

Are the long-term effects of 'Ecstasy' iatrogenic ?

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The media have always had a fascination with illegal drug use and, in particular, they have sensationalised the negative effects of 'Ecstasy'. 'Ecstasy' and raves are a cultural phenomenon. Their impact upon what is currently known in the UK as the 'Chemical Generation' is believed by some to be the defining moment of the late 1980's and early 1990's. All night dancing with the aid of stimulant drugs has been known since the emergence of cocaine in 1920's London. Stimulant-fueled dancing has continued throughout most of the 20th Century.

The major difference between these youth subcultures is the sheer scale of the numbers that have used 'Ecstasy' and other dance drugs. Recent surveys of young people's drug use has indicated that in the UK about 10% of young adults aged between 15 and 29 have tried 'Ecstasy' (e.g. Ramsey *et al.*, 1999), although this figure jumps to around 90% when the respondents are attending raves or nightclubs on a regular basis (e.g. Bean *et al.*, 1997).

'Ecstasy' is the colloquial name used to describe the entactogen, 3,4-methylenedioxymethamphetamine (MDMA). Entactogens are drugs that have been used medicinally to aid the psychotherapeutic process by enabling patients to access and deal with repressed painful emotional issues. MDMA became a drug of abuse in the early 1980's and its use was restricted to several areas of the USA. In the mid to late 1980's MDMA crossed the Atlantic and became part of the of illegal drug scene.

As with all illegal drugs, purity became an important issue - now it is difficult to know for certain exactly what 'Ecstasy' is. 'Ecstasy' tablets are sold under brand names, such as white dove or Mitsubishi, which refer to imprints stamped onto the tablet. Manufacturers of 'Ecstasy' constantly change their brand names due to fraudulent copies rapidly following the emergence of a new design. This has led to a plethora of designs and a corresponding problem in estimating the purity of 'Ecstasy' tablets without a full chemical analysis.

Other drugs have masqueraded as MDMA, the most common being other entactogens, and other drugs have been mixed to produce an MDMA-like effect, such as ketamine and ephedrine. Some tablets contain no active ingredients at all or legal drugs, such as pain killers. It is difficult in this context for anyone to know with any certainty the actual drug intake of an 'Ecstasy' user.

'Ecstasy' has a high public profile due to the media coverage of deaths that have been associated with its use. The Office of National Statistics report that in the UK between 1993 and 1997 there were 72 deaths due to 'Ecstasy'. During the same time period there were 158 deaths due to amphetamine. In contrast, every year around 50,000 people die as result of their alcohol use and around 120,000 as a result of smoking. While every death from the use of drugs is an avoidable tragedy, the perceived 'safety' of 'Ecstasy' has encouraged its use among young people.

If the statistics from the UK and the USA are compared, the toxicological effects of MDMA become even more convoluted. In the USA, the fatalities recorded for MDMA intoxication differ radically in both symptomatology and number from the UK. If MDMA is found in the bloodstream of a dead subject then it is recorded as a cause of death, even if the primary cause of death was something entirely different, such as carbon monoxide poisoning or a fall (e.g. Dowling, 1990). Even with this very broad inclusion criteria, the

number of recorded fatalities due to MDMA are very low. In the UK, however, the picture is entirely different as the majority of cases can be directly attributed to the use of MDMA or related drugs.

The most profound adverse reaction to MDMA is hyperthermia, with body temperatures reaching as high as 44 °C, usually followed by multiple organ failure. The overwhelming majority of these adverse reactions occurred at the weekend after using 'Ecstasy' in raves or nightclubs. This has led to the use of the term "Saturday Night Fever" by staff at Accident and Emergency departments (Williams *et al.*, 1998).

Harm reduction literature was produced which advocated methods of reducing body temperature and replacing fluids lost through sweating. While this advice has undoubtedly reduced the incidence of overheating after taking 'Ecstasy', it has created a new problem. Misinterpretation of this advice by intoxicated users has led to a number of adverse reactions due to unrestricted water intake. Too much water can lead to swelling of the brain and in some cases death.

