

MDMA Research Update

by Earth Erowid

A lot has happened during the past year of MDMA research. As evidence continues to build about MDMA's neurotoxic effects and as long-term negative side effects become clearer, arguments suggesting that the evidence is purely prohibitionist rhetoric grow weaker. However, the evidence remains complex and the documented negative consequences of use appear to increase with maximum dosage and frequency of use: users who use more score worse. A variety of interesting papers have been published about MDMA's effects on memory, cannabis use as a confounding factor, MDMA pharmacokinetics, side effects profile, gender differences in effects and dosage, and other areas worth further study.

The following is not an introduction to or overview of the complex issue of brain changes related to MDMA and potential long term consequences of use, it is a set of brief summaries of some of the most interesting new developments in the field. This article is intended for those who already have some familiarity with the topic, for an introduction, please see http://erowid.org/mdma/mdma_research1.shtml.

Ecstasy and Memory

A number of studies during the past year have focused on the mounting evidence that heavy ecstasy use causes reductions in short-term verbal memory abilities, such as

recalling a list of words. While several of these studies were hopelessly flawed and nearly all were exaggerated by the media as evidence that ecstasy causes irreversible stupidity, depression, and forgetfulness, some were well-designed and conducted by more neutral researchers.

These suggest that there is reason for concern about the negative side-effects of ecstasy use on attention and short-term memory, especially among those who use more frequently or at higher doses.

One of the best studies (Gouzoulis-Mayfrank 2000) compared ecstasy users to both non-users and cannabis users (see Cannabis Confound below). Subjects in this study had an average lifetime use of 120 ecstasy tablets, over a 28 month period. In several tests, the ecstasy users scored worse than both comparison groups. The most concerning results involved verbal short-term memory and 'executive function' (puzzle solving, relies on working memory) on which ecstasy users have scored worse than non-users in a growing number of studies.

Memory: Longitudinal Data

A promising directions of research is found in a paper by Zakzanis published in Neurology (2001), where ecstasy users had their memories tested and then were interviewed and tested a year later. Average use in the group had gone up by 26 sessions

during the year, with an average of 4 tablets per month. Scores declined in the two subtests related to short-term verbal memory (recalling details of a short story). While this study is far from a final say on the matter, its longitudinal design is more convincing than simple comparison group testing. It would be particularly interesting if this same group were studied again in the future and a non-using comparison group was included.

Memory: Research Summaries

Perhaps the most compelling evidence that MDMA causes moderate long-term declines in working memory are two review papers published in 2000, one by Morgan in Psychopharmacology and the other by Gamma on MAPS.org. Both authors conclude that there is sufficient reason to believe that high dose or frequent (twice a month) use of ecstasy leads to measureable declines in short-term memory performance. Although I believe the issue of pre-existing differences has not been adequately addressed and there are many limitations to the available data, these problems should not be dismissed. In the last few years, most of the informed community has come to the conclusion that heavy or sustained recreational ecstasy use leads to measureable cognitive decline lasting an unknown period of time.

Memory: Cannabis Confound

One of the recurring questions in ecstasy research is what role cannabis use plays in memory test findings. A handful of studies have shown that recent cannabis use can affect short-term memory skills. Since ecstasy users participating in these studies have predominantly been regular cannabis smokers, it is possible that memory problems found in ecstasy users are partially the result of recent cannabis use. Several research groups, recognizing this possibility, have recruited non-ecstasy using cannabis smokers as a comparison group.

Unfortunately, the influence that cannabis smoking has on the test results is not yet fully understood. While Gouzoulis-Mayfrank found that ecstasy users scored worse than their cannabis-only comparison group, a similar study by Croft (Psychopharmacology 2001) found that cannabis smokers and ecstasy users scored nearly identically. This data suggests that

Terminology

5-HT: 5-hydroxy-tryptamine, serotonin.

transporter: Neurotransmitter reuptake site on a neuron.

free radical: a usually short-lived, highly reactive molecular fragment that contains one or more unpaired electrons.

in vitro: 'in glass', in petri dishes or test tubes, rather than in a living animal.

longitudinal study: a study taking place over time, where specific individuals are tested on more than one occasion in order to watch for changes in those individuals.

nystagmus: eye twitching or wiggling. Common side effect of ecstasy use.

