

## Editorial

# What Is the Evidence That Ecstasy (MDMA) Can Cause Parkinson's Disease?

Stephen J. Kish, PhD\*

*Human Neurochemical Pathology Laboratory, Centre for Addiction and Mental Health, Toronto, Ontario, Canada*

Ecstasy (MDMA; 3,4-methylenedioxyamphet-amine) is a derivative of amphetamine used widely by young adults for its reported ability to induce a state of heightened empathy and introspection and to cause an increase in energy.<sup>1</sup> In our neuropsychiatric studies of Ecstasy users, for example, we find that the typical user of this illicit recreational substance takes the drug in a group/social setting at a dance club.

Although the mechanism of action of Ecstasy is not known with certainty, the "social" effect of the drug is probably related to the ability of Ecstasy to promote release of the neurotransmitter serotonin in brain, whereas the stimulant action might be explained by a somewhat less intense release of the neurotransmitter dopamine, as occurs with other stimulant drugs such as methamphetamine.<sup>2-6</sup>

Because Ecstasy is assumed widely to cause "brain damage," our laboratory and some neurologists are approached occasionally by young patients having a variety of medical problems who suggest that the condition was caused by exposure to Ecstasy. In this issue of *Movement Disorders*, O'Suilleabhain and Giller<sup>7</sup> describe a 38-year-old man, a self-reported Ecstasy user, who developed parkinsonism and they suggest that the movement disorder may have been caused by Ecstasy. To date, two additional case reports describing parkinsonism (but see below) in self-reported Ecstasy users have been published.<sup>8,9</sup> Based on the suspected high number of Ecstasy users worldwide these findings would seem to raise the possibility of a future epidemic of middle-aged Parkin-

sonian Ecstasy users. This Editorial focuses on whether this concern is reasonably justified based on the scientific evidence and also how such single case reports should best be provided to the medical community.

### **Strength of the Evidence That Ecstasy Damages Brain Monoamine Nerve Endings in Humans**

#### **Serotonin**

Historically, almost all of the interest on the possibility of Ecstasy and brain damage has focused on the question whether Ecstasy damages brain *serotonin* (i.e., not dopamine) neurones. Good evidence indicates that high doses of Ecstasy administered to experimental animals can damage brain serotonin nerve terminals (but not cell bodies), as indicated by loss of serotonin nerve terminal markers (serotonin and its transporter and biosynthetic enzyme<sup>10-13</sup>). Studies of the integrity of the brain serotonin system in human Ecstasy users have been limited largely to measurement, by neuroimaging procedures, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) of levels of the serotonin transporter (SERT).<sup>14-19</sup> Unfortunately, it is not possible to derive any clear conclusion or consensus from these investigations because of the uncertainty, in most and perhaps all of the studies, that SERT was ever measured reliably, a problem related to the use of radioligand probes that are suboptimal in terms of sensitivity and validity.<sup>20</sup> For example, of the two PET studies of Ecstasy users conducted, the first,<sup>14</sup> reporting a massive 50 to 85% loss of SERT throughout the brain, employed SERT-binding values in normal subjects so variable that the data had to be transformed logarithmically, whereas a recent larger independent replication study<sup>18</sup> disclosed no brain SERT loss in former drug

users and only a 4 to 5% reduction, limited to two of four examined brain areas of subjects withdrawn recently from drugs.

### Dopamine

Although it has been assumed generally that the neurotoxic action of Ecstasy is limited to brain serotonin neurones, a recent investigation in nonhuman primates reported that a binge-dosing regimen of Ecstasy (which caused death in some animals) can lead to reduced striatal (caudate, putamen) levels of dopamine (dopamine and its transporter, vesicular monoamine transporter) and serotonin nerve terminal markers (but see below).<sup>21</sup>

These animal findings, which provided up to September 2003 the central thrust for the public health concern that Ecstasy might cause Parkinson's disease, suggested that if the dose is sufficiently high, Ecstasy will damage brain dopamine nerve terminals in human users of the drug. It should be mentioned, however, that because dopamine nerve endings can at the present time only be identified using markers to neuronal components that are known to or have the capacity to up- and downregulate independently of changes in neuronal density,<sup>20</sup> it may never be possible to establish whether low striatal levels of dopamine terminal markers in humans indicates actual physical loss of dopamine nerve terminals or only components therein (the "Kish uncertainty principle").