Recently attention has moved from the acute toxicity of 'Ecstasy' and onto its long-term effects. MDMA has been found to produce long-term changes in the structure and function of the brains of various species. These changes involve the neurotransmitter serotonin. They are typically characterised as degeneration of the fibres emerging from serotonergic cell bodies. The cell bodies themselves are unaffected. This has led to the classification of MDMA as a neurotoxin.

As the serotonergic cell bodies are spared and regenerate these fibres, some have questioned whether this classification is appropriate. These researchers advocate that a true neurotoxic effect involves the robust and well validated biological measures of cell body degeneration, changes which are not present after MDMA administration (e.g. O'Callaghan and Miller, 1993).

The doses required to produce the long-term changes in the serotonergic system far exceed those used by recreational users. This recreational dose is estimated to be about 1.9 mg/kg if an average person takes a 'standard' 100 mg tablet. Animal experiments typically involve high doses administered over several days. To equate human and animal doses mathematical methods can be employed. They are not 100% accurate as there are differences between species in the absorption and metabolism of drugs.

Most experiments looking at long-term changes in rats use a minimum of 40 mg/kg of MDMA administered as 10 mg/kg injections over 6 hours at 2 hour intervals (e.g. Fischer *et al.*, 1995). Primate studies typically use a total of 40 mg/kg administered as 5 mg/kg injections over 4 consecutive days at 12 hour intervals (e.g. Fischer *et al.*, 1995). In both cases the dosing pattern is not that typically used by recreational 'Ecstasy' users. They normally take 1.9 mg/kg through the oral route of administration.

There is strong evidence that injection of MDMA is 2-3 times more neurotoxic than oral administration in the primate (Ricaurte *et al.*, 1988). For example, squirrel monkeys given 2.5 mg/kg of MDMA orally every 2 weeks for 4 months, did not show reduced serotonergic function (Ricaurte, 1993 personal communication to the Swiss Federal Ethical Committee cited in Vollenweider *et al.*, 1999).

The potential neurotoxic effects of MDMA has led some researchers to investigate the long-term effects of 'Ecstasy' in recreational drug users. The findings from these studies have been avidly reported by the media, in particular magazines and programmes aimed at young people. The number of web sites dealing with drugs, and 'Ecstasy' in particular, shows that the users themselves are interested in the outcome of these studies. Some researchers have deliberately courted media attention and have held press conferences to report their findings (e.g. the Guardian 16/5/2000).

The general consensus appears to be that 'Ecstasy' causes long-term damage to recreational users and this fact is promoted through the media (e.g. Mixmag 2/1997; the Face 6/98; the Guardian 16/5/2000). However, upon closer inspection there are methodological problems with these studies which preclude such a cause and effect relationship to be demonstrated unequivocally.

Most studies looking at the long-term effects of 'Ecstasy' use similar recruitment methods, with the most widely used being the 'snowball technique'. This involves getting subjects to advertise the study to their peers, and in particular their 'Ecstasy'-using peers. In practice, this normally equates with a largely student-based population as recruitment tends to occur in and around universities as part of final year projects or doctoral theses. Therefore, one can question whether these samples represent the population as a whole as they are both self-selected and exclusive, as they largely consist of people who have attained a certain academic level.

Given the large media profile of the long-term effects of 'Ecstasy', one must also question whether the subjects are coming forward to confirm their fears about any adverse reactions that they may have suffered. In some studies there are even differences in the backgrounds between the 'Ecstasy' users and their control group, for instance the control group displays a higher level of education. A more extreme example is the use of 'Ecstasy' users from the UK in studies conducted in the USA. As it is not reported in the relevant study where the subjects actually came from, there is the possibility of cross-cultural contamination of the results (McCann *et al.*, 1998a; 1998b). These inherent differences may have influenced the results obtained, for instance subjects with higher educational attainment are bound to obtain better scores on cognitive tests.

