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A global review

Executive summary

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PLEASE WRITE TO

WHO
MANAGEMENT OF SUBSTANCE DEPENDENCE
20, AVENUE APPIA
1211 GENEVA 27
SWITZERLAND
e-mail: carusop@who.int

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Ecstasy, MDMA and other ring-substituted amphetamines: a global review

Linda R. Gowing[1], Susan M. Henry-Edwards[1], Rodney J. Irvine[2], Robert L. Ali[1,2]

[1]Drug and Alcohol Services Council and [2]Clinical and Experimental Pharmacology, University of Adelaide, South Australia, Australia.

Executive Summary

The term "ecstasy" is primarily applied to 3,4-methylenedioxymethamphetamine (MDMA) but other drugs are sold as ecstasy, and ecstasy tablets can contain a range of drugs in addition to, or in place of, MDMA.

MDMA combines stimulant and hallucinogenic properties. Its use has been associated with a global trend of dance parties and "techno" or dance music.

In the 1970s, MDMA was increasingly being used in the USA as an adjunct to psychotherapy. In 1985, the US Food and Drug Administration classified MDMA as Schedule I (no acceptable therapeutic use). Debate regarding the decision may have unintentionally increased public awareness of the drug and its psychoactive effects.

Illicit production of MDMA is relatively easy but quality control is difficult to achieve. Forensic analysis of drugs seized as "ecstasy" have revealed other amphetamine-type stimulants as well as chemically unrelated compounds with little or no psychotropic activity. Wide variations in the dose of MDMA contained in tablets have also been detected.

Epidemiological information on ecstasy use is sparse and data collection procedures are variable, complicating analysis. However, it is clear that there was significant growth in the popularity of amphetamine-type stimulants during the 1990s with use now a global phenomenon.

Data from Europe and the USA indicate that ecstasy has ever been tried by between 0.5 and three per cent of the general population and from one to five per cent of young adults. In general ecstasy is the third most used illicit drug, after cannabis and amphetamines.

In most countries ecstasy is used recreationally as part of a particular youth culture centred on dance parties and raves and a preference for specific types of music. Users tend to be young, well educated, socially well integrated, with high levels of employment and less likely to have a criminal record than other populations of illicit drug users. However, ecstasy is also part of a pattern of polydrug use.

Sociability is a major characteristic of ecstasy use. It is almost exclusively taken in a social setting with partners or groups of friends. Users particularly seek the feelings of empathy and closeness with others, which result from ecstasy use, to foster a group identity and sense of belonging. Use of ecstasy by friends is a significant factor in initiation and continuation of ecstasy use.

Ecstasy is associated with a variety of specific cultural trends in particular networks where the importance of the group is emphasised, for example the gay club and party scene and the "techno" music scene.

Ecstasy is primarily used recreationally, mainly at weekends in association with social events, but studies, particularly in the UK and Australia, have identified regular and intensive use. There may also be a trend of increasing use by injection. Most users appear able to regulate their use of ecstasy but some progress to problematic use. Some researchers have suggested that problematic use might constitute dependence but this is an aspect for further debate.

MDMA has high affinity for serotonin receptors and transport sites in the brain. Serotonin-producing neurones in the brain regulate aggression, mood, sexual activity, sleep and sensitivity to pain. Serotonin is also important in memory and temperature regulation.

MDMA initially enhances extracellular brain concentrations of serotonin, but eventually this leads to depletion of the neurotransmitter and hence a decrease in serotonin levels. MDMA also increases release of dopamine, another neurotransmitter that is involved in the control of movement, cognition, motivation and reward.

Findings of surveys of users and studies using controlled administration of MDMA are consistent, namely immediate positive psychological effects of euphoria, increased energy, and a feeling of closeness to others, and negative psychological effects of paranoia, anxiety and depression. Common short-term physical effects are pupil dilation, increased jaw tension and grinding of teeth, loss of appetite, dry mouth, tachycardia, hot and cold flushes, and sweaty palms. Longer term effects reported by users include insomnia, depression, headaches and muscle stiffness.

Tolerance to the effects of MDMA appears to develop rapidly. In surveys users report a decrease in "postive" effects and an increase in "negative" effects with successive doses. "Negative" effects are also reported to increase, and "positive" effects decrease, with increasing doses of ecstasy.

MDMA is well absorbed from the gastrointestinal tract. Following oral administration, effects become apparent in about 20 minutes and last for about four hours. Recent evidence indicates that the relationship between MDMA dose and blood concentration may not be linear. Hence small increases in dose may produce disproportionate increases in effect, possibly contributing to toxicity.

