Reply to Mark Easton, BBC,

From Professor Andy Parrott, Swansea University, Wales.

I would like to reply to the Mark Easton 'Blog' about my MDMA-presentation to the Advisory Council on the Misuse of Drugs. This 20 minute Power-point presentation comprised numerous simple bullet points – which I then debated and discussed during my talk to the committee. Mark Easton criticized these bullet points as representing a series of 'errors'. I welcome this opportunity to respond to these criticisms, by talking about the scientific evidence for them in more detail.

MDMA related deaths.

The expert on MDMA-related deaths in the UK is Professor Fabrizio Schifano, and one of his studies is cited by Mark Easton. Fabrizio Schifano noted that the majority of deaths had involved polydrug usage (i.e. MDMA plus other drugs); Mark further noted that I acknowledged this in my research papers. Indeed nearly all Ecstasy/MDMA users are polydrug users, with around 90% taking cannabis and/or alcohol, and a large majority also taking other stimulant drugs such as cocaine and amphetamine. Hence most MDMA–related deaths involve the use of other co-drugs. This makes it difficult to attribute the exact cause of death to any one drug – whether it is amphetamine, methamphetamine, or MDMA. Furthermore the exact causes of death can be quite variable. Again this is debated more fully by Professor Schifano in his many papers on this topic (Schifano, 2003, 2004, 2006).

There are equivalent research papers from other countries. The following report is from the Department of Forensic Medicine, Ghent, Belgium. It is entitled: 'Amphetamines as potential inducers of fatalities: a review in the district of Ghent from 1976-2004' (De Letter et al, 2006). The authors wrote: "Abuse of amphetamine (AMP) and its derivatives, such as 3, 4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'), 3, 4-methylenedioxyethylamphetamine (MDEA, MDE), and 3, 4-methylenedioxyamphetamine (MDA) is an important public issue. Fatalities following ingestion of these substances are not infrequent in current forensic practice..... In 34 fatalities, amphetamines were involved and the majority were men, under the

age of 25 years. A wide range of blood levels was found: e.g. MDMA blood concentrations in cases of 'pure' intoxication were found between 0.27 and 13.51 microg/ml. The age and sex distribution as well as the broad range of quantified amphetamines blood levels were in line with those reported in the literature. In our study group, 'pure' intoxications with amphetamines, polydrug overdoses, and the combination of amphetamines use and polytrauma were the most prominent causes of death. Considering the manner of death in these fatalities, unintentional overdoses were most frequent, though suicides, traffic accidents, and criminal offences associated with amphetamines use also accounted for significant percentages. Acute to subacute cardiopulmonary failure was the most frequent mechanism of death, followed by (poly) trauma, mechanical asphyxia, and hyperthermia, respectively. In conclusion, although amphetamines-related fatalities are only a fraction of the total number of fatalities studied at our Department, their contribution to current forensic practice has been increasing during the last few years…".

In these and other reports it has been noted that MDMA related fatalities are difficult to predict, and can occur after low doses. The Ghent report also noted more death in males, but in other aspects females are more vulnerable. For instance, one potential danger with MDMA is hyponatraemia (excessive dilution of sodium in the blood through excessive water-intake). This proved fatal in Leah Betts, although these days acute hyponatraemia is generally treated successfully by rapid medical intervention (with sodium replacement) – so preventing a fatal outcome. In a recent article entitled 'Patterns of ecstasy-associated hyponatraemia in California' (Rosenson et al, 2007) it was noted that "Female sex was associated with increased odds of hyponatraemia and increased odds of hyponatraemia-associated coma".

Since there may be physicians and paramedics reading this 'Blog', I would like to recommend the following articles which outline the optimal medical treatment for recreational stimulant drug users in acute distress. In an article entitled 'Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management', Hall and Henry (2008) noted that: "While the phenomenon of hyperpyrexia and multi-organ failure is now relatively well known, other serious effects have become apparent more recently. Patients with acute MDMA toxicity may present to doctors working in Anaesthesia, Intensive Care and Emergency Medicine. A broad knowledge of these pathologies and their treatment is necessary for anyone working in an acute medical speciality". In a subsequent review, Devlin and Henry (2008) outlined the treatment options for emergency admissions related to all recreational drug

users. They noted: “Because of its marked cardiovascular effects, cocaine is also a major cause of coronary syndromes and myocardial infarction. Amphetamines may produce similar effects less commonly. Hyperthermia may occur with cocaine toxicity or with 3,4-methylenedioxymethamphetamine (MDMA) due to exertion or from serotonin syndrome. Cerebral haemorrhage may result from the use of amphetamines or cocaine. Hallucinations may follow consumption of LSD, amphetamines, or cocaine. MDMA is a major cause of acute severe hyponatraemia and also has been linked with hepatic syndromes. Collapse, convulsions, or coma may be caused in different circumstances by opioids, MDMA, or gamma hydroxybutyrate and may be aggravated by other sedatives, especially alcohol and benzodiazepines. Recognition of these acute complications is urgent, and treatment must be based on an understanding of the likely underlying problem as well as on basic principles of supportive care”. To summarize, MDMA is just one of several powerful CNS stimulant drugs, which can occasionally cause medical emergencies. It is largely due to the skills and dedicated work of numerous doctors and their emergency medical teams that the annual deaths rates from MDMA and related stimulant drugs are not higher.

Finally, in his ‘Blog’ Mark Easton has stated that: ‘Prof Parrott himself… ‘notes that the death data are pretty meaningless’. I am appalled that this callous statement has been attributed to my name. These deaths are all tragic – especially since they are in young healthy individuals who would still be enjoying life if it was not for ‘Ecstasy’ and related drugs.