Unfortunately, the high-profile animal study aroused much controversy by not disclosing in the publication that two independent neuroimaging investigations (employing a dopamine transporter probe used widely in Parkinson's disease investigations) had reported previously no evidence for striatal dopamine nerve terminal damage in *human* Ecstasy users,<sup>15,22</sup> leaving the clinical relevance of the monkey study uncertain. In addition, in the single postmortem brain study conducted to date, we reported distinctly normal dopamine levels in putamen (the motor component of the striatum) of a forensically proven (brain, blood, hair) polydrug user of ecstasy, whereas serotonin concentration was, as expected, decreased markedly.<sup>23</sup>

More recently, and after the original submission of this editorial, Ricaurte and colleagues, the authors of the investigation<sup>21</sup> purporting to demonstrate brain dopamine neurone damage in nonhuman primates after Ecstasy exposure, retracted their finding upon their discovery that all of the animals had been treated mistakenly with methamphetamine (a known dopaminergic neurotoxin) rather than Ecstasy.<sup>24</sup> In fact, subsequent experiments (reported anecdotally by Ricaurte in a Letter to the Editor<sup>24</sup>) showed an absence of any brain dopamine neurone toxicity in nonhuman primates treated with oral

or systemic administration of Ecstasy. To the extent that nonhuman primate findings can predict toxicity in humans, these new findings, if replicated in independent investigations, now suggest that Ecstasy is unlikely to damage brain dopamine neurones in human users of the drug.

### Parkinsonism in Ecstasy Users

There is no epidemiological evidence that parkinsonism or any neurological abnormality, with the possible (but as yet unproven) exception of mild memory loss,<sup>25</sup> is a persistent (months to years after last use) consequence of exposure to Ecstasy, a drug that has been used widely worldwide. In principle, the absence of any significant clinical literature on parkinsonism and Ecstasy could still be consistent with some damage to nigrostriatal dopamine neurones but of a severity not sufficient to cause parkinsonism, or with the possibility that doses of Ecstasy taken by humans are too low to cause neurotoxic damage.

Although one group has reported recently, in a provocative title, "Parkinson's disorder, psychomotor problems, and dopaminergic neurotoxicity in recreational ecstasy/MDMA users",<sup>26</sup> the evidence of "Parkinson's disorder" in this investigation seems limited to "off-drug tremors or twitches" in some drug users who reported the problem via an internet website.<sup>27</sup> In this regard, there is an obvious need for careful neurological investigation by a movement disorder neurologist of a representative number of forensically proven Ecstasy users.

### Three Single Case Studies of "Parkinsonism" in Self-Reported Ecstasy Users

To date, three case studies purporting to demonstrate the presence of parkinsonism in former Ecstasy users have been published<sup>7-9</sup> (see Table 1 for summary). Of the three reports, the most recent investigation<sup>9</sup> (a peer-reviewed Letter to the Editor) includes only limited information on a patient for which parkinsonism cannot be established, as insufficient information was provided (no formal information on the neurological examination was included in the report) on this patient. The subject, who had a family history of parkinsonism, was observed to have a resting tremor and had reported some "difficulty in rising from bed."

The first case report by Mintzer and colleagues<sup>8</sup> (also a peer-reviewed Letter to the Editor) describes in detail a 29-year-old man who developed a rapidly progressive parkinsonism that was not responsive to dopamine substitution therapy, whereas the patient described by O'Suilleabhain and Giller<sup>7</sup> was a 38-year-old man, also with rapidly progressive parkinsonism but who re-

**TABLE 1.** Studies addressing question of Ecstasy and brain dopamine neurone damage in experimental animal and human brain

Investigation	Investigators	Finding	Comment
Experimental animal study	Ricaurte et al. <sup>21</sup>	Striatal DA markers are decreased in "Ecstasy"-exposed nonhuman primates (but see comment).	Findings retracted and anecdotal data reported in a letter to the Editor <sup>24</sup> suggesting that Ecstasy does not damage DA neurones in nonhuman primate brain.
Human neuroimaging studies	Semple et al. <sup>15</sup>	Striatal $\beta$ -CIT binding to DA transporter is normal in Ecstasy users (some forensically confirmed).	Neuroimaging data suggest that Ecstasy might not damage DA neurones in human brain.
	Reneman et al. <sup>22</sup>	Striatal $\beta$ -CIT binding to DA transporter is elevated slightly in Ecstasy* users who do not report use of amphetamine.	
Human postmortem study	Kish et al. <sup>23</sup>	Striatal DA is normal but serotonin decreased in polydrug chronic Ecstasy user.	Single (only) case study suggests that Ecstasy might have more marked affect on depletion of striatal stores of serotonin vs. DA in humans.
Human case studies of "parkinsonism" in ecstasy* users	Mintzer et al. <sup>8</sup>	Rapidly progressive bradykinesia and postural instability (no tremor) in 29-year-old male Ecstasy* user; normal MRI, FDG-PET; not responsive to levodopa/pramipexole	What is the brain pathological basis of parkinsonism and status of nigrostriatal dopamine neurones in the levodopa-nonresponsive patient? Parkinsonism caused by Ecstasy vs. sporadic parkinsonian disorder with striatal pathology not yet evident on MRI?
	Kuniyoshi and Jankovic <sup>9</sup>	Trihexyphenidyl-responsive resting tremor plus? in 19-year old male Ecstasy* user; normal MRI; family history of parkinsonism	Insufficient information provided to meet criteria for parkinsonism
	O'Suilleabhain and Giller <sup>7</sup>	Bradykinesia, resting and postural tremor, and rigidity in 38-year old male Ecstasy* user; normal MRI; at least partially responsive to levodopa and subthalamic nuclei stimulation	Parkinsonism caused by Ecstasy vs. young-onset idiopathic Parkinson's disease?

