

An Exchange of Views About MDMA Neurotoxicity and MDMA Research

Commentary by **Matthew Baggott**

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A RECENT PAIR OF LETTERS and an accompanying editorial in *Neuropsychopharmacology* highlight the controversy over clinical research with MDMA, and over extrapolating from nonhuman animal neurotoxicity studies to human MDMA use. An initial letter by Harm Gijsman and colleagues (1999) argued that the risk of long-term neurotoxicity was so great that MDMA should not be administered to human volunteers. Because this letter was in response to a study by Vollenweider and colleagues (1998), those authors were given the opportunity to discuss the risk that a single oral dose of 1.7 mg/kg MDMA might be neurotoxic. The relationship between possible serotonin neurotoxicity and any functional consequences, which is the crucial issue, was not the subject of these articles.

The ethics of research

These publications come at a time when there is increasing focus on the ethics of research with human volunteers. As the accompanying editorial (Lieberman and Aghajanian, 1999) points out, even studies which obtained all the appropriate permissions from ethics committees and government agencies may be subsequently criticized. A number of studies using schizophrenic volunteers have been criticized for employing protocols designed to increase symptoms of the illness without offering any possible benefits to the volunteers. A recent issue of *Biological Psychiatry* (Vol. 46, No. 8, Oct 15, 1999) is mostly dedicated to presenting views and information on the issue of deciding what risks are acceptable in a research context. Of course, risks must always be balanced against possible benefits. However, recent human MDMA work consists of basic science research; none of the published studies are designed to produce or measure possible benefits to volunteers. Instead, the studies attempt to provide additional knowledge to science and society. Although it is accepted that ethics can be different in different locations, it is generally accepted that possible benefits to society cannot justify risks to individuals. Therefore, basic science studies using human volunteers can only be justified if the risks to volunteers are low.

Which measures to use?

In order to determine the risks of MDMA-induced neurotoxicity in human volunteers, it is necessary to extrapolate from the complex and extensive nonhuman animal literature. Deciding which measures of serotonergic functioning are good indicators of damage is one important task. In their letter, Vollenweider and colleagues (1999)

argue that changes in serotonin reuptake transporter density (which can be measured using [3H]-paroxetine binding) is a better index of serotonergic damage than levels of the neurotransmitter serotonin (5-HT) or its metabolite 5-HIAA. I think that one of the more important aspects of this letter is the clarity with which the authors argue this point. There is disappointingly little discussion in the neurotoxicity literature concerning the degree to which different indices of serotonergic functioning are sensitive or selective for neurodegenerative changes. Because serotonin transporter density is a measure of a structural feature on the serotonin axon, it is likely a better indicator of whether the axons are damaged or absent than serotonin levels, which are dependent on diet and enzyme activity and can be depleted by nondamaging drugs. However, as Vollenweider and colleagues point out, changes in serotonin transporter density may also indicate adaptive changes, although evidence for this is limited (Benmansour et al., 1999; Qian et al., 1997; Ramamoorthy and Blakely, 1999).

Is neurotoxicity dose-dependent?

Having argued that serotonin transporter density be used as a marker of neurodegeneration, Vollenweider and colleagues discuss the relationship between dose and toxicity. Animal studies indicate that neurotoxicity is dose-dependent. That is, higher doses produce greater damage. Vollenweider and colleagues point out that there are currently no studies reporting decreased serotonin transporter density at doses close to 1.7 mg/kg in any species. The strength of this point is limited as it is not clear how much we need to consider the faster metabolisms of nonhuman animals when comparing doses between species. Because of their higher metabolisms, smaller animals often clear drugs from their bodies faster and therefore frequently experience less toxicity than humans. However, since we do not thoroughly understand the causes of MDMA-induced neurotoxicity, we cannot predict the magnitude of these species differences.

The importance of human studies

Studies in human users are therefore important. Vollenweider and colleagues discuss the recent PET study of MDMA users conducted by McCann and colleagues (1998). McCann and colleagues reported that human volunteers who had taken MDMA an average of 228 times had serotonin transporter densities which were approximately 25 percent lower than those of control volunteers. McCann and colleagues concluded that there was a linear dose-response relationship between the estimated amount of MDMA used and average reductions in serotonin transporter density. If this linear relationship applies to lower dose and less frequent MDMA use, then the risk of neurotoxicity after a

maps updates

few administrations of 1.7 mg/kg MDMA in a clinical setting appears low. Further research using the volunteers with less MDMA experience would be necessary to test whether this linear relationship extends to lower, less frequent doses.

Of course, there are limitations to arguments which extrapolate human doses from those of nonhuman animals or which use a group of very experienced illicit MDMA users to draw conclusions about the effects of single doses in clinical settings. Ultimately, prospective studies which examine serotonergic and neurocognitive functioning before and after MDMA administration to humans will be necessary if we are to settle the question asked in the title of one of the letters: is a single dose of MDMA harmless? •

Commentary by Rick Doblin

THE EDITORIAL by Jeffrey Lieberman and George Aghajanian in *Neuropsychopharmacology* (Caveat Emptor: Researcher Beware, 21(4), (1999) 471-472) supports the ethics of Franz Vollenweider's research in MDMA-naïve subjects over the strong objections of the Dutch doctors who raise the issue of MDMA neurotoxicity. The views of the authors of the editorial are even more important than I realized at first.

I have been reviewing new Federal policies that govern research in patients with mental illnesses, just the sorts of patients we hope to be treating with psychedelics (patients with depression, PTSD, OCD, etc.). There has been a backlash against ketamine research in schizophrenics, with lawsuits, investigations, and lots of bad

press. New, tighter standards for acceptable risk and informed consent procedures have been proposed by the National Bioethics Advisory Committee (NBAC) for research on people with impaired decision-making ability due to mental illness. NIMH has also developed new tougher standards for research that exacerbates symptoms, like psychedelics certainly can during a difficult (but potentially productive) psychedelic session.

At the end of 1998, Dr. Steve Hyman, Director of NIMH, convened an Ad Hoc Committee of 20 outside psychiatric researchers to review all of NIMH's intramural research. More than a few projects were halted due to ethical concerns, lack of sufficiently important knowledge generated that didn't outweigh the risk to subjects, too high a risk, etc. The co-chair of the committee that reviewed

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NIMH's intramural projects and recommended that some be halted or changed was Dr. Jeffrey Lieberman, the co-author of the editorial in *Neuropsychopharmacology*. In the *Neuropsychopharmacology* editorial, Dr. Lieberman expressed the view that MDMA research was ethical and appropriate, and that the evidence does not show that 1.7 mg/kg of MDMA is likely to produce damage to serotonin terminals. In light of Dr. Lieberman's expertise in reviewing psychiatric research protocols, his support of the ethics of MDMA research is promising.

An additional perspective on the *Neuropsychopharmacology* editorial comes from Mark A. Geyer, PhD, Professor of Psychiatry and Neurosciences, University of California, San Diego. He says:

I can add to Rick's comments that it appears that Neuropsychopharmacology is taking the position that the journal should continue to publish high-quality scientific work and not avoid politically sensitive issues for only political reasons. The publishers have reported that one of the two most cited papers in the journal in 1995 was the study by Lahti in which ketamine was administered to patients with schizophrenia.

The exchange of views in *Neuropsychopharmacology* about the risks of MDMA neurotoxicity and MDMA research provide an additional reason for FDA officials to feel comfortable approving Dr. Charles Grob's MAPS-supported MDMA cancer patient project. Protocol development for that study is still underway. •