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Ecstasy versus alcohol: Tolstoy and the variations of unhappiness

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The Russian classic *Anna Karenina* commences with the following sentence 'Happy families are all alike; each unhappy family is unhappy in its own way.' (Tolstoy, 1877). The same might be said for the social recreational drugs, since they all enhance personal feelings of well-being, but cause distress in many different ways. Cannabis, alcohol, amphetamine and ecstasy/MDMA, all generate pleasant feelings for a period – which is why they are taken. The problem is that their regular usage generally leads to psychobiological distress, although the pattern of this distress is different for each type of drug. In the May editorial of the *Journal of Psychopharmacology*, David Nutt (2006) contrasted the psychobiological costs of two recreational drugs – ethanol/alcohol and ecstasy/MDMA. The alcohol findings were based on a series of papers from that issue, where the need for a less damaging alternative to alcohol was proposed (Nutt, 2006; Cox, 2006; others). Ecstasy was selected as the comparison, because the March and May issues also contained the papers from a special ecstasy/MDMA issue, which I had helped to organize and edit (Parrott and Marsden, 2006).

Nutt (2006) noted that alcohol drinking was extremely harmful, with around 22 000 premature deaths in the UK each year, and numerous other alcohol-related incidents, including interpersonal violence, road traffic deaths, brain damage, liver damage and heart disease (Table 1 in Nutt, 2006). Psychopharmacologists were urged to develop a less damaging happy pill, more equivalent to Aldous Huxley's *soma* (Cox, 2006). It was then suggested that these sorts of problem did not generally arise with recreational ecstasy/MDMA. Hence in Nutt's Table 1 it was noted that ecstasy was associated with around ten deaths per year, there was no interpersonal violence, no road traffic deaths, no heart damage, no cirrhosis and that the evidence on brain damage was 'unsure'. This led Nutt (2006) to ask: 'Why is ecstasy illegal, when alcohol, a considerably more harmful drug, is not?' This conclusion about their comparative dangers was based on a series of statements about ecstasy/MDMA which I found very surprising. Hence this Editorial Reply. In particular I would like to note the empirical evidence on each of the above topics, since it shows that MDMA is damaging in all of these areas.

In relation to aggression, the acute administration of MDMA induces feelings of warmth and empathy in humans (Cohen, 1998), and reduces aggressive behaviour in mice (Navarro and Maldonado, 1999). However this pro-social period lasts for only a few hours. Afterwards there is a more prolonged period of serotonergic depletion, when a number of psychobiological functions (including aggression) are adversely affected. In a prospective investigation of young recreational ecstasy users, Curran *et al.* (2004) reported a significant increase in aggressive feelings, and behavioural indices of aggressiveness, 4 days after recreational MDMA, with values returning to baseline after 7 days. In an extension of the study, this significant increase in mid-week

Table 1 Some of the harmful psychobiological changes associated with recreational Ecstasy/MDMA

Car driving impairments	Brookhuis *et al.*, 2004; Logan and Couper, 2001
Behavioural Aggression	Curran *et al.*, 2004; Gerra *et al.*, 2001; Hoshi *et al.*, 2006
Liver damage	Montiel-Duarte *et al.*, 2002; Maurer *et al.*, 2004; Smith *et al.*, 2005
Cardiac damage	Gesi *et al.*, 2002; Setola *et al.*, 2003
Neurotoxicity	Reneman *et al.*, 2006; Easton and Marsden, 2006; Thomasius *et al.*, 2006
Memory-cognitive deficits	Zakzanis and Campbell, 2006; many others
Frontal-executive cognitive deficits	Fox *et al.*, 2002; Reay *et al.*, 2006
Immuno-competence impaired	Connor, 2004; Pacifici *et al.*, 2002
Psychiatric distress: complex interactions	Parrott, 2006a; many others
Cortisol and other hormonal changes	Gerra *et al.*, 2001: Lock *et al.*, 2006
Social intelligence reduced	Reay *et al.*, 2006
Oxidative stress increased	Zhou *et al.*, 2003
Death	Schifano et al, 2006

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aggression was found to occur in both females and males (Hoshi *et al*., 2006). Depression was also significantly increased, while other mid-week rebound/recovery problems include unsociability, reduced appetite and poor sleep (reviews: Parrott, 2001, 2006a). Compared with the hangover effects of alcohol, the recovery problems of MDMA are longer lasting, and generally more pervasive. Gerra *et al.* (2001) found that drug-free ecstasy users also had higher levels of aggressiveness, and that the extent of this behavioural aggression correlated significantly with lifetime usage.

