



MDMA and Parkinson's: Lots of Research, Few Practical Answers

Ilsa Jerome, Ph.D.
ilsa@maps.org

Does MDMA/Ecstasy cause Parkinson's disease (PD)? Or does it help cure it? Both questions have been raised in the past about MDMA and the chronic, debilitating movement disorder.

... we can be pretty sure that MDMA does not cause Parkinson's disease.

In September 2002, NIDA-sponsored researchers George Ricaurte and Una McCann reported some widely-publicized findings in the journal *Science* claiming that MDMA damaged dopamine neurons in primates, speculating that it could even lead to Parkinson's disease (PD). Prior to this publication, there was at least one study showing signs of PD among Ecstasy users (Mintzer et al. 1999), but the significance of this remained controversial (Baggott et al. 1999; Borg 1999). The findings published in *Science* were considered evidence supporting a link between MDMA and PD, and several other cases of PD in former Ecstasy users appeared soon after their publication (Kuniyoshi and Jankovic 2003; O'Suilleabhain and Giller 2003). Imaging studies of Ecstasy users published before these findings failed to find reductions in dopamine transporters (Reneman et al. 2002; Semple et al. 1999), and a post-mortem investigation also found reduced serotonin neurons, but no reduction in dopamine neurons, in a heavy Ecstasy user (Kish et al. 2000).

However, as it turned out, Ricaurte and colleagues retracted their findings a year later, once it was discovered that they had administered methamphetamine, and not MDMA, to the monkeys and baboons in the study. The controversy continued over what conclusions, if any, can be drawn from case reports of PD in Ecstasy users (Jerome et al. 2004; Kish 2003). Later, when the same team of investigators gave monkeys the same or higher doses of genuine MDMA, they failed to find any dopamine toxicity, even when finding serotonin toxicity (Mechan et al. 2005). Monkeys that gave themselves MDMA over an 18-month period also did not have any dopamine toxicity (Fantegrossi et al. 2004).

From these reports, we can be pretty sure that MDMA does not cause Parkinson's disease. The next question is: can it treat PD? Recently, studies conducted at Duke University Medical Center (Sotnikova et al. 2005) found that MDMA was the most effective of 60 drugs tested in a mouse model of PD. Previously, other researchers reported reversal of PD-like symptoms, such as being unable to move or being stuck in one position, in rats and monkeys given MDMA or MDMA-like compounds (MDE, MDA), as well as non-entactogenic amphetamines (Banjaw et al. 2003; Iravani et al. 2003; Lebsanft et al. 2003; Lebsanft et al. 2005; Schmidt et al. 2002). In the previous studies, the researchers modeled PD either by giving animals a drug that interferes with the dopamine system, or they damaged the animal's dopamine system. The Duke team simulated PD by looking at genetically engineered mice lacking the dopamine transporter (the molecule that recycles dopamine) before and after giving them a drug that stopped them from making dopamine. They examined a large number of compounds, including drugs that influenced the serotonin and dopamine systems. Very high doses of MDMA improved PD-like symptoms in the mice, and lower doses of MDMA combined with anti-PD drugs, such as carbidopa or L-DOPA, also helped the dopamine-deficient mice.

Much of this research seems to have been instigated by the account of Tim Lawrence, a British man with young-onset PD who appeared in the media claiming that he gained symptomatic relief after MDMA/Ecstasy use (see Concar 2002; Margolis 2001). However, the problem that Ecstasy apparently fixed was not PD itself, but a side effect of PD medication (dyskinesia, a movement problem that includes twitching). It is possible that MDMA helped Lawrence by directly or indirectly boosting dopamine function (see comments by D. Nichols; <http://www.maps.org/mdma/nichols.html>), but some findings in the monkey and mouse studies suggest that MDMA and related drugs might help through a different route unrelated to dopamine. The Duke team believes that MDMA and other drugs may help treat PD symptoms through their

action on the newly discovered trace amine receptor.

However, none of the findings described above suggest that MDMA or any related entactogens are going to be a suitable PD medication. Even if low doses of MDMA do treat PD when combined with other medications, they are not likely to be a viable, practical solution, since daily dosing with MDMA is likely to increase risks of potential neurotoxicity. More to the point, unlike Tim Lawrence, most people with PD are older and are more likely to have, or be at risk for, conditions that make using MDMA a bad idea, such as heart problems or stroke risk.

In the initial tests performed by the Duke team, the doses of MDMA used were extremely high, bordering on acutely toxic—in some cases up to sixty times higher than doses that can be safely administered to humans. They used doses comparable to those used by humans in later tests, but in these cases the researchers combined MDMA with other drugs that increase or enhance dopamine, such as carbidopa or L-DOPA. Previous studies, like that of Iravani and colleagues, used lower doses, between 10 mg/kg and 12 mg/kg in marmosets, which are not lethal but still probably neurotoxic.

There are at least four good reasons not to encourage people to self-medicate with street Ecstasy, and at least three for not even doing so with pure MDMA. These include general problems with the identity and strength of anything bought on the street, general health-related issues (everything from tolerance to the possibility of neurotoxicity arising from daily dosing), and health issues in people with Parkinson's disease (cardiovascular problems or hidden cerebrovascular problems).