PET Scan: Positron Emission Tomography. Imaging technique using radioactive tracer molecules that emit positrons with large, expensive detector equipment.

pharmacokinetics: the process by which a drug is absorbed, distributed, metabolized and eliminated by the body.

radio ligand: a radioactive chemical marker which binds to certain cells and is used to allow areas inside the body or brain to be mapped or measured.

the types of memory problems seen in ecstasy users could be substantially attributable to recent cannabis use.

Another interesting piece of data reported by Croft is that although the cannabis smokers had been asked to remain abstinent for 48 hours prior to testing, the actual period of abstinence was much shorter. After testing was completed and participants had been paid, researchers asked how long they had actually abstained. A number of participants admitted to having smoked within the 48 hour abstinence period. Unfortunately, the implications of this type of rule-breaking on other research are difficult to gauge.

MDMA Half-life

In the last few years there has been some good research done on the pharmacokinetics of MDMA by Mendelson and colleagues at UCSF (unpublished) and by de la Torre and colleagues, published in the *Annals of the New York Academy of Science* (2000). One major piece of pharmacology which most users don't know and isn't intuitively obvious is that MDMA's elimination half-life in humans is quite long, around 9 hours. This means that 9 hours after you swallow a single dose of ecstasy, concentrations in the blood have only dropped to half of their peak levels. MDMA levels are still at 1/4 their peak 18 hours after ingestion and 1/8 of their peak levels at 27 hours. It isn't until more than a day and a half after taking MDMA that the body is no longer experiencing direct pharmacological effects of the chemical.

Although MDMA remains in the blood at relatively high concentrations for more than a day and a half, most people experience primary effects for only 4-5 hours.

One proposed mechanism for MDMA neurotoxicity is that after ingestion, MDMA breaks down into a variety of metabolites, some of which are highly reactive molecules called 'free radicals'. Unless properly handled by the brain, these free radicals will damage neurons through a process called 'oxidative stress'. If MDMA concentrations remain high enough for a long enough period of time, the neurons' capacity for processing these metabolites fails, though if doses are low enough, the brain is able to keep up and no damage occurs. Another theory, by Nichols at Purdue, is that the free radicals result from an abnormal metabolism of dopamine.

The longer the brain is exposed to high

doses of MDMA, the more likely it is to suffer cell damage. Boosting (taking a second dose after some period of time) exacerbates the problem because it extends the period of time during which cells are exposed as well as increasing the peak concentrations of MDMA in the system. This increases the likelihood of neuron damage, as well as increasing side effects such as jaw clenching, nystagmus, dry mouth, and dizziness. Extrapolating from recent studies, it appears that taking a 100 mg tablet and then an additional 100 mg after 2 hours is as hard on the brain as taking a single 200mg dose.

Non-linear Pharmacokinetics

The pharmacokinetic data in humans also points out that within the range of therapeutic doses, small increases in dose can cause large increases in blood levels. In the de la Torre paper, an increase from 100 to 150 mg more than doubled the peak plasma levels and therefore increased risk of damage.

Anti-oxidants Reduce Damage

Also important to users is research over the last few years showing that anti-oxidants injected into rats before MDMA exposure reduces or eliminates damage to 5-HT neurons. A recent paper by Shankaran and colleagues (*Synapse* 2001) showed that anti-oxidants also reduce tolerance between exposures: rats given MDMA with anti-oxidants had stronger effects on their next dose of MDMA than rats who weren't given anti-oxidants. Although its unknown how oral anti-oxidant doses in humans compare with those injected in the rats, users should consider using anti-oxidants such as vitamin C and E, and/or alpha-lipoic acid before, during, and after taking ecstasy to minimize risks of cell damage.

