

# Where are the Ecstasy casualties ?

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The British Crime Survey indicates that around 2 million people in the UK have used Ecstasy . If exposure to Ecstasy causes brain damage then we have a very serious public health problem. However there is no credible evidence that the NHS is overrun with Ecstasy casualties. As both Professor Parrott and Dr Morgan state, Ecstasy users are unaware that they have any problems *until* they take part in studies. We believe that impairment equates with a clinical problem. Therefore unimpaired individuals are being told by the media that they are brain damaged and have psychological problems. We believe that this quite neatly fits our definition of an iatrogenic disorder. We are not suggesting that the differences are due to autosuggestion. We are instead suggesting that these differences are not clinically significant but they are being reported as if they are.

The sole theory put forward for the observed results is that MDMA is a neurotoxin. None of our colleagues questioned the fact that animal studies routinely fail to demonstrate any functional effect of MDMA exposure. Why is it so easy to demonstrate differences in humans but not animals ? The animal studies don t have the same confounds. We can demonstrate unequivocally that MDMA-induced neurotoxicity was the causal agent. Yet, we fail to see any reliable behavioural or cognitive changes. This suggests that MDMA-induced neurotoxicity does not cause cognitive or psychological impairment. As our colleagues did not question this we must assume that they agree with us.

Professor Parrott has provided us with a review of the relevant data. Although he fails to actually answer our main criticisms of that data (see Figure 1). In addition, there are a number of problems with his comments;

1. The available evidence does not support the energy exhaustion model of serotonin neurotoxicity. Drug treatments which maintain energy balance within the presynaptic terminal actually potentiate neurotoxicity. This is the precise opposite of what this model would predict. Also MDMA injected directly into the brain does not produce the neurotoxicity that this model would predict. Instead it indicates that a toxic metabolite formed outside of the CNS causes the damage.

2. Although MDMA-induced neurotoxicity is altered by increased temperature, so is the toxicity. Over a third of animals die when administered MDMA at the temperatures required to increase neurotoxicity. This would suggest a much higher number of fatalities if his theory is correct.
3. Ecstasy users frequent hot crowded environments as nightclubs pack large numbers of them into small spaces with inadequate ventilation, not because it alters the effect of their Ecstasy .
4. The cognitive deficits and psychological problems that he describes are also seen in users of cocaine, alcohol, and cannabis. None of these drugs is considered a serotonergic neurotoxin. His theory cannot account for this data.
5. If serotonin is implicated in so many functions why are verbal memory deficits the only consistent finding ?
6. In the brain imaging studies all subjects with a psychiatric problem were excluded. Any observed differences cannot be the cause of psychiatric problems if the subjects didn't have any. This argues against the notion that Ecstasy users are at greater risk of developing psychiatric problems.
7. Anxiety is produced by an increase in 5-HT function. Anti-anxiety drugs work by reducing 5-HT activity. If Ecstasy users have reduced 5-HT function then they should be less anxious. This is the exact opposite of the data he presents.
8. The brain imaging studies have been heavily criticised in the literature for numerous methodological problems. The authors of these papers have stated that their results should be interpreted cautiously because of this.
9. The criticisms which he applies to Dr Croft's study can also be applied to the other studies he reviews.
10. In a recent survey, 91% of users reported that they used Ecstasy to help them keep going on a night out with friends and 80% to enhance an activity, such as listening to music. This demonstrates that Ecstasy and other drugs are used to aid dancing at nightclubs.
11. Although the notion of light versus heavy users is used there is no attempt to determine if neurotoxic doses of MDMA have been taken. Interspecies dose scaling was rejected by the editors of the journal Neuropsychopharmacology. We therefore have no idea whether human users are using neurotoxic doses of MDMA.

Our colleagues have all agreed that the Ecstasy literature is plagued with a large number of confounds (see Figure 1). The question is how these confounds affect our interpretation of the data. There is a large body of data demonstrating consistent differences. We are not disputing this fact. We simply do not feel comfortable with the notion that millions of young people are being told that they are brain damaged based upon confounded data. Alternative explanations exist and they need to be tested.

The US Food and Drug Administration have recently approved a clinical trial using MDMA in the treatment of Post Traumatic Stress Disorder. There is another similar trial going on in Spain and one planned in Israel. MDMA has been given to human volunteers in the UK, USA, Spain, Germany, Switzerland, and Holland. Ethics committees appear to be unconvinced by the argument that acute doses of MDMA cause neurotoxic damage and long-term harm. These studies have so far failed to cause either psychiatric problems or cognitive difficulties in their subjects.

The converging evidence that Dr Croft refers to is somewhat circumstantial. The brain imaging studies were done in subjects who were not depressed and clinical depression has never been identified in any random sample of Ecstasy users. This suggests that the observed differences are not causing clinically relevant depression. Several of our studies have failed to find any psychiatric problems in Ecstasy users.

No one should underestimate the dangers of illegally using controlled drugs. There is the very real possibility that Ecstasy use will cause long-term changes in the brain. However, the animal data demonstrates that simplistic theories based on MDMA-induced neurotoxicity are inadequate. Ecstasy research needs to move beyond description and start to provide mechanisms for the observed differences. Only then can we start to effectively warn drug users about the long-term effects of their drug use.

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1. Polydrug use
2. Pre-morbid differences
3. Co-morbid differences
4. Quantifying drug intake
5. Urine testing to ensure subjects are drug free
6. Sleep disruption over extended periods of time
7. Altered nutritional status
8. Subject selection
9. Motivation for taking part

Figure 1: The confounds in Ecstasy Research.