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David and I have broadly similar views on alcohol, since we are both aware of its damaging social and psychobiological effects (Nutt, 2006). In a recent summary chapter I wrote: 'In global terms, alcohol is one of the most damaging drugs known to mankind' (Chapter 15 in Parrott *et al.*, 2004). Hence I agree with David that all governments need to take the problems of alcohol drinking, and indeed tobacco and cannabis smoking, far more seriously. However, we seem to have very different views on two other topics. First, the relative costs and dangers of using ecstasy/MDMA versus alcohol. Second, on whether it might be possible to develop a psychopharmacologically safe recreational drug.

On the first question, I suspect that most people might agree with David that alcohol is more dangerous than ecstasy/MDMA. Alcohol is widely used, many individuals have personal experiences of its deleterious effects, and its adverse consequences are manifest every day in our towns and cities. In contrast, few adults have any direct knowledge or experience about ecstasy/MDMA, its use is quite rare even amongst young people, so that fortunately there are comparatively few people with ecstasy-related problems. This may help to explain why on the scale of socially constructed dangers, MDMA would be far lower than alcohol. However in many ways MDMA is more damaging than alcohol. The acute physical effects of MDMA are extremely powerful and wide-ranging (see initial reply), so that neural overstimulation is an intrinsic part of the drug experience (Parrott, 2002). Hence the positive mood effects of MDMA can only be achieved at psychophysiological costs. The chronic problems of MDMA are also subtle and insidious. The first psychobiological deficits to be recognized were in memory and depression; these have been followed by more recently demonstrated deficits in cognitive planning, impulsivity, emotional intelligence, social awareness and other functions (Parrott, 2006). MDMA is also a powerful metabolic stressor, and it has basic (cellular) effects which may eventually prove even more troublesome; hence the increase in markers for oxidative stress, reduced immunocompetence, and the cardiac, hepatic and other changes noted in my initial reply. At the risk of repeating myself, let me note that MDMA is a far more powerful psychoactive drug than alcohol, its acute effects are more profound, the post-drug recovery problems are more pervasive and prolonged, and chronically it can have a range of adverse effects after a far shorter period of usage (Parrott, 2006). Hence on a direct drug-for-drug comparison, MDMA is potentially far more damaging than alcohol.

Turning to the broader question, I do not believe that it is possible to design a neurochemically safe drug of pleasure. There are many psychoactive drugs with acute mood enhancing properties; not only alcohol and MDMA, but also cannabis, amphetamine, cocaine and the opiates. The main problem is that they all have many adverse effects: acute, subacute and chronic. Furthermore these deleterious aspects are an intrinsic part of the overall equation; they reflect a number of basic psychopharmacological processes, with neuroadaptation being a core element. Hence the paradox for all drugs of pleasure is that their positive effects are countermanded by numerous negative sequelae (again see Chapter 15 in Parrott *et al.* 2004 for a fuller discussion). Since this pattern is true for opiates, cocaine, nicotine, amphetamine, cannabis and alcohol, I see no reason why any new drug would not display a similar adverse cost–benefit ratio. Even 'soma', which Aldous Huxley (1932) invented for his novel *Brave New World*, was not problem free. In Huxley's idealistic, yet ultimately dystopic view of the future, soma was used as a universal drug of pleasure: 'Delicious soma, half a gram for a half-holiday, a gram for a week-end, two grams for a trip to the gorgeous East, three for a dark eternity on the moon.' Its acute pharmacodynamic profile was surprisingly similar to MDMA: 'By this time the soma had begun to work. Eyes shone, cheeks were flushed, the inner light of universal benevolence broke out on every face' ... The warm, richly coloured, infinitely friendly world of soma-holiday. How kind, how good-looking, how delightfully amusing every one was' (Huxley, 1932). However soma also caused psychobiological problems, including rebound negative moods, tolerance and dependence: 'If the morning after was disagreeable, it was ... only by comparison with the joys of the holiday. The remedy was to make the holiday continuous. Greedily she clamoured for ever larger, ever more frequent doses' (Huxley, 1932). To summarize, it is probably impossible to design a safe and effective drug of pleasure without untoward side effects. Alcohol clearly fits the picture, the modern 'designer' drug MDMA illustrates the same pattern, while even Aldous Huxley's mythical soma is consistent with this general principle.

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