Psychopharmacology (2004) 171:229–230

COMMENTARY

H. R. Sumnall · L. Jerome · R. Doblin · M. C. Mithoefer

Response to: Parrott AC, Buchanan T, Heffernan TM, Scholey A, Ling J, Rodgers J (2003) Parkinson's disorder, psychomotor problems and dopaminergic neurotoxicity in recreational ecstasy/MDMA users. Psychopharmacology 167(4):449–450

Received: 6 May 2003 / Accepted: 24 June 2003 / Published online: 21 November 2003

To the Editors; In their recent letter, Parrott and colleagues discussed the human implications of findings of dopaminergic neurotoxicity in non-human primates after repeated doses of MDMA (three injections of 2 mg/kg within 6 h) (Ricaurte et al. 2002). Parrott and colleagues are concerned that like the known neurotoxin MPTP, MDMA might only produce observable effects in a minority of ecstasy users. They supported their concerns by citing a survey conducted over the internet that yielded reports of tremors and twitches in 20% of 282 ecstasy users. However, scientists disagree on the human implications of Ricaurte's findings, and an examination of the literature fails to support a link between ecstasy use and dopaminergic neurotoxicity or motor problems (Holden 2002).

The MDMA dose regimen used by Ricaurte and colleagues produced 20% mortality in their animals, a figure that far exceeds the estimated percentage of deaths in ecstasy users (Gore 1999; Gill et al. 2003; Henry and Rella 2001). An additional 20% of their test animals were not administered the third injection due to obvious signs of behavioural toxicity. Clearly, the dose regimen employed in this study was not analogous to common patterns of ecstasy use.

At present, two studies of cerebrospinal fluid and two imaging studies in heavy ecstasy users, and one post-mortem examination of brain tissue from a heavy ecstasy user have all failed to find evidence for ecstasy-related dopamine neurotoxicity (Ricaurte et al. 1988, 1990; McCann et al. 1994, 1999; Semple et al. 1999; Kish 2000; Reneman et al. 2002), although one of these imaging studies found a relationship between amphetamine use and reduced striatal dopamine (Reneman et al. 2002). As Parrott and colleagues stated themselves, any research testing hypotheses concerning ecstasy use and dopaminergic neurotoxicity must take into account use of amphetamine and other psychostimulants.

Parrott and colleagues presented data from their online survey of ecstasy users and described anecdotal accounts of movement problems in ecstasy users (Parrott et al. 2002). Participants reporting motor problems in this and other studies (Parrott and Lasky 1998; Rodgers 2000) did not undergo clinical assessments of psychomotor function, and, in one case, reports were elicited in response to a specific question (Rodgers 2000). Responses from ecstasy users were not compared with comparable samples, such as polydrug users with no reported ecstasy use. Subjects in this study also generally reported fewer ecstasy episodes than the aforementioned imaging studies, suggesting that underlying dose-related dopaminergic neurotoxicity must be discounted as a causal mechanism. In contrast with these findings, a survey of 500 ecstasy users failed to report a significant number of complaints of psychomotor problems after ecstasy use (Cohen et al. 1995).

The lack of independent verification of symptoms is particularly important, since the links between symptom reporting and results of objective measures are not strong. Studies of memory and executive function in ecstasy users failed to find relationships between self-reported cognitive difficulties attributed to ecstasy use and performance on tests of spatial memory, verbal memory and executive function (Rodgers 2000; Fox et al. 2001; Heffernan 2001, study 2). In the study conducted by Fox and colleagues, lifetime ecstasy consumption was a better predictor of performance on measures of spatial memory

H. R. Sumnall (✉)
Centre for Public Health,
Liverpool John Moores University,
70 Great Crosshall Street, Liverpool, L3 2AB, UK
e-mail: h.sumnall@livjm.ac.uk

L. Jerome · R. Doblin
Multidisciplinary Association for Psychedelic Studies,
2105 Robinson Avenue, Sarasota, FL 34232, USA

M. C. Mithoefer
208 Scott Street, Mt. Pleasant, SC 29464, USA

and executive function than the presence of self-reported problems attributed to ecstasy use (Fox et al. 2001).

