Journal of Psychopharmacology 16(2) (2002) 189–191

SAGE Publications, London, Thousand Oaks, CA and New Delhi
0269–8811[200206]16:2; 189–191; 023160

What is a dose of ecstasy?

J. C. Cole, H. R. Sumnall and G. F. Wagstaff

Psychology Department, Liverpool University, Liverpool, UK.

Fox *et al.* (2001) describe an interesting set of data which, they argue, represents the dose-dependent effects of ecstasy. However, the World Health Organization has concluded that the term 'ecstasy' is generic for a wide range of compounds (WHO, 1997). So exactly what is a dose of ecstasy?

Ecstasy is commonly believed to be the entactogen, 3,4-methylenedioxymethamphetamine (MDMA). Tablet testing studies in the UK have routinely demonstrated that MDMA is present in less than 50% of samples (Milroy *et al.*, 1996; Sherlock *et al.*, 1999; Ramsey *et al.*, 2001). The remaining tablets contain a range of other (non)controlled substances which supports the conclusions of the WHO. This would indicate that any dose-related effects of ecstasy are not associated with a single compound. As not all of these drugs are believed to be serotonergic neurotoxins, this presents major problems for the causal mechanism proposed by Fox and colleagues (2001).

In psychopharmacology, it is standard practice to define a dose as either the weight of drug (e.g. mg) or the weight of drug as a proportion of the body weight of the subject (e.g. mg/kg). Fox *et al*. (2001) do not present any data to indicate what doses of any drug have been consumed by their subjects, and use instead the rather nebulous terms, 'light', 'medium' and 'heavy'. These categories are based upon arbitrary criteria where, following an earlier paper by this group, they defined a 'light' user as an individual consuming less than 20 tablets and anyone consuming over this amount, a 'heavy' user (Parrott *et al.*, 2000). For the observed differences to be the result of a neurotoxic insult, it is essential to demonstrate that a neurotoxic dose has been ingested. It is impossible to determine whether this has occurred from their data.

The purported evidence for a neurotoxic insult in ecstasy users is not as straightforward as one might assume. Reneman *et al*. (2001) recently demonstrated that men who have used over 500 ecstasy tablets do not demonstrate any reduction in serotonin (5-HT) transporter binding, although women do. There was also evidence of recovery, indicating that it may not actually be a permanent neurotoxic insult. Weight loss causes a drop in binding to the 5-HT transporter (Zhou *et al.*, 1996), which suggests that extra-pharmacological factors can mediate what Fox *et al*. (2001) believe to be a direct pharmacological effect. The neuroendocrine evidence of serotonergic dysfunction is also seen in alcohol dependent patients, cocaine users, cannabis users, marathon runners, depressed patients and victims of child abuse (Yatham and Steiner, 1993; Buydens-Branchey *et al.*, 1997; Broocks *et al.*, 1999; Buydens-Branchey *et al.*, 1999; Rinne *et al.*, 2000; Becker *et al.*, 2001; Haney *et al.*, 2001). Changes in executive function are also observed in alcohol, cocaine and amphetamine users (Bolla *et al.*, 1998; Lyvers, 2000). These deficits are also observed in children whose parents have a substance-related psychiatric problem (Giancola *et al.*, 1996). Some or all of these alternative causal mechanisms could account for the observed results.

The 'heavy' and 'medium' ecstasy users all consumed amphetamine, cannabis, cocaine and LSD. This suggests that labelling them as 'ecstasy polydrug users who use ecstasy as a drug of preference' is creating the very confounds, as Fox *et al*. (2001) argue, that limit the interpretation of their data. These subjects use these drugs in nightclubs to aid the clubbing experience and therefore a more appropriate term is 'dance drug' users. Simply because the subjects express a preference for one type of drug does not automatically mean that it is the sole causal mechanism of any observed impairments. No sound theoretical reason is given for the *a priori* rejection of alternative hypotheses concerning other drugs. For example, Fox *et al*. (2001) suggest that increased use of ecstasy may produce deficits similar to those observed in amphetamine dependent patients on *d*-amphetamine maintenance therapy (Ornstein *et al.*, 1999). Because the ecstasy users all used amphetamine, surely the most logical causal mechanism for this hypothesized result would be continued amphetamine use?