While the idea is intriguing, it's difficult to see MDMA or a known entactogen being used as a treatment for PD. One important avenue of research, however, could be the use of an entactogen as a "rescue" medication for dyskinesia, but MAPS isn't in a position to initiate such research since we still have several MDMA psychotherapy studies that need funding. It is possible but unlikely that the future treatment for PD might be an entactogen, but it's way too early to tell. •

It is possible but unlikely that the future treatment for Parkinson's might be an entactogen, but it's way too early to tell.

References

- Baggott M, Mendelson J, Jones R. (1999) More about parkinsonism after taking Ecstasy. *N Engl J Med* 341:1400-1401.
- Banjaw MY, Mayerhofer A, Schmidt WJ. (2003) Anticatalytic activity of cathinone and MDMA (Ecstasy) upon acute and subchronic administration in rat. *Synapse* 49:232-238.
- Borg GJ. (1999) More about parkinsonism after taking Ecstasy. *N Engl J Med*; 341:1400.
- Concar D (2002) Ecstasy has dramatic effect on Parkinson's disease symptoms. *New Scientist* November 6
- Fantegrossi WE, Woolverton WL, Kilbourn M, Sherman P, Yuan J, Hatzidimitriou G, Ricaurte GA, Woods JH, Winger G. (2004) Behavioral and Neurochemical Consequences of Long-Term Intravenous Self-Administration of MDMA and Its Enantiomers by Rhesus Monkeys. *Neuropsychopharmacology* 29:1270-1281.
- Iravani MM, Jackson MJ, Kuoppamaki M, Smith LA, Jenner P. (2003) 3,4-methylenedioxymethamphetamine (Ecstasy) inhibits dyskinesia expression and normalizes motor activity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates. *J Neurosci* 23: 9107-9115.
- Jerome L, Doblin R, Mithoefer MC (2004) Ecstasy use-Parkinson's link tenuous. *Mov Disord* 18: 1386.
- Kish SJ, Furukawa Y, Ang L, Vorce SP, Kalasinsky KS (2000) Striatal serotonin is depleted in brain of a human MDMA (Ecstasy) user *Neurology* 55:294-296.
- Kish SJ. (2004) What is the evidence that Ecstasy (MDMA) can cause Parkinson's disease? *Mov Disord*.18:1219-1223.
- Kuniyoshi SM, Jankovic J. (2003) MDMA and Parkinsonism. *N Engl J Med* 349 (1): 96-97.
- Lebsanft HB, Mayerhofer A, Kovar KA, Schmidt WJ. (2003) Is the Ecstasy-induced ipsilateral rotation in 6-hydroxydopamine unilaterally lesioned rats dopamine independent? *J Neural Transm* 110:707-718.
- Lebsanft HB, Kovar KA, Schmidt WJ. (2005) 3,4-Methylenedioxymethamphetamine and naloxone in rat rotational behaviour and open field. *Eur J Pharmacol* 516:34-39.
- Margolis J (2001) Ecstasy's Dividend. *New York Times* Feb 25, 2001
- Mechan A, Yuan J, Hatzidimitriou G, Irvine RJ, McCann UD, Ricaurte GA. (2006) Pharmacokinetic Profile of Single and Repeated Oral Doses of MDMA in Squirrel Monkeys: Relationship to Lasting Effects on Brain Serotonin Neurons. *Neuropsychopharmacology* 31:339-350.
- Mintzer S, Hickenbottom S, Gilman S. (1999) Parkinsonism after taking Ecstasy. *N Engl J Med* 340: 1443.
- O'Suilleabhain P, Giller C (2003) Rapidly progressive Parkinsonism in a self-reported user of Ecstasy and other drugs. *Mov Disord* 18: 1378-1403.
- Reneman L, Booij K, de Bruin K, Reitsma JB, de Wolff FA, Gunning WB, den Heeten GJ, van den Brink W (2001) Effects of dose, sex, and long-term abstinence from use on toxic effects of MDMA (Ecstasy) on brain serotonin neurons. *Lancet* 358:1864-1869.
- Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD (2002) Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("Ecstasy"). *Science* 297: 2260-2263.
- Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD. (2003) Retraction. *Science* 301: 1479.
- Schmidt WJ, Mayerhofer A, Meyer A, Kovar KA (2002) Ecstasy counteracts catalepsy in rats, an anti-parkinsonian effect? *Neurosci Lett* 330: 251-254.
- Simple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC. (1999) Reduced *in vivo* binding to the serotonin transporter in the cerebral cortex of MDMA ('Ecstasy') users. *Br J Psychiatry* 175: 63-69.
- Sotnikova TD, Beaulieu JM, Barak LS, Wetsel WC, Caron MG, Gainetdinov RR. (2005) Dopamine-independent locomotor actions of amphetamines in a novel acute mouse model of Parkinson disease. *PLoS Biol.* 2005 Aug;3(8):e271. Epub 2005 Aug 2.

