MDMA research reviewed

Studies of MDMA users

MDMA was the topic of a symposium at the *1997 Annual Conference of the British Psychological Society*. The symposium received some press, including an article in the June 21, 1997 issue of *New Scientist*. This article, along with an editorial supporting MDMA research in humans, is available over the web:

http://www.newscientist.com/ns/970621/necstasy.html
http://www.newscientist.com/ns/970621/editorial.html

Of the studies presented at this meeting, I believe only H. Valerie Curran and Ross A. Travill's work has been published (*Addiction*, 1997 Jul, 92(7):821-31). Their paper, entitled "Mood and cognitive effects of +/- 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low," compares the acute and residual effects of alcohol and MDMA.

In this work, the researchers recruited 24 volunteers from a night club and measured their mood, reported physical symptoms, and performance on several memory and attentional tasks. Twelve volunteers reported using alcohol alone, while another 12 said they used MDMA alone. (Unfortunately, the volunteers' reports were not verified with urine or blood samples and some of the MDMA users later admitted to using small amounts of alcohol also.) The first measurements occurred on a Saturday night while the volunteers were experiencing the effects of their chosen drug. Subsequent measurements were made the next afternoon (Sunday) and again on Wednesday.

Measurements of depression

Although some differences were found in the memory and attentional tasks, the most pronounced differences were detected using the Beck Depression Inventory (BDI). The BDI is a widely used 21-item questionnaire which asks about mood, sleep, decision making, interest in others, and other aspects of life which are made worse by depression. The researchers found that MDMA users were distinctly *not* depressed while experiencing MDMA. However, their scores became worse the next day and even worse on Wednesday. In fact, some volunteers had Wednesday BDI scores which suggested they might have mild to moderate clinical depression. Alcohol users, in contrast, had middling moods which remained on the worse end of the normal range.

These data are interesting and raise several questions. Without a true baseline measurement, it is difficult to tell how much the Wednesday scores reflect a residual effect of the drug and how much they reflect the drug-free condition of these subjects. If it is largely a residual drug effect, it would be particularly interesting to know how long the depressed mood lasted. Depressed mood has been previously reported by users (e.g., Peroutka et al., 1988), but its time course and severity have not been measured using a standard method.

The researchers raise the possibility that the volunteers' depressed mood might be due to the unpleasant experience of returning to mundane life after experiencing "utter fulfillment." If this psychological explanation is true, it suggests that MDMA's putative therapeutic effect is not automatically achieved by taking the compound and that additional factors may be needed for it to improve the user's life.

Stimulant use study

It is worth noting that depressed mood is well documented after stimulant use and is not usually thought to be related to neurotoxic effects. A newly published survey by Sara Williamson, Michael Gossop, Beverly Powis, Paul Griffith, Jane Fountain, and John Strang nicely illustrates this. This research, published in *Drug and Alcohol Dependence* (1997, 44:87-94) as "Adverse effects of stimulant drugs in a community sample of drug users," compared 158 London-area users' reports of the adverse effects of MDMA, cocaine hydrochloride, and amphetamine.

The study found a suprisingly similar incidence and severity of severe side effects from MDMA and cocaine hydrochloride (which is not considered neurotoxic). For example, when asked whether they had ever had a bad experience with the drug, 21% of subjects said "yes" for MDMA and 24% for cocaine. A little under 10% of subjects reported experiencing severe depression after MDMA or cocaine. (Of course, these subjects are almost certainly using a nontechnical definition of depression, and are not necessarily identifying themselves as having been clinically depressed.) By quantifying the reported severity of ten possible adverse effects, the researchers created adverse effect severity scores for the three drugs. Cocaine received a severity score of 8.3, MDMA a score of 9.6 and amphetamine a score of 12.4.

Given the different reputations of MDMA and cocaine, their similarity in this study is a little suprising. This may be a reflection of the particular subjects in the study, who were mostly white, unemployed, polydrug users who reported regular use of stimulants. Their experiences may not be the same as other populations with other patterns of use. Controlled, clinical use of stimulants is likely to involve fewer adverse effects. On the other hand, out-of-control, dependent use of stimulants will produce more frequent and severe adverse effects than were reported in this study. Subjects in this study also generally snorted cocaine, which is associated with reduced adverse effects in comparison to smoking or injecting it (Gossop et al., 1994).

I also suspect that individuals who experience severe adverse reactions to one stimulant are subsequently more likely to experience them after other stimulants. Preclinical studies of sensitization to the effects of regular stimulant use (Segal and Kucsenski, 1987) and clinical studies of amphetamine psychosis (Angrist, 1994) provide some support for this idea. If so, a history of adverse reactions to stimulants might have predisposed the subjects to adverse events with MDMA. However, this is just speculation. The data in this study were not analyzed in a way that lets us tell whether the individual subjects reported similar profiles of adverse effects for the three drugs (as my theory would predict).