The most interesting question raised by these data is why that less than 50% of the ecstasy using subjects reported an ecstasy-related cognitive problem when they had equivalent cognitive impairments. An interesting hypothesis is that these subjects have been exposed to, and believe, media reports of ecstasy-related brain damage. In support of this, there is a substantial literature indicating that interpretations of cognitive performance can be influenced by expectancy effects and contextual factors such that perceived and objective performance are discrepant. For example, subjects who are given suggestions that their performance will change (for better or worse) on tests of mental alertness and auditory acuity consequently show significant changes in their perceived ability to perform these tasks in the absence of any objective change (Reilley and Rodolfa, 1981; Spanos *et al.*, 1982). Similarly, work on eyewitness testimony has shown that the confidence of witnesses in their identification abilities can be influenced by contextual factors, such as whether they believe others have made similar identifications, regardless of accuracy (Luus and Wells, 1994). Other studies suggest that pain judgments can be significantly influenced by manipulating expectations as to whether the stimulus will be experienced as pleasant, tolerable or unpleasant, independent of psychophysiological and neurophysiological indicators of perceptual sensitivity to noxious stimulation (Spanos, 1989; Rainville *et al.*, 1997). Page and Handley (1993) also found that a short lecture dispelling 'myths' about the negative effects of hypnosis was effective in reducing subjective reports of long-term negative sequelae following participation in hypnosis. Indeed, Page and Handley (1993) advise that the best way to

reduce the frequency of long-term negative effects of hypnosis is to dispel myths about the nature of hypnosis, and make no mention of its after effects when assessing hypnotic susceptibility.

In this context, it may not be wise to advise ecstasy users that they might have cognitive problems of which they are unaware. Despite over two million people using ecstasy in the UK, there is no credible evidence that the NHS is currently overrun with ecstasy-related problems. At what point is it appropriate for a clinical intervention? If ecstasy users believe themselves to be brain damaged when they are not, then they may come forward for unnecessary treatment. This will create a public health problem and cause major difficulties for the provision of health care to those who actually need it.

References

Becker S, Daumann J, Pelz S, Tuchtenhagen F, Bogusz M, Kock R, Gouzoulis-Mayfrank E (2001) Neuroendocrine probes as an index of central serotonergic neurotoxicity in ecstasy users: cannabis use is an important interfering variable. World J Biol Psychiatry *2*: P015–P020

Bolla K I, Cadet J-L, London E D (1998) The neuropsychiatry of chronic cocaine abuse. J Neuropsychiatry Clin Neurosci *10*: 280–289

Broocks A, Meyer T, George A, Hillmer-Vogel U, Meyer D, Bandelow B, Hajak G, Bartmann U, Gleiter C H, Rüther E (1999) Decreased neuroendocrine responses to meta-chlorophenylpiperazine (m-CPP) but normal responses to ipsapirone in marathon runners. Neuropsychopharmacology *20*: 150–161

Buydens-Branchley L, Branchley M, Fergeson P, Hudson J, McKermin C (1997) Hormonal, psychological, and alcohol craving changes after *m*-chloropiperazine administration in alcoholics. Alcohol Clin Exp Res *21*: 220–227

Buydens-Branchley L, Branchey M, Hudson J, Rothman M, Fergeson P, McKernin C (1999) Serotonergic function in cocaine addicts: prolactin responses to sequential D, L-fenfluramine challenges. Biol Psychiatry *45*: 1300–1306

Fox H C, Parrott A C, Turner J J D (2001) Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug. J Psychopharmacol *15*: 273–281

Giancola P R, Moss H B, Martin C S, Kirisci L, Tarter R E (1996) Executive cognitive functioning predicts reactive aggression in boys at high risk for substance abuse: a prospective study. Alcohol Clin Exp Res *20*: 740–744

Haney M, Ward A S, Gerra G, Foltin R W (2001) Neuroendocrine effects of *d*-fenfluramine and bromocriptine following repeated smoked cocaine in humans. Drug Alcohol Depend *64*: 63–73

Luus C A E, Wells G L (1994) The malleability of eyewitness confidence: Co-witness and perseverance effects. J Appl Psychol *79*: 714–723

Lyvers M (2000) 'Loss of control' in alcoholism and drug addiction: a neuroscientific interpretation. Exp Clin Psychopharmacol *8*: 225–249

Milroy C M, Clark J C, Forrest A R W (1996) Pathology of deaths associated with 'ecstasy' and 'eve' misuse. J Clin Pathol *49*: 149–153

Ornstein T J, Iddon J L, Baldacchino A M, Sahakian B J, London M, Everitt B J, Robbins T W (2000) Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology *23*: 113–126

Page R A, Handley G W (1993) The effect of preventative measures in reducing after effects to hypnosis. Am J Clin Hypnosis *36*: 26–37

Parrott A C, Sisk E, Turner J J D (2000) Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. Drug Alcohol Depend *60*: 105–110

Rainville P, Duncan G H, Price D D, Carrier B, Bushnell M C (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science *277*: 986–971

Ramsey J D, Butcher M A, Murphy M F, Lee T, Johnston A, Holt D W (2001) A new method to monitor drugs at dance venues. BMJ *323*: 603

