REVIEW ARTICLES

Ten years of 'ecstasy'

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Ecstasy is a popular name for the drug 3,4-methylenedioxymethamphetamine (MDMA), although the term is also used to cover a group of drugs including MDMA, 3,4-methylenedioxyethylamphetamine (MDEA), 3,4-methylenedioxyamphetamine (MDA) and N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB). These drugs are all phenethylamines, a group that includes amphetamine, the name amphetamine being derived from *alpha-methylphenethylamine*. Their misuse has been particularly popular in the UK. In this paper the term 'ecstasy' will be used for the group of drugs described above, with specific compounds such as MDMA described where appropriate. This is because, when a user takes a tablet of ecstasy, it may not contain MDMA (*vide infra*), so 'ecstasy' in that context is a more appropriate term[1].

The 'rave' movement, which spawned the widespread use of ecstasy is now 10 years old. This paper reviews its history and the medical problems that have resulted[2,3].

HISTORY

First synthesized by Merck in 1912, MDMA was patented in 1914. There has been some dispute as to whether it was manufactured as an appetite suppressant or whether it was merely an intermediate chemical. It was never marketed and disappeared into obscurity. MDMA was studied by the US Army in the 1950s as a potential agent in psychological warfare, but the results were not declassified for two decades[2].

In 1965 Alexander Shulgin manufactured MDMA in his laboratory, but it was not until the 1970s that MDMA began to be used in psychotherapy where, *inter alia*, it was described by one user as 'penicillin for the soul'. Although then virtually unknown in the UK, in 1977 MDMA was made illegal in the UK under the 1971 Misuse of Drugs Act, when all compounds structurally derived from N-alkyl-α-methylphenethylamine were made a class A drug. MDMA remained legal in the USA until 1985. Its use among university students was common; a survey of undergraduates at Stanford University revealed that 39% had tried ecstasy at least once, with a median of 4 occasions and a mean of 5.4 (range 1–38)[4].

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MDMA was still not commonly used in Europe, but with the death of the Bhagwan Rajneesh, his followers, who used MDMA as a source of 'self-enlightenment', were said to have brought the drug when they dispersed around the world from their base in Oregon. At the same time a music movement was developing in Ibiza and during the winter of 1987–1988 ecstasy reached the island. People returning to the UK brought back the musical concept along with the use of ecstasy and so was born the rave scene in the UK. Raves are large gatherings of young people in warehouses or disused air hangars or the open air where many hundreds or thousands of people gather and dance to the music until dawn or beyond. The scene was also called 'acid house' and developed its own symbols, such as the 'smiley face'[2,3].

Because of the size of the gatherings, Parliament introduced legislation to stop these events, passing the Entertainments (Increased Penalties) Act 1990, commonly known in the dance scene as the 'Acid House Bill'. It allowed for a fine of up to £20 000 and six month's imprisonment for the organizers. Subsequently further measures were enacted including the Criminal Justice and Public Order Act 1994 in which raves were defined as 'Gathering on land in the open air (including a place partly open to the air) of 100 or more persons (whether or not trespassers) at which amplified music is played during the night (with or without intermissions) and such as, by reason of its loudness and duration at the time at which it is played, it is likely to cause serious distress to the inhabitants of the locality'. Music was defined as 'sounds wholly or predominantly characterised by the emission of a succession of repetitive beats'.

The Act gave the police additional powers to stop people attending and to remove vehicles and sound equipment. When organization of illegal raves became more difficult, ecstasy moved into legitimate clubs, where it is now most commonly used in the UK.

DRUG USE

Ecstasy use is common among the younger citizens of the UK. A survey of school children in England and Scotland showed that 15.8% of boys had been offered ecstasy and 5.7% had taken it, whilst the comparable figures for girls were 13.7% and 3.0%. Cannabis was the most common

survey of 16–29-years-olds showed that 9% had used ecstasy. When more specific groups are examined, the use of ecstasy and other drugs is even higher. An examination of members of the dance scene in Scotland revealed that 91% had used ecstasy, with 80% using the drug at the dance club, whereas only 24% used alcohol at the dance scene. Other drugs commonly used at dances were amphetamines (61%), nitrites (60%), and LSD (42%). Although ketamine is increasingly used as a dance drug, the survey found greater use at home (61%) than at dances (33%). 15% said they had taken it. Cocaine, benzodiazepines, cannabis, heroin and tobacco were all more commonly used away from the dance scene[5].