The typical design of a study investigating the long-term effects of 'Ecstasy' is to compare a group of users to a group of non-users at a single time point and usually within 3 weeks of using 'Ecstasy'. As detailed above, 'Ecstasy' users form a distinct subculture of individuals who attend raves and use dance drugs to aid their

experience. Within this subculture it is very difficult to identify individuals who haven't used 'Ecstasy' as surveys estimate that up to 90% of this group have used it (e.g. Bean *et al.*, 1997). This means that there are lifestyle factors that may explain the results.

One of the most common side effects reported by this group of users is sleep disturbance. Typically characterised by insomnia and accompanied by fatigue and exhaustion. This is possibly a result of staying awake all night and dancing while under the influence of 'Ecstasy' and other drugs, although similar results have been obtained from clinical studies that involved administering MDMA during the day (e.g. Vollenweider *et al.*, 1998). Airline stewardesses exposed to repeated circadian disruption in a similar fashion to 'Ecstasy' users report similar symptoms and have altered cognitive abilities (e.g. Cho *et al.*, 2000). As the majority of the dance drugs are anorectic, another common side effect is a reduced appetite and weight loss.

Both of these major side effects would not be experienced by non-drug using controls and represent non-drug related differences between the groups. More importantly, controls who have used drugs other than 'Ecstasy' but not attended raves would be in a similar position - even though they appear to control for the non-'Ecstasy' drug use. The lifestyle differences between the two groups suggest that there may be factors outside of the use of 'Ecstasy' which could explain any observed differences between them.

'Ecstasy' use has been associated with psychopathology in both case reports and surveys. The two broad types of psychopathology observed are related to the temporal proximity of 'Ecstasy' ingestion. Acute intoxication producing panic attacks, anxiety, and psychotic reactions, and depression is most commonly associated with long-term use. The majority of the community-based studies have failed to find a definitive cause and effect relationship between 'Ecstasy' use and psychopathology as these disorders are also found in non-'Ecstasy' users (e.g. Schifano *et al.*, 1998).

Most users of 'Ecstasy' in the UK start during adolescence, a period of great changes in their life. It is known that adult psychopathology is starting to emerge during these formative years. Therefore the relationship between psychopathology and drug use may be more complex than a simple neurotoxic effect. It is impossible to accurately determine from retrospective self-reports whether the drug use preceded the onset of symptomatology. In the context of media reports of 'Ecstasy' causing psychopathology (e.g. Mixmag 2/1997) it is highly possible that the causal attributions of individuals may distort the temporal relationship between their drug use and their symptoms.

The concept of the 'Ecstasy' user implies that there exists a population of drug users that exclusively use 'Ecstasy' on a regular basis and that any observed effects in this population are due solely to the effects of MDMA. Epidemiological surveys of drug use amongst young people have routinely failed to identify such a group. To date there has only been a single study on the long-term effects of 'Ecstasy' where the subjects only used 'Ecstasy' and no other drugs that could account for the observed results (Gerra *et al.*, 1998). This suggests that this group is not typical of recreational 'Ecstasy' users.

The overwhelming majority of studies sample from a population that uses a variety of drugs and which sometimes uses these drugs simultaneously. Some of these drugs, such as amphetamine and cannabis, are known to produce very similar long-term effects as those reported for 'Ecstasy'. No study published to date has actually quantified the amount of MDMA or other drugs consumed by its subjects. Very few studies even urine test on the test day to check that their subjects are drug free.

Whilst some researchers have attempted to statistically control for this confound (e.g. Morgan, 1998), others have simply renamed their sample as "MDMA polydrug abusers" (e.g. Parrott *et al.*, 2000). The former approach goes some way to addressing the issue of whether other drugs are causing the effect. But as it is known that some drugs have effects when combined it is plausible that simultaneous drug use may be the

causal agent - this type of analysis would not detect this. The latter approach is logically flawed as the subjects are polydrug users and therefore any of the drugs consumed could account for the observed effects - some authors even concede this in their papers (e.g. Parrott *et al.*, 2000).