Reilley R R, Rodolfa E R (1981) Concentration, attention and hypnosis. Psychol Reports *48*: 811–814

Reneman L, Booij J, de Bruin K, Reitsma J B, de Wolff F A, Gunning W B, den Heeten G J, van den Brink W (2001) Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. Lancet *358*: 1864–1869

Rinne T, Westenberg H G M, den Boer J A, van den Brink W (2000) Serotonergic blunting to meta-chlorophenylpiperazine (m-CPP) highly correlates with sustained childhood abuse in impulsive and autoaggressive female borderline patients. Biol Psychiatry *47*: 548–556

Sherlock K, Wolff K, Hay A W M, Conner M (1999) Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. J Accident Emerg Med *16*: 194–197

Spanos N P (1989) Experimental research on hypnotic analgesia. In Spanos N P, Chaves J F (eds), Hypnosis: the cognitive-behavioral perspective. Prometheus, New York

Spanos N P, Jones B, Malfara A (1982) Hypnotic deafness: Now you hear it – now you still hear it. J Abnorm Psychol *90*: 75–77

World Health Organization (1997) Amphetamine-type stimulants. A report from the WHO meeting on amphetamines, MDMA and other psychostimulants, Geneva, 12–16 November 1996. WHO, Geneva

Yatham L N, Steiner M (1993) Neuroendocrine probes of serotonergic function: a critical review. Life Sci *53*: 447–463

Zhou D, Huether G, Wiltfang J, Hajak G, Rüther E (1996) Serotonin transporters in the rat frontal cortex: lack of circadian rhythmicity but down-regulation by food restriction. J Neurochem *67*: 656–661

Probable serotonin syndrome variant in a patient receiving a selective serotonin reuptake inhibitor and a 5-HT_3 receptor antagonist

Steven M. Sorscher

Department of Oncology and Transplantation, Duke University Medical Center, Durham, NC, USA.

Recently, Gillman offered a thorough review of the serotonin syndrome in the *Journal of Psychopharmacology* (Gillman, 1999). This syndrome has been associated with a variety of drugs, singly or in combination and is felt to be related to excess intra-synaptic 5-hydroxytryptamine (5-HT). The syndrome had not been described secondary to 5-HT_3 receptor antagonist drug interactions. More recently in the Journal, a case of delerium was reported in a patient recovering from anaesthesia and the authors suggested an interaction between the 5-HT_3 receptor antagonist odansetron and paroxetine as one possible explanation (Stanford and Stanford, 1999). While the inhibition of CYP2D6 was offered by the authors as a possible mechanism for the interaction, additional scientific evidence was later presented in the form of an Editorial suggesting that this mechanism was not a likely contributor in the case reported (Palmer, 2000).

As a medical oncologist, I recently encountered a case which I believe represents a variant of the serotonin syndrome, and which is relevant to the articles described. A 49-year-old woman receiving sertraline (Zoloft) for some time without incident received her first cycle of adjuvant chemotherapy for breast cancer with cyclophosphamide and doxorubicin, and was premedicated with 100 mg of dolasetron (Anzemet), a commonly used 5-HT_3 receptor antagonist. Shortly after the infusion, she developed symptoms of profound agitation and elation. At the same time, however, she described an overwhelming desire to commit suicide and was disoriented. The symptoms resolved within hours without pharmacological intervention. Three weeks later, she received the same medications with no changes, except substitution of a different 5-HT_3 receptor antagonist, 20 mg odansetron (Zofran). With this second cycle, she experienced no adverse effects. While it is difficult to determine the actual relative pharmacological effects of these two 5-HT_3 receptor antagonists, it should be noted that the only change made was substitution of odansetron for dolasetron, and the substitution was at a dose that likely represented less 5-HT_3 receptor antagonism. This suggests a selective serotonin reuptake inhibitor (SSRI) and 5-HT_3 receptor antagonist interaction. In addition, the chemotherapy drugs described do not have established interactions with 5-HT_3 receptor antagonists.

A number of possible mechanisms for the interaction of SSRIs and 5-HT_3 receptor antagonists may be proposed. I believe that a variant of the serotonin syndrome can rarely be seen when drugs of these two classes are coadministered, as commonly occurs in cancer patients. Clinicians should consider this possibility in patients experiencing side-effects consistent with the serotonin syndrome.

References

Gillman P K (1999) The serotonin syndrome and its treatment. J Psychopharmacol *13*: 100–109

Palmer J L (2000) Postoperative delirium indicating an adverse drug interaction involving the selective serotonin reuptake inhibitor, paraxetine? [letter]. J Psychopharmacol *14*: 186–188

Stanford B J, Stanford SC (1999) Postoperative delirium indicating an adverse drug interaction involving the selective serotonin reuptake inhibitor, paraxetine? J Psychopharmacol *13*: 313–317