Gender Differences

An interesting piece of research recently published was Liechti, Gamma, and Vollenweider's paper "Gender differences in the subjective effects of MDMA" (*Psychopharmacology* 2001). Data was collected which supports anecdotal reports that women experience a higher level of effects than men, given the same dose per bodyweight. This paper combines data from multiple studies to reach a total of 74 total subjects: 54 male, 20 female. On almost every side effect measure given, women reported higher levels of effects than men, though their reporting of side effects on placebo days were nearly identical.

Unexpectedly, men's blood pressure went up more than women's given the same mg/kg dose. This data confirms a growing body of knowledge showing that women may be more sensitive to mdma than men and suggests strongly that users and therapists should take gender into account when choosing doses.

Side Effects Profile

Another aspect of Liechti's "Gender differences" paper is a profile of side effects reported by the 74 participants who were given MDMA. While the results are not surprising (jaw clenching and lack of appetite), it is some of the first well collected data on the side effects of pure MDMA. While most users know that jaw clenching is common, its interesting to read that it was experienced by only 60% of those given MDMA in this study (none with placebo), 60% of the subjects reported difficulty concentrating (15% with placebo), 40% experienced some dizziness (1% with placebo), and 53% experienced dry mouth (3% with placebo). Whether interested in therapeutic or personal use, this paper contains some of the most practical information.

Serious Adverse Reactions

While most users don't experience life threatening or dangerous side effects from MDMA, our understanding of the negative reactions continues to deepen. Matthew Baggott, as part of a huge literature review he's been working on over the last 2 years, has written a summary of the medical emergency data available as of March 2001. His review should be available on MAPS.org

MDMA Side Effects

(Liechti, Gamma, Vollenweider 2001)

Side Effect	MDMA	Placebo
Difficulty Concentrating	59	15
Jaw Clenching	58	0
Lack of Appetite	54	4
Dry Mouth / Thirst	53	3
Impaired Balance	49	0
Restless Legs	41	1
Sensitivity to Cold	41	1
Dizziness	38	1
Sweating	31	0
Nausea	14	3

in the next few months and most of the following information comes from his work.

Serious hyperthermia (overheating) makes up about 25% of published reports of ecstasy related emergencies. The somewhat less discussed problem of hyponatremia (see below) accounted for about 10% of the published cases. The other two largest causes for ecstasy-related cases were "psychiatric complications" (psychotic episodes, panic attacks, severe depression) making up 22% of cases, and liver toxicity which made up about 16% of cases.

Hyponatremia

Hyponatremia (literally "low salt") is a condition where the salt and electrolyte levels in the blood fall dangerously, which can lead to brain damage and death. A common understanding of ecstasy-related hyponatremia has been that it is caused only by drinking dangerously large quantities of water.

One of the growing areas of understanding is that ecstasy-related

hyponatremia may be exacerbated by a direct pharmacological action of MDMA. MDMA has been shown to cause an increase in the anti-diuretic hormone (ADH or Vasopressin). While diuretics cause increased urination, increases in anti-diuretic hormone reduce urination and levels of salt in the bloodstream. Drinking too much water and an increase of ADH combine to make hyponatremia more likely.

Data shows that cases of ecstasy-related hyponatremia can occur at very low doses (1/2 a tablet) and while most cases occur after heavy obsessive water drinking, this is not true in all cases. Users should be warned about this issue and people showing symptoms of hyponatremia (see sidebar) should be treated by medical professionals immediately.

Liver toxicity

A less well known ecstasy-related medical problem is hepatotoxicity (liver toxicity). 16% of available adverse case reports involved liver problems. Although its known that hyperthermia can cause liver damage, several in vitro studies show that MDMA on its own can cause damage to liver cells. While this is an emerging area of study, users should be aware that recurring flu-like symptoms for days or weeks after last use or jaundiced (yellowed) skin tone can be symptoms of liver toxicity. If these symptoms occur, a trusted doctor should be consulted.