Car driving is also adversely affected by ecstasy/MDMA (Table 1). Logan and Couper (2001) reviewed the effects of ecstasy on psychomotor skills and car driving. They also described 18 case studies, including six where the drivers' blood samples had tested positive for MDMA alone: 'Most subjects displayed muscle twitching and body tremors, dilated pupils, slow pupillary reaction to light, elevated pulse and blood pressure, lack of balance and coordination, and most were perspiring profusely. Five of the six subjects were given field sobriety tests, and all performed poorly.' This allowed the authors to conclude: 'MDMA use is not consistent with safe driving, and impairments of various types may persist for a considerable time after last use.' Brookhuis *et al*. (2004) assessed Ecstasy users' performance on a driving simulator under three conditions: when drug free, soon after self-administering recreational ecstasy/MDMA and following MDMA-polydrug use at a party. Driving errors were significantly increased by MDMA alone, and simulator driving was further impaired after MDMA-polydrug usage. Brookhuis *et al.* (2004) concluded: 'Driving under the influence of MDMA alone is certainly not safe; however, driving back home after a dance party ('rave') where MDMA users regularly combine MDMA with a host of other drugs can be described as extremely dangerous.'

MDMA also affects liver function. Montiel-Duarte *et al*. (2002) noted that MDMA had hepatotoxic properties and that in cultured liver cells it induced apoptosis or programmed cell death. It is one of several designer drugs with adverse hepatic properties (Maurer *et al*., 2004). Recreational users may not be aware of these subclinical hepatic changes, although occasionally this damage can be severe and life threatening. In a review of (non-paracetamol) drug-induced fulminant hepatic failure cases in Scotland, Smith *et al*. (2005) noted that ecstasy was commonly implicated in those presenting with this rare disorder from the younger age groups. Many CNS stimulants also adversely affect cardiac functioning. The adverse effects of cocaine are well known, but MDMA is another powerful and potentially damaging cardiac stimulant. Setola *et al*. (2003) noted that MDMA had similar adverse cardiac properties to fenfluramine, and they predicted that: 'Long-term MDMA use could lead to the development of fenfluramine-like valvular heart disease.' Gesi *et al*. (2002) noted that 'Persons abusing ecstasy typically suffer cardiac symptoms, such as tachycardia, hypertension, and arrhythmia.' They also investigated its effects on the structural integrity of cardiac cells in laboratory mice. Cardiac cell mitochondrial damage was greatest when MDMA was administered under loud noise: 'Our findings did not show any myocardial lesion detectable under light microscopy. In contrast, alterations were visible at the ultrastructural level as mitochondrial changes. In particular, we found a marked enhancement in the number of altered mitochondria when MDMA was administered during exposure to loud noise.' These cardiac findings in laboratory animals are consistent with the 'energetic stress' model for recreational MDMA users, where the adverse metabolic effects of MDMA are exacerbated by concomitant non-drug stimulation (Parrott, 2006a; Parrott *et al*., in press).

With reference to serotonergic neurotoxicity, although the animal data is robust and extensive (Green *et al*., 2003; Easton and Marsden, 2006), in humans the evidence is certainly far more variable. Serotonergic deficits have been observed in some studies, but not in others, and there is evidence for structural recovery following drug cessation. This topic was extensively debated in the special *Journal of Psychopharmacology* issue (Reneman *et al*., 2006; Easton and Marsden, 2006; Thomasius *et al*., 2006). Nutt (2006) also suggested that ecstasy was not associated with dependence, but while MDMA is not a strong drug of dependence, it does have dependence-inducing properties (Cottler *et al*., 2001), and 20% of users feel dependent on it (Milani and Parrott, 2004). In relation to annual deaths, Schifano *et al*. (2006) suggested an annual UK death rate of around 40–70/year, although they noted the many difficulties in arriving at these estimates, since most fatalities are in ecstasy polydrug users. Indeed all the functional and structural data on recreational ecstasy/MDMA is confounded by other drug and non-drug factors, so that our explanatory models need to be complex and multifactorial (Parrott, 2006a). It is less widely recognized that the empirical data on alcohol drinking is *also* confounded with lifestyle (health, psychosocial, psychiatric), and other-drug factors. Around 90% of heavy drinkers smoke tobacco, and nicotine dependency leads to greater stress and depression (Parrott, 2003, 2006b), along with physical ill-health. Cannabis is another damaging co-drug for many younger drinkers. Hence our neuropsychobiological models for alcohol use also need to be more complex and multifactorial.

