that many people report long-term benefits resulting from their use of MDMA.
Over the last twenty years, millions of people have tried MDMA. This use of MDMA, though not conducted in the context of a scientifically controlled experiment, does provide an opportunity for a very large epidemiological study. Similarly, over fifty million people have tried a prescription drug called fenfluramine, a diet aid prescribed for daily use for months or years at a time that causes the same kind of neurotoxicity in animals as does MDMA.\(^{(9,10)}\) The absence of a single confirmed case of functional or behavioral consequences related to serotonin neurotoxicity as a result of the use of fenfluramine\(^{(11)}\) or MDMA does not mean that these drugs are without neurotoxic consequences. Appropriate epidemiological studies have not yet been conducted. Nevertheless, the lack of evidence of neurotoxic damage after such an enormous population of people has been exposed to these drugs certainly suggests that if any neurotoxicity-related problems have resulted, they are subtle and rare.

It does seem possible that some physiological mechanism may partially explain the diminishing returns that many people report from continued use of MDMA. This is a negative consequence only to the extent that the MDMA experience is considered beneficial.

After reviewing the new data reported by Fisher et al., I remain of the opinion that the risk of MDMA neurotoxicity is of no practical significance when typical or even somewhat larger doses of MDMA are used on an infrequent basis in therapeutic, sacramental or recreational contexts by people with normal brain function. Of course, I don't know this for sure, and neither does anyone else. I do know or have heard about many people who have used MDMA hundreds of times and seem unharmed and even helped by their use. As a result, I think that Dr. Ricaurte is being conservative when he states that "people could probably take normal amounts of MDMA three or four times a year without noticing any neuropsychiatric problems." While there is evidence that the neurotoxicity of MDMA can be blocked by the co-administration of Prozac or other selective-serotonin reuptake inhibitors (SSRIs)\(^{(12,13)}\) and that such drugs do not alter the MDMA experience in some people,\(^{(14)}\) such protective measures do not seem to me to be necessary in normal use. Such measures might possibly be worth the trouble when exposure approaches seven or eight doses a night, a level which Dr. Ricaurte stated "could be inviting problems."

Ironically, one could argue that MDMA neurotoxicity research in humans, with its spinal taps and injections of radioactive substances, is more dangerous than MDMA itself. Nevertheless, it is crucial that MDMA neurotoxicity research continue, and also research into the beneficial therapeutic uses of MDMA, so that the risks and benefits of MDMA can be accurately balanced. To that end, MAPS salutes the work of Dr. Ricaurte and associates and Dr. Grob and associates. MAPS remains committed to devoting the bulk of its financial resources to MDMA psychotherapy research.
References:


(2) Ibid. Fischer, 1995.