Superscript numbers correspond to the list of References.

\*Self-reported use of ecstasy without forensic confirmation to prove actual use of the drug.

DA, dopamine; MRI, magnetic resonance imaging; FDG-PET, 18-fluorodeoxyglucose positron emission tomography; striatal, caudate/putamen.

sponded at least partially to levodopa (L-dopa) and dopamine agonist medication. Magnetic resonance imaging (MRI) findings were negative for both patients.

What are we to make of the anecdotal case studies of Mintzer and colleagues<sup>8</sup> and O'Suilleabhain and Giller<sup>7</sup> describing parkinsonism in self-reported Ecstasy users? Although the brain pathological bases of the L-dopa-responsive<sup>7</sup> and nonresponsive<sup>8</sup> parkinsonisms are likely to have been different, both investigations must be taken seriously and warrant further consideration and investigation by neurologists and public health officials.

The simplest and, I believe, probably correct explanation for the presence of parkinsonism in an Ecstasy user, however, in the context of the widespread use of the drug over the past 10 years, is that the young-onset parkinsonism and drug exposure are coincidental (i.e., both can coexist independently). In this context, the statement of Mintzer and colleagues<sup>9</sup> that "...there are no other tenable explanations" for the patient's parkinsonism other than Ecstasy exposure is surprising and unjustified. Fi-

nally, the serious limitation of all the case studies<sup>7-9</sup> is the lack of any forensic evidence that the subjects ever used Ecstasy on even a single occasion, given the wide variation of quality control of Ecstasy manufacture in the marketplace.

#### How Should Information on Ecstasy and Parkinsonism be Presented to Neurologists?

It is clearly in the public interest to be advised of the possibility that a widely used recreational drug might damage the brain. For the investigation of O'Suilleabhain and Giller,<sup>7</sup> however, there was a strong diversity of opinion among the reviewers whether this case study should merit publication in *Movement Disorders* because of the uncertainty, on scientific grounds, that Ecstasy had some reasonable likelihood of being the causal agent.

It is reasonable to publish such single case studies for which the causal link to a toxic substance is suggestive, but only if the information is provided to the reader in a

balanced manner and can be justified on scientific grounds.

This is particularly important in the case of illicit recreational drugs, as the published reports provide the immediate basis for governmental drug policy and for sentencing of drug users. A strong argument can be made that case studies purporting to demonstrate harm caused by a recreational drug should be, as with all scientific data, subjected to rigorous peer-review before publication to insure that the conclusions are justified and that the data are assessed in light of all relevant human literature.

In this regard, the O'Suilleabhain and Giller investigation,<sup>7</sup> which was subjected to an intensive review process in this journal, stands in contrast to the two previous (Letter to the Editor) case reports,<sup>8,9</sup> which did not even acknowledge the theoretical possibility that the Ecstasy exposure and parkinsonism might have been coincidental, that no proof had been obtained that the patients had ever used Ecstasy or, in the case of the most recent report, that previous neuroimaging investigations found no evidence of striatal dopaminergic damage in human Ecstasy users. Clearly, a much tighter external peer-review process needs to be employed before publication of such anecdotal case reports.

### Conclusions

Notwithstanding the publication of three suggestive case studies, the evidence that Ecstasy might cause Parkinson's disease or any movement disorder rested almost exclusively on the results of an experimental animal investigation in nonhuman primates.<sup>21</sup> However, the findings of this study have now been retracted,<sup>24</sup> and new anecdotal data suggest that Ecstasy does not damage dopamine neurones in nonhuman primates.<sup>24</sup>

As both movement disorders and Ecstasy use occur during young adulthood, it can be predicted that additional reports of the two conditions occurring in individual cases will continue to be presented in the literature. Such studies (especially Letters to the Editor) need to be subjected to a rigorous peer-review process to ensure that all statements are justified on scientific grounds and presented in a balanced manner so that neurologists and the general public are not misled, and the actual nature of the relationship between Ecstasy and parkinsonism can finally be understood.