MDMA and alcohol are therefore both damaging; so how do they directly compare? In acute terms, MDMA is a far more powerful drug than alcohol. Baylen and Rosenberg (2006) listed the following acute somatic effects of ecstasy/MDMA (occurring in various proportions of users): nausea, jaw clenching, teeth grinding, headache, body temperature changes, accelerated heartbeat, muscle aches, fatigue, dizziness, vertigo, dry mouth, thirst, increased energy, sweating, numbness, tingling skin, ataxia, unsteadiness, tics, tremors, restlessness, agitation and nystagmus. Acute hormonal changes can also occur. In our most recent study, we directly compared the effects of self-administered MDMA, and alcohol drinking, in a small group of dance clubbers who acted as their own controls (Lock *et al*., 2006). In the alcohol-alone condition there was a rise in cortisol from baseline of around 100%, whereas under MDMA the mean increase in this 'stress hormone' was around 800%. Testosterone was also significantly increased under MDMA, but was unchanged by alcohol. The mood enhancing effects of MDMA are also far more powerful than alcohol, but so are the rebound mood decrements (Parrott, 2006a). Turning to their chronic effects, many studies of recreational ecstasy/MDMA users have compared them to legal drug users – who typically comprise alcohol drinkers (often in a polydrug context). Many of these studies have demonstrated selective cognitive/psychobiolog-

ical deficits in the ecstasy/MDMA users (review: Parrott, 2006a; Parrott *et al*., 2001). Further deficits in functions not previously investigated were noted in the special *Journal of Psychopharmacology* issue. To take one example, Reay *et al.* (2006) found significant impairments in 'emotional intelligence' and 'social intelligence', along with frontal cognitive task deficits, in their ecstasy users. Many other factors will obviously be associated with these relative deficit profiles. However the crucial point is that acute recreational ecstasy/MDMA use is associated with significantly more psychobiological distress, than recreational alcohol drinking.

Moving from Russian to British literature, during the *Lady Chatterley's Lover* obscenity trial in the 1960s, the judge asked the jury if they would let their servant read the book.* This question can be given a psychopharmacological slant. Would you want your daughter or son to take either of these drugs, and if so, which would it be? Nutt (2006) suggested that alcohol was more damaging. In contrast, I would suggest that MDMA is more powerful and potentially more damaging. In particular, the high incidence of alcohol-related problems is mainly a reflection of its ready availability and widespread usage. The trend towards more intensive patterns of drinking is therefore a matter of great concern. Politicians need to follow the advice of Nutt (2006), and take practical steps to reduce alcohol consumption dramatically. But the problems of alcohol will not be solved by adding yet another damaging *soma* – or happy pill. MDMA is a powerful metabolic stressor, but this means it can impair well-being within a short time span of usage. Topp *et al*. (1999) noted that young regular users reported an average of eight physical and four psychological problems which they attributed to their Ecstasy use. Zakzanis and Campbell (2006) noted that continuing MDMA use led to a *further* deterioration of memory test performance, when retested 1 year later. Fortunately, only 3–4% of the population have ever taken ecstasy/MDMA, but most are former users, and the proportion of current regular users is much lower (Parrott, 2005). If MDMA were to be downgraded, as the British politician David Cameron has suggested (Nutt, 2006), there would be no real benefits, but there would be numerous adverse costs (Table 1). Any increase in overall consumption would create more MDMA-related distress, and so bring it closer to the high rates of alcohol-induced unhappiness seen currently.

* International readers may be pleased to hear that nowadays, the British do allow their servants to read the D.H. Lawrence classic.

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