Interspecies Scaling Debate

One ongoing debate in MDMA research is the issue of interspecies scaling. The debate itself is quite academic, but it directly affects both users and therapists because it is the link between animal data on neurotoxicity and human use.

Since most toxicity research with MDMA has been done with rats, mice, and non-human primates, the question arises of how valid the results are for humans. This is a complicated area of the science and is debated in all the fields that use animals to test for toxicity. In a series of articles and letters in Neuropsychopharmacology, several groups of researchers have argued back and forth whether the doses used in Ricaurte's animal studies indicate that a single 1.7 mg/kg oral dose of MDMA is likely to produce damage in humans (1.7 mg/kg is a solid, full-effect dose for most people). This dose has been used by Vollenweider and colleagues for research done in Switzerland. Ricaurte

and McCann argue that, based on their calculations, this dose is neurotoxic.

Vollenweider, Jones, and Baggott argue that variations in metabolism between humans and other animals radically affect how toxic a particular chemical is in a species and that generalized formulas cannot describe the complexity of interspecies scaling. They argue that the current theories for the mechanism of MDMA-related neurotoxicity involve oxidative metabolites (not MDMA itself) and therefore the exact way humans metabolize MDMA is key in determining its dangerous levels.

Single Dose, No Damage Found

A study conducted in Switzerland by Vollenweider, Gamma, and colleagues found that a single, effective, oral dose of MDMA in a comfortable clinical setting caused no detectable change in 5-HT transporter binding. They used the same PET scan techniques developed by the Ricaurte / McCann to show lower 5-HT transporter levels in ecstasy users. Although the number of subjects was small and there is some question about whether these tests could detect small changes, this preliminary research suggests that, in clinical settings, a single 1.7mg/kg dose of MDMA doesn't cause large changes in 5-HT transporters.

References

- Croft RC, Macay AJ, et al (2001) The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology (Berl)* 153:373-9
- de la Torre R, Farre M, et al(2000) Pharmacology of MDMA in humans. *Ann N Y Acad Sci*, 914:225-37
- Gamma A (2001) Does Ecstasy cause memory deficits? <http://www.maps.org/research/mdma/gamma2000.pdf>
- Gamma A, Buck A, et al. (2001) No difference in brain activation during cognitive performance between Ecstasy (MDMA) users and controls: a [H2(15)O]-PET study. *J Clin Psychopharmacol*, 21(1):66-71
- Gouzoulis-Mayfrank E, Daumann J, et al (2000) Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *J Neurol Neurosurg Psychiatry* 68:719-725
- Lieberman JA, Aghajanian GK, McCann UD, Vollenweider FX (1999-2001) Letters to the Editor. *Neuropsychopharmacology*
- Liechti ME, Gamma A, Vollenweider FX (2001) Gender Differences in the Subjective Effects of MDMA. *Psychopharmacology* 154:161-168
- Morgan MJ (2000) Ecstasy (MDMA): a review of its possible persistent psychological effects. *Psychopharmacology (Berl)* 152(3):230-48
- Zakzanis KK, Young DA (2001) Memory impairment in abstinent MDMA ("Ecstasy") users: A longitudinal investigation. *Neurology* 56:966-969

Signs of Hyponatremia

Early

Anorexia
Headache
Nausea
Emesis
Muscular cramps
Weakness

Advanced

Impaired response to verbal stimuli
Impaired response to painful stimuli
Bizarre (inappropriate) behavior
Hallucinations (auditory or visual)
Asterixis
Obtundation
Incontinence (urinary or fecal)
Respiratory insufficiency

Far Advanced

Decorticate / decerebrate posturing
Bradycardia
Hyper- or hypotension
Hyper- or hypothermia
Dilated pupils
Seizure activity (usually grand mal)
Respiratory arrest
Coma
Polyuria (secondary to central diabetes insipidus)