### REFERENCES

- Kalant H. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *CMAJ* 2001;165:917-928.
- Nichols DE, Lloyd DH, Hoffman AJ, Nichols MB, Yim GK. Effects of certain hallucinogenic amphetamine analogues on the release of [<sup>3</sup>H]serotonin from rat brain synaptosomes. *J Med Chem* 1982;25:530-535.
- Kankaapää A, Meririnne E, Lillsunde P, Seppälä T. The acute effects of amphetamine derivatives on extracellular serotonin and dopamine levels in rat nucleus accumbens. *Pharmacol Biochem Behav* 1998;59:1003-1009.
- Liechti ME, Baumann C, Gamma A, Vollenweider FX. Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology* 2000a;22:513-521.
- Liechti ME, Saur MR, Gamma A, Hell D, Vollenweider FX. Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT(2) antagonist ketanserin in healthy humans. *Neuropsychopharmacology* 2000b;23:396-404.
- Liechti ME, Vollenweider FX. Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans. *Eur Neuropsychopharmacol* 2000;10:289-295.
- O'Suilleabhain P, Giller C. Rapidly progressive parkinsonism in a self-reported user of Ecstasy and other drugs. *Mov Disord* 2003;18:1378-1381.
- Mintzer S, Hickenbottom S, Gilman S. Parkinsonism after taking ecstasy. *N Engl J Med* 1999;340:1443.
- Kuniyoshi SM, Jankovic J. MDMA and Parkinsonism. *N Engl J Med* 2003;349:96-97.
- Stone DM, Merchant KM, Hanson GR, Gibb JW. Immediate and long-term effects of 3,4-methylenedioxymethamphetamine on serotonin pathways in brain of rat. *Neuropharmacology* 1987;26:1677-1683.
- Battaglia G, Yeh SY, O'Hearn E, Molliver ME, Kuhar MJ, De Souza EB. 3,4-Methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine destroy serotonin terminals in rat brain: quantification of neurodegeneration by measurement of [<sup>3</sup>H]paroxetine labeled serotonin uptake sites. *J Pharmacol Exp Ther* 1987;242:911-916.
- Commins DL, Vosmer G, Virus RM, Woolverton WL, Schuster CR, Seiden LS. Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther* 1987;241:338-345.
- Ricaurte GA, DeLanney LE, Irwin I, Langston JW. Toxic effects of MDMA on central serotonergic neurons in the primate: importance of route and frequency of drug administration. *Brain Res* 1988;446:165-168.
- McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998;352:1433-1437.
- Simple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC. Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ("ecstasy") users. *Br J Psychiatry* 1999;175:63-69.
- Reneman L, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeten GJ, Booij J. Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. *Arch Gen Psychiatry* 2001;58:901-906.
- Reneman L, Booij J, de Bruin K, et al. Effects of dose, sex, and long-term abstinence from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet* 2001;358:1864-1869.
- Buchert R, Thomasius R, Nebeling B, et al. Long-term effects of "ecstasy" use on serotonin transporters of the brain investigated by PET. *J Nucl Med* 2003;44:375-384.
- Thomasius R, Petersen K, Buchert R, et al. Mood, cognition and serotonin transporter availability in current and former Ecstasy (MDMA) users. *Psychopharmacology (Berl)* 2003;167:85-96.
- Kish SJ. How strong is the evidence that brain serotonin neurons are damaged in human users of ecstasy? *Pharmacol Biochem Behav* 2002;71:845-855.

21. Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD. Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy"). *Science* 2002; 297:2260–2263.
22. Reneman L, Booij J, Lavalaye J, et al. Use of amphetamine by recreational users of Ecstasy (MDMA) is associated with reduced striatal dopamine transporter densities: a [<sup>123</sup>I]beta-CIT SPECT study—preliminary report. *Psychopharmacology (Berl)* 2002;159: 335–340.
23. Kish SJ, Furukawa Y, Ang L, Vorce SP, Kalasinsky KS. Striatal serotonin is depleted in brain of a human MDMA (Ecstasy) user. *Neurology* 2000;55:294–296.
24. Ricaurte G, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD. Retraction: Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of methylenedioxymethamphetamine (MDMA). *Science* 2003;301:1479.
25. Verbaten MN. Specific memory deficits in Ecstasy users? The results of a meta-analysis. *Hum Psychopharmacol* 2003;18:281–290.
26. Parrott AC, Buchanan T, Heffernan TM, Scholey A, Ling J, Rodgers J. Parkinson's disorder, psychomotor problems and dopaminergic neurotoxicity in recreational ecstasy/MDMA users. *Psychopharmacology (Berl)* 2003;167:449–450.
27. Parrott AC, Buchanan T, Scholey AB, Heffernan T, Ling J, Rodgers J. Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. *Hum Psychopharmacol* 2002;17:309–312.7