In the liver, MDMA is metabolised by a number of cytochrome P450-mediated pathways. One of the enzymes involved, CYP2D6 exhibits genetic variability such that some people have low activity of the enzyme and are denoted poor metabolisers. It has been suggested that these people, due to reduced metabolism, will be at greater risk of MDMA toxicity. However, no evidence has been found to support this hypothesis. It is likely that, in vivo, other enzyme pathways make up for the deficit. Some of the metabolic products of MDMA are bioactive and may also contribute to toxicity. MDMA is metabolised in the liver and eliminated via the urine.

Drug interactions may influence MDMA toxicity by altering the elimination of MDMA from the body, or through an additive effect if the interacting drug has a similar effect to MDMA. Reported cases of adverse reactions possibly arising from drug interaction involved fluoxetine (two cases) and ritonavir (one case).

Animal studies have shown that administration of MDMA produces damage to axons and axon terminal fibres containing serotonin. Decreases in the density of brain serotonin axons have been seen in squirrel monkeys more than seven years after MDMA administration. Some regrowth of axons occurs, but is abnormal and incomplete.

These findings in animals are the basis of concerns regarding neurotoxicity of MDMA. Although animal studies are indicative of effects in humans, there always remains a degree of uncertainty about transferability of findings. However, a series of studies using sophisticated

brain imaging techniques to assess different aspects of the human brain have found persisting abnormalities in brain morphology in ex-users of ecstasy, even with moderate use. These studies tended to use small numbers of users and many are confounded by uncertain histories of MDMA use and use of other drugs. Although providing additional evidence of neurotoxicity, these imaging studies do not indicate the functional significance of the changes in brain morphology.

The functional significance of the neurotoxic effects of ecstasy has been explored in a number of recent studies using psychological tests to assess cognitive function, memory and aspects of mood in current and former ecstasy users compared to non-using controls. Again, these studies are confounded to some extent by small numbers of participants, difficulties in determining histories of ecstasy use, concomitant use of other drugs such as cannabis, and the lack of baseline data from periods prior to ecstasy use (some differences between ecstasy users and non-users, such as impulsivity, may reflect existing personality differences rather than the effects of ecstasy). Despite these limitations, and despite some variability between studies, there is a consistent finding of impairment in short-term memory function in ecstasy users that cannot be attributed to concomitant use of other drugs, in particular cannabis.

Overall the combination of animal and human studies constitutes mounting evidence of ecstasy having a neurotoxic effect. However, the long-term functional consequences of ecstasy use in humans will remain uncertain pending large scale epidemiological studies. The mechanism of MDMA's neurotoxicity is also uncertain, and an area of active research.

Any analysis of case reports of adverse health effects will inevitably be biased. More serious effects, particularly cases with fatal outcomes, and more unusual cases are more likely to be published. Published reports are also likely to follow areas of debate at a particular time, such as the use of dantrolene in the treatment of ecstasy-related hyperthermia. A further limitation of case report analysis is the inability to relate the number of case reports to a population base. This makes it impossible to quantify relative risks of the various adverse effects reported. However, in the absence of structured epidemiological studies, analysis of case reports constitutes the best evidence available on the risks associated with use of ecstasy.

The first reports of deaths involving MDMA use appeared in scientific literature around 1987. A subsequent surge in case reports of significant health effects seems to be associated with a change in the setting in which the drug was most commonly used – from the clinical psychotherapy setting of the 1970s to the dance party and "rave" setting of the 1990s. MDMA can produce hyperthermia in quiet surroundings, when taken in sufficient quantity, but in the setting of "raves" or dance parties, the toxicity appears to be enhanced. It is probably a combination of direct effects of MDMA, high ambient temperature, sustained physical activity and inadequate fluid replacement, all impairing temperature regulation, that creates the greatest toxicity.

Given the hundreds of thousands of ecstasy tablets that are probably consumed each weekend, the number of published cases of adverse effects (we located 160) is very small. This, combined with the findings of the surveys of users that have been undertaken, indicates that the prevalence of serious acute adverse events arising from ecstasy use is low. It is the unpredictability of those adverse events and the risk of mortality and substantial morbidity in young people that makes the health consequences of ecstasy significant.

We identified from published reports, 69 separate cases of acute reactions to "ecstasy" involving hyperthermia, 48% of which resulted in death. Hyperthermia is typically accompanied by a number of clinical problems, induced or made worse by the hyperthermia, including seizures or convulsions, abnormalities in blood coagulation, rhabdomyolysis, and impairment of kidney and liver function. There is an apparent correlation between body temperature and mortality, with around two-thirds of cases where the body temperature exceeded 41.5°C ending in death.