Some authors have attempted to correlate the scores of 'Ecstasy' users with the lifetime dose of MDMA. This is based upon the number of self-reported exposures to 'Ecstasy' assuming that each tablet contains 100 mg of MDMA (e.g. Bolla *et al.*, 1998). One study found that there was huge variation in the quantity of MDMA (19-140 mg) within a single brand of tablet (white dove) and that other tablets contained no MDMA at all (Sherlock *et al.*, 1999). This is supported by reports from all over Europe and the United States that indicate that there is wide variation in the content of 'Ecstasy' tablets.

This indicates that attempting to quantify the amount of MDMA consumed based upon the self-reported use of 'Ecstasy' tablets is inaccurate. Therefore any calculations based upon this are fundamentally flawed. In some studies using this technique the observed effects are only statistically significant when the lifetime dose of MDMA is manipulated as an independent variable (e.g. Bolla *et al.*, 1998; see also Grob, 2000).

A more extreme example of how the measurement of 'Ecstasy' use can produce unrealistic results is the study by Wareing and colleagues (2000). Based on the reported average usage of 'Ecstasy' tablets in this study, we calculate that the 'Ecstasy' users had taken on average around 1300 tablets. The reported pattern of use suggests that they had been using up to four tablets of 'Ecstasy' every four days for around four years. This pattern of drug use is not normal for recreational drug users. As these users are spending a significant proportion of their time intoxicated with 'Ecstasy' and other drugs it is hardly surprising that they are showing cognitive deficits.

In studies using laboratory animals it is possible to ascertain the dose dependent effects of MDMA on the brain and behaviour of subjects using a cross sectional design. Two groups of subjects can be obtained where the experimenter knows both their experiential and genetic background. As both groups are exposed to the same environment, the observed effects of the treatment can be used to determine a cause and effect relationship with a high degree of certainty.

Such animal studies have routinely failed to find changes in the behaviour of MDMA-treated animals, even when there was an 80% drop in the markers for serotonergic function and using tests which are sensitive to other serotonergic neurotoxins (e.g. Seiden *et al.*, 1993). Some studies have found that when appropriately challenged, behavioural deficits do appear but these studies tend to be in the minority (e.g. Marston *et al.*, 1999). When challenged with drugs the performance of the MDMA-treated animals is found to be different. This suggests that there are underlying neurochemical changes which are not manifested behaviourally. It remains to be determined what this will actually mean for users of 'Ecstasy'.

The pressure to publish positive results has meant that some papers minimise the impact of data which suggests that 'Ecstasy' exposure is not having any long-term effects. In these papers there are numerous tests run on the subjects but only the ones that work are reported in detail or negative data is only reported as meeting abstracts (e.g. Morgan *et al.*, 1998; Wareing *et al.*, 2000). This suggests that hypotheses concerning the long-term effects of 'Ecstasy' are not being substantiated and lends support to the idea that 'Ecstasy' is not causing long-term effects associated with a loss of serotonin.

The public health implications of potential MDMA-induced neurotoxicity are important. It is essential that the long-term effects of MDMA on recreational drug users are discovered. On the other hand, telling the 'Chemical Generation' that they are brain damaged when they are not, creates a public health problem. Effective harm reduction relies upon accurate information being delivered to the user by a credible source.

Misinterpretation of harm reduction information about 'Ecstasy' has already had fatal consequences and it is important that this is not repeated.

The methodological problems outlined above indicate that the existing studies are a long way from determining a cause and effect relationship between 'Ecstasy' use and long-term problems. This has not stopped researchers from publishing papers with titles stating a cause and effect relationship between MDMA and their results (e.g. Bolla *et al.*, 1998; Wareing *et al.*, 2000).

Iatrogenic disorders are defined by the New Webster's Dictionary as "caused by the mannerisms or treatment of a physician, an imaginary illness of the patient brought about by the physician". We are concerned that the long-term effects of 'Ecstasy' could be iatrogenic because researchers and the media are discussing a hypothesised cause and effect relationship as if it were fact. Due to the presence of confounds there are possibly alternative explanations for the observed effects. In addition, these effects are not supported by animal experiments where a cause and effect relationship can be reliably determined.

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