Administration of MDMA in the laboratory

Jordi Camí and his colleagues described the results of their double-blind, placebo-controlled MDMA research at the 1997

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College on Problems of Drug Dependence meeting in June. No really earthshaking findings, just a careful preliminary study which further demonstrates that MDMA can be safely administered in the lab. What follows is the abstract:

Pharmacological Effects of MDMA in Humans: Dose-Finding Pilot Study.

Camí J; Mas M, Farré M, San L, Roset PN, Mas A, Poudevida S, de la Torre R, Dept of Pharmacology and Toxicology, Institut Municipal d'Investigació Mèdica (IMIM), Universitat Autónoma de Barcelona, Barcelona, Spain.

3,4-Methylenedioxymethamphetamine (MDMA) is a synthetic amphetamine derivative. Although MDMA is an increasingly popular recreational drug among American and European young people, there are only a few experimental data of its pharmacological properties in humans (Grob et al., *Behav Brain Res* 1996; 73: 103-7). This study was designed to assess the acute pharmacological effects of MDMA, and to determine the dose to be used in future investigations. Six healthy male recreational users of MDMA participated in different experimental sessions (4-8). They received single oral doses of MDMA (50, 75, 100, 125 and 150 mg), amphetamine sulphate (AMP 20, 30, 35, 40 mg) or placebo. Drugs were administered double-blind and randomized (lower doses were allocated before higher doses for safety reasons). Study variables included: vital signs (blood pressure, heart rate, temperature, pupil diameter), psychomotor performance (reaction time, DSST, Maddox-wing), and subjective effects (visual analog scales, ARCI-49 item short form and POMS questionnaire). MDMA and AMP produced a dose-related increase in blood pressure, heart rate (different time profile for both drugs) and pupil size (only MDMA). No significant changes were found on psychomotor tasks, although AMP produced a slight improvement. MDMA produced higher scores on subjective effects and drug-induced euphoria ("high," "liking," ARCI-MBG) than AMP. A dose-response relationship was found for MDMA effects. Only MDMA produced slight changes in visual and body perceptions. The results seem to indicate that MDMA could have high abuse potential. This study was supported by grants: FIS 97/1198, CIRIT 95-SGR-00432, ISC-III 97/43444 and CITRAN.

Fenfluramine neurotoxicity review paper: a model of clarity

Una McCann, Lewis Seiden, Lewis Rubin, and George Ricaurte recently published an excellent review article in *JAMA* (August 27, 1997-Vol 278(8): 666-672) entitled "Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine: a systematic review of the evidence." Although fenfluramine and dexfenfluramine are not psychedelic, they can produce long-term brain effects (neurotoxicity) in animals similar to those found with MDMA.

Determining the relevance of fenfluramine and MDMA animal toxicity data to human use is difficult. Comparisons across species involve many subtleties. For example, if MDMA toxicity is related to the levels of drug in the brain (a plausible if unproven theory), it may not be sufficient to use a normal human dose (about 2.0 mg of drug per kg of body weight) in a rat study. Because rats tend to metabolize drugs faster, higher doses may be needed in rats to achieve the drug concentrations normally reached in the human brain. Of course, increasing the doses rats receive may produce other effects which do not normally occur in humans. These sorts of toxicokinetic issues are central to the question of MDMA's safety.

Unfortunately, most publications in the MDMA neurotoxicity literature extensively describe their technical findings and only briefly discuss the relevance of these findings to human use. This is somewhat understandable since the main goal of the research is often limited to understanding the mechanisms of MDMA's pharmacological effects. Still, animal toxicity data research is largely interesting because it is believed relevant to humans. It is unfortunate that clear discussions of this topic are rare.

In contrast to the average technically focused paper, McCann and her colleagues provide an admirably clear, if brief, review of these matters. They carefully define their use of terms like "long term" and "neurotoxicity" and mention three different ways of trying to compare doses in animals to humans. Papers such as this go a long way towards clarifying the toxicokinetic issues at hand. When issues are clearly stated, they can be studied and our understanding of animal models of neurotoxicity improved. Along with controlled human studies, this will do a lot to resolve the safety issues concerning MDMA.

Addendum

After this essay was written, another paper from the British Psychological Society meeting was published: Davison D.; Parrott, A.C. (1997) Ecstasy (MDMA) in Recreational Users: Self-Reported Psychological and Physiological Effects, *Human Psychopharmacology*, 12:221-226. In this paper, 20 MDMA users were asked to describe the psychological and physiological effects of MDMA. In addition, George Ricaurte's group has presented at the *1997 Annual Meeting of the Society for Neuroscience* evidence of reduced serotonin transporters in MDMA users when compared to a drug-experienced control group.•

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