This data emphasises rapid reduction of temperature as the most important response to hyperthermia related to MDMA use. It also indicates the importance of educating users on strategies to avoid hyperthermia, and to seek medical assistance promptly if hyperthermia becomes apparent.

Adequate fluid intake and rest periods in a cool room are important measures for the prevention of hyperthermia, but excessive fluid intake can also be harmful. We identified 14 cases with features of confusion, reduced consciousness and, in some cases, seizures or convulsions, apparently induced by disturbances in salt or water balance following ecstasy use. Three of the cases were fatal; consumption of copious water was reported to have occurred in five of the 14 cases.

Other reported acute adverse effects included:

- seizures without hyperthermia or hyponatraemia (possibly due to consumption of amphetamine derivatives other than MDMA);
- disturbances of cardiac function (often associated with pre-existing cardiac disease);
- cerebral ischaemia or blood vessel ruptures (possibly related to the stimulatory action of ecstasy, or to the presence of amphetamine in the "ecstasy" or taken concurrently with "ecstasy");
- respiratory difficulties;
- trauma whilst intoxicated;
- chest pain not related to cardiac factors (air in tissues, spasm of intercostal muscles from strenuous exercise);
- ophthalmic conditions (probably related to extended periods of activity with reduced blinking and tear formation); and
- aplastic anaemia (the link with ecstasy use is unclear).

Longer term physical effects include excessive toothwear arising from tooth-grinding and jaw clenching associated with ecstasy use. One limited study has also identified a possible increased risk of birth defects following ecstasy use during pregnancy. The study had insufficient statistical power to confirm a causal relation but, given the young age of ecstasy users, is an aspect that should be monitored.

An issue with analysis of case reports is the lack of certainty as to the nature and amount of drugs consumed, which makes it difficult to attribute adverse effects specifically to MDMA use. For 108 of the 158 cases of acute adverse effects we examined, drug use was confirmed by analysis of blood and/or urine samples. Although these analyses indicate the presence, in some cases, of a number of amphetamine derivates, alcohol or other drugs, they also support a conclusion that MDMA alone can produce adverse effects including hyperthermia, disturbances of sodium and fluid balance, disturbances of cardiac function, cerebral haemorrhage, disturbed respiratory function, sudden collapse and trauma whilst intoxicated.

The dose of MDMA taken (as indicated by recorded serum levels of MDMA) is not predictive of the severity of outcome. Variable individual susceptibility to the effects of MDMA has been suggested as an explanation for the lack of correlation, but, as yet, plausible explanations of individual susceptibility have not been found in cases of severe reactions. In addition there appears to be a mix of first time and experienced MDMA users affected, making this explanation unlikely, or at least uncommon. The detection of MDMA in some cases of adverse effects, and reports of the affected person using from the same supply as others who were not affected, also makes contaminants an unlikely basis for adverse reactions. It seems most likely that it is the combination of dose, setting and individual behaviour that determines the outcome of MDMA use. Whether this is also true for PMA and other amphetamine derivatives, which may be more toxic than MDMA, is unclear – to date all reported cases of adverse effects subsequent to PMA use have been fatal.

Severe liver damage can occur shortly after ingestion of ecstasy, typically in conjunction with hyperthermia. However, liver damage, apparently unrelated to hyperthermia, can also occur days or weeks after single or multiple episodes of ecstasy use. We identified 39 such cases. The majority of these cases resolved spontaneously over weeks to months, but 11 cases required some form of transplant and six cases were fatal. It also appears that those who resume ecstasy use after recovery are at risk of a recurrence of their liver damage and the development of chronic hepatitis. The mechanism of ecstasy-related liver damage is uncertain.

Our search of published literature also resulted in the identification of 44 separate cases of psychiatric sequelae attributed to ecstasy use. Nine of these cases involved alterations in mental state associated with intoxication, four were suicides, and 31 cases involved persistent or chronic sequelae.

Alterations in mental state appear atypical of MDMA intoxication – information relating to several of the reported cases is suggestive of contaminants being a factor. In most cases symptoms resolved in hours to days with minimal or no treatment.

The 31 cases of post-acute sequelae generally comprise persistent episodes of depression, panic disorders, "flashbacks" and delusions. A delay of days to weeks between last ecstasy use and presentation for assessment prevented toxicological confirmation of drug use. It appears from the reports that these more severe psychiatric sequelae are probably related to ecstasy use but generally only in individuals made vulnerable by personal or family history, or by concurrent use of other drugs such as cannabis. However, there appears to be a clear association between ecstasy use and short-term mood changes.