Only one case of Parkinsonism or motor problems after ecstasy use has been reported in the medical literature (Mintzer 1999), and the conclusions drawn in this report were disputed by the patient (Borg 1999) and by others (Baggott et al. 1999). Searches conducted through the PubMed database in September 2002 and April 2003 using "MDMA" and "motor problems", "ecstasy" and "Parkinson's disease" and "ecstasy" and "parkinsonism" did not uncover any additional reports of ecstasy-use related psychomotor problems. It is true that no systematic investigations have assessed psychomotor function in ecstasy users, and this requires further study. However, if psychomotor symptoms after ecstasy use were as common as they were among respondents on the on-line survey (20%), then the lack of case reports and research is especially surprising.

In conclusion, there is currently no human evidence for dopaminergic neurotoxicity and no objectively measured increased incidence of psychomotor problems in regular ecstasy users. Even if such a link were established, a definitive link between ecstasy use and dopamine neurotoxicity or psychomotor problems would be difficult to establish, as most ecstasy users are polydrug users. A significant number of ecstasy users report consumption of drugs known to affect dopamine function, such as amphetamine or methamphetamine. Whilst we encourage future research into potential long-term effects of regular ecstasy use, there is at present no reason to believe that ecstasy users are subject to the dopaminergic neurotoxicity seen in squirrel monkeys and baboons injected with repeated doses of MDMA. By suggesting an analogy between MDMA and MPTP, Parrott and colleagues appear to be overstating the potential long-term effects of ecstasy use, despite the fact that findings from studies in ecstasy users and a search of the literature fail to support these concerns. It is essential that scientists, policymakers, health workers and ecstasy users themselves be provided with accurate evidence-based information. Speculative claims should be fully qualified so as not to further diminish the credibility of warnings on drug-related harms.

References

Baggott M, Mendelson J, Jones R (1999) More about parkinsonism after taking ecstasy. N Engl J Med 341:1400–1401

Borg GJ (1999) More about parkinsonism after taking ecstasy. N Engl J Med 341:1401

Cohen RS (1995) Subjective reports on the effects of the MDMA ("ecstasy") experience in humans. Progr Psychopharmacol Biol Psychiatry 19:1137–1145

Fox HC, Parrott AC, Turner JJD (2001) Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug. J Psychopharmacol 15:273–281

Gill JR, Hayes JA, deSouza IS, Marker E, Stajic M (2003) Ecstasy (MDMA) deaths in New York City: a case series and review of the literature. J Forensic Sci 47:121–126

Gore SM (1999) Fatal uncertainty: death rate from use of ecstasy or heroin. Lancet 354:1265–1266

Heffernan TM, Jarvis H, Rodgers J, Scholey AB, Ling J (2001) Prospective memory, everyday cognitive failure and central executive function in recreational users of ecstasy. Hum Psychopharmacol Clin Exp 16:607–612

Henry JA, Rella JG (2001). Medical risks associated with MDMA use. In Holland J (ed) Ecstasy: the complete guide. Inner Traditions, Rochester, VT

Holden C (2002) Neuroscience: drug find could give ravers the jitters. Science 297:2185–2187

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

McCann UD, Ridenour A, Shaham Y, Ricaurte GA (1994) Serotonin neurotoxicity after (+/-) 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy"): a controlled study in humans. Neuropsychopharmacology 10:129–138

McCann UD, Mertl M, Eligulashvili V, Ricaurte GA (1999) Cognitive performance in (+/−) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. Psychopharmacology 143:417–425

Mintzer S, Hickenbottom S, Gilman S (1999) Parkinsonism after taking ecstasy. N Engl J Med 340:1443

Parrott AC, Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology 139:261–268

Parrott AC, Buchanan T, Scholey AB, Heffernan T, Ling J, Rodgers J (2002) Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. Hum Psychopharmacol 17:309–312

Reneman L, Booij J, Lavalaye J, de Bruin K, Reitsma JB, Gunning B, den Heeten GJ, van Den Brink W (2002) Use of amphetamine by recreational users of ecstasy (MDMA) is associated with reduced striatal dopamine transporter densities: a [^{123}I]beta-CIT SPECT study—preliminary report. Psychopharmacology 159:335–340

Ricaurte GA, DeLanney LE, Irwin I, Langston JW (1988) Toxic effects of MDMA on central serotonergic neurons in the primate: importance of route and frequency of drug administration. Brain Res 446:165–168

Ricaurte GA, Finnegan KT, Irwin I, Langston JW (1990) Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: preliminary observations. Ann N Y Acad Sci 600:699–710

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

Rodgers J (2000) Cognitive performance amongst recreational users of "ecstasy." Psychopharmacology 151:19–24

Semple 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