Brain damage

Cowan (2007) has written that: “Only investigations employing nuclear imaging methods to assay brain 5-HTT levels have been replicated across methods and research laboratories. These studies have found reduced levels of the 5-HTT in recently abstinent MDMA users with some evidence for normalization of 5-HTT levels with prolonged abstinence”. In a more recent review, Cowan et al (2008) wrote that; “Neuropsychological, neuroendocrine, and neuroimaging studies have all suggested that human MDMA users may have long-lasting changes in brain function consistent with 5-HT toxicity. Data from animal models leads to testable hypotheses regarding MDMA's effects on the human brain. Because neuropsychological and neuroimaging findings have focused on the neocortex, a cortical model is developed to provide a context for designing and interpreting neuroimaging studies in MDMA users. Aspects of the model are supported by the available neuroimaging data, but there

are controversial findings in some areas and most findings have not been replicated across different laboratories and using different modalities. This paper reviews existing findings in the context of a cortical model and suggests directions for future research.'

The most advanced study in this area has been undertaken in the Netherlands, and it is still ongoing. Several important reports have emerged from this group. De Win (2008) tested 188 young people at baseline (before taking MDMA), then some time later - after some of them had taken ecstasy, while the others had not. At the second testing there were 59 ecstasy users (who had taken an average of 6 tablets in total) and 56 controls who had not taken any ecstasy tablets. An extensive battery of measures was taken. The Ecstasy users showed reduced regional relative cerebral blood volume values, some differences in other measures, while many of the others were unchanged. The authors concluded: "These findings suggest sustained effects of ecstasy on brain microvasculature, white matter maturation and possibly axonal damage due to low dosages of ecstasy. Although we do not know yet whether these effects are reversible or not, we cannot exclude that ecstasy even in low doses is neurotoxic to the brain". In another report (Schildt et al, 2007), the non-users showed improved memory scores, while the Ecstasy users did not. The authors conclude that there was evidence for memory problems after taking an average of just 3 ecstasy tablets.

Aggression

In Parrott (2007) I outlined how Ecstasy/MDMA usage was associated with changes in aggression. "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 et al, 1999). However this pro-social period lasts for only a few hours. Afterwards there is 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 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, 2006). 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".

The practical implications can be illustrated with a report about road rage in Canada. Butters et al (2005) analysed the types of drug used by individuals in the most severe category of 'road rager'. They reported: "Frequent road ragers, accounting for 5.3% of the sample, were involved in the most severe forms of road rage behaviour and were most likely (24%) to report problem drinking and past year cannabis (23.8%), cocaine (5.4%), and ecstasy (10%) use. These data indicate that illicit drug use and alcohol problems are significantly greater for those involved in the most serious forms of road rage behaviour."

Car Driving Impairments

In the same Editorial (Parrott, 2007) I briefly noted some of the evidence about MDMA and car driving: "Logan and Couper (2001) reviewed the effects of Ecstasy on psychomotor skills and car driving. They also described eighteen 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'.".

Heart and Liver Damage

In the same article (Parrott, 2007) I also noted some of the empirical literature on the effects of MDMA upon the liver (hepatic effects) and heart (cardiac effects): “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 sub-clinical 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, 2006).

Ecstasy/MDMA dependence

In my ACMD presentation I did not have time to describe the empirical data on Ecstasy dependence in any detail. However, to cite just one study, Topp et al (1997) reported a rate of Ecstasy dependence at around 64%. Other studies have cited lower and higher rates. In a chapter I have just finished writing for an American medical textbook, (Parrott, in press), I noted that: “Topp et al (1997) showed that MDMA dependence had a bifactorial structure, with two components, compulsive and escalating use. ‘Compulsive usage’ loaded on questions such

as continuing to use despite Ecstasy-induced problems, unsuccessful attempts at cessation, and spending an excessive amount of time and effort in obtaining MDMA and using it. The 'escalating usage' factor loaded on needing higher doses, taking it for longer than intended, and periods of bingeing. Most regular users take serial repeated doses, while some heavy users have continuous binges which last 48 hours or more (Topp et al, 1999). This is broadly similar to the 2-3 day binges of some heavy cocaine users. Bruno et al (2008) confirmed the same two-factor structure for MDMA dependency, in a large study of 1662 regular Ecstasy users". For those interested in Ecstasy cravings, I recommend the real-time prospective study by Hopper et al (2006).

Relative harm

My ACMD presentation was also concerned with Professor Nutt's article published in the Lancet (Nutt et al, 2007). This article had attributed very low scores to MDMA on every harm scale, and so concluded that MDMA was one of the least harmful all the recreational drugs (18th out of 20). Unfortunately none of these statements was based on cited reference sources. When I re-scaled these scores using scientific data, then MDMA emerged as the 5th most harmful drug on this list (lower than heroin and cocaine – but broadly similar to some of the other Class A drugs). The Lancet article contains numerous incorrect statements about MDMA. One of the strangest statements made by Nutt et al (2007), was that ecstasy generated less pleasure than smoking a cigarette.

Final Overview

I welcome the opportunity to present some of the scientific evidence about the damaging effects of MDMA or 'ecstasy' in humans. For those who would like to read more about MDMA, I have written several reviews of its effects in recreational users (Parrott, 2000, 2001, 2002, 2004, 2006). There many other reviews, for instance Green et al (2003), Hegadoren et al (1998), McCann et al (2007), Morgan (2001), Schifano (2000), and others.

A few years ago the ACMD re-classified methamphetamine – moving it up from class B to class A. Now the ACMD wants to downgrade MDMA from class A to class B – although

MDMA is technically a methamphetamine derivative. Both drugs are damaging to health and well-being, although in different ways. MDMA should therefore remain in the same category as its parent compound – class A.

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