Prevention aims to reduce the demand for drugs by decreasing the risk factors associated with drug use and increasing protective factors. There is very little specific literature on prevention of ecstasy use. However, the principles of prevention are applicable to all drugs.

Prevention programs are of three types: primary (addressing uptake of drug use); secondary (interventions early in use to prevent progression to problematic use and to minimise the risks of adverse effects); and tertiary (treatment to minimise the extent of damage caused by drug use).

The two most common forms of primary prevention are school-based education and media information campaigns.

To be effective, school-based programs should be culturally and developmentally appropriate; promote peer influence; promote anti-drug use social norms; foster bonding to the school and the community; teach drug resistance skills through interactive teaching and learning methods; use a well-tested standardised intervention with detailed lesson plans and student materials; be ongoing with sequence progression and continuity over time; and target children at all stages of their school life.

Information only approaches and personal development approaches are generally ineffective at reducing drug use, while 'scare' tactics are counterproductive. Programs which are part of the school health curriculum and taught by regular teachers have more effect that those which rely on specific sessions taught by outside experts.

The major role for mass media campaigns is raising awareness and agenda setting. The effectiveness of school drug education and mass media campaigns can be enhanced if they are used as components of comprehensive, community based, multi strategy prevention programmes.

Hyperthermia and hyponatraemia are the most significant, and potentially life-threatening, acute adverse effects associated with ecstasy use. Given that both appear to arise largely as a result of the setting of use and individual behaviour, it is a good target for secondary prevention initiatives. Obvious measures include the provision of free water and temperature control at venues, together with education to increase the knowledge of users, venue operators and support staff, about the importance of controlling body temperature and fluid intake, how to recognise early signs of adverse effects, and the importance of seeking medical assistance promptly. A number of countries have developed guidelines for dance parties and night clubs that support this approach.

Testing of ecstasy tablets has some value in enabling users to avoid more toxic substances, such as PMA, but it is important that users are aware that use of MDMA by itself can result in adverse effects. Testing of tablets should therefore always be accompanied by secondary preventive education.

Currently there are no treatment interventions designed specifically to address ecstasy use. Interventions that would be most appropriately applied to ecstasy use are those non-pharmacological approaches which have demonstrated the most efficacy in treating psychostimulant users. These are relapse prevention (particularly for heavy users), cue exposure/response prevention, and possibly multifaceted behavioural therapy. Contingency management approaches may also be of value.

In general, however, ecstasy users do not present for treatment, except in instances of adverse effects serious enough to require medical assessment, or in instances of significant concomitant use of alcohol or other drugs. An approach that is well suited to this situation is that of brief intervention. Brief intervention aim to investigate a potential problem and motivate an individual to begin to do something about their substance use. Brief interventions can be delivered opportunistically when ecstasy users are identified, such as at emergency departments of hospitals, support services at major events such as dance parties, primary health care, law enforcement settings, and through computer based applications. While brief interventions are of potential value, much of the evidence of their effectiveness relates to alcohol abuse. It is desirable for there to be development, and evaluation through structured

research, of brief interventions appropriate to ecstasy users and the contexts for delivery of the interventions.

Treatment of adverse effects related to ecstasy is largely a case of selecting medical procedures suitable to the symptoms exhibited. Particular attention should be given to monitoring and control of hyperthermia and hyponatraemia, both of which can quickly become life threatening.

Medical personnel need to be informed of the nature of adverse effects that may arise subsequent to ecstasy use. This would support the opportunistic identification of ecstasy use, as well as indicating the pattern of monitoring of health status that is appropriate for ecstasy users.

There remain many gaps and inadequacies in our knowledge of the health effects of ecstasy. Systems of monitoring emergency room attendances should be considered as means of monitoring the prevalence of adverse effects. Such systems can also help to identify emerging problems. Controlled epidemiological studies to establish the prevalence of harms, to quantify the risks of ecstasy use, and assess the long-term functional consequences of ecstasy use are also desirable. The question of whether ecstasy does produce dependence remains unanswered. If the answer is yes, it is then of interest to determine whether the assessment of ecstasy dependence is of diagnostic value. A final, important research direction is that of the pharmacology and toxicology of MDMA and other amphetamine derivatives in animals, in vitro cellular systems, and humans. Increased understanding of the mechanisms and toxicity of these compounds is critical if we are to respond to changes in illicit drug markets and predict the likely adverse effects in a given situation.

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