MECHANISM OF ACTION

The effects of MDMA on mood are mediated by actions on dopamine and serotonin pathways. In addition it acts on noradrenergic pathways, which may contribute to alterations in thermoregulation[6].

PHYSICAL AND EMOTIONAL EFFECTS

MDMA is taken because of its mood-altering properties. Users of MDMA report that it promotes empathy. Indeed, there is a story that one of the early promoters of MDMA was going to call it 'empathy', but felt that 'ecstasy' was a better marketing term. Users are said to feel relaxed and happy, warm towards others, with sensations from touching enhanced. Mild euphoria may be present. Aggression is reduced, with less fear and defensive behaviour. Visual and time perception are altered. The combination of ecstasy and music and dancing is said to produce an exhilarating state akin to that experienced in tribal or religious ceremonies[2]. Nausea and sweating may occur, the jaws may clench, and muscles may ache. Hypertension, tachycardia, and cardiac arrhythmias may occur. Sleep may become disordered, and appetite may be reduced for up to a week. A degree of depressed mood is common, with midweek blues following weekend use. Physical and mental tasks may be more difficult to perform, with less desire to perform them[7–10]. MDEA and MDA are less popular with ecstasy users since they produce less empathy.

CONTENT AND PURITY OF STREET ECSTASY

Street drugs sold as ecstasy are not manufactured by ethical pharmaceutical companies and the content of tablets varies. Ecstasy tablets often have specific names such as snowball, white cally and triple X. Many have logos relating to well-recognized commercial brand names. Not all tablets with the same logo or name are necessarily produced by the same illicit laboratory or contain the same substances. An examination of a series of tablets purchased as ecstasy in Sheffield revealed a variable mix of active substances including MDMA, MDEA, MDA, amphetamines, triprolidine, ephedrine, pseudoephedrine and caffeine[11]. Often very little pharmacologically active substance was present. An examination of tablets sold as ecstasy in Europe in 1995–1997 was published by the late Nicholas Saunders, an ecstasy enthusiast, in his book *Ecstasy Reconsidered*[2]. This revealed that, of sixty-nine tablets with an identifying logo, thirty contained MDMA with a mean content of 91.3 mg (range 2–149) and nineteen MDEA with a mean content of 106.8 mg (range 36–167). One tablet contained 184 mg of MBDB. Eight tablets contained a mixture of substances including MDMA, MDEA, amphetamine and caffeine and one tablet contained just ecstasy. An examination of forty-six tablets without a logo revealed only one not containing MDMA or MDEA. 72% contained between 80 and 140 mg MDMA, 12% MDEA. Overall the unbranded tablets had a higher quality than the branded pills. Results of testing of ecstasy tablets may be found on the Internet. Overall, in the past few years 10% of tablets contained no active ingredient or were aspirin or a similar substance; 5% contained amphetamine, ephedrine and caffeine, 60% MDMA, 20% MDEA and 10% MBDB[2].

MEDICAL PROBLEMS FROM ECSTASY USE

The first reports of deaths from MDMA and MDEA use emanated from the USA. Dowling *et al.*[12] described five cases in which MDMA or MDEA was detected via post-mortem toxicology. In one fatality, death was directly attributed to use of MDMA. In the other four cases, one was the result of electrocution, and the other three were attributed to natural disease. In the former case the behaviour of the victim may well have been precipitated by use of MDMA. In the latter cases the natural disease process may have been exacerbated by use of MDMA and MDEA.

Hyperpyrexia (heatstroke) deaths

Following the development of the 'rave' scene in the UK, deaths began to be reported both in the UK and other European countries[13 20]. The mechanism of death was different from that in fatalities reported from the USA, with hyperthermia the most significant feature, the victims collapsing at raves and dances. In 1991 a death with disseminated intravascular coagulopathy was reported and in 1992 Henry and colleagues from the UK's National Poisons Unit reported seven deaths occurring in 1990 and 1991, together with reports of non-fatal cases[13,15]. All those who died had been admitted to hospital with a raised body temperature (40°–43°C). Five patients had disseminated intravascular coagulation and three had rhabdomyolysis and acute renal failure. One patient developed liver failure and underwent transplantation, but died from graft rejection. Similar problems were reported in patients who

survived. A post-mortem study of seven deaths associated with ecstasy use was reported in 1996[11]. In two cases there was documented hyperpyrexia. These cases showed the pathological changes reported in heatstroke, and in two other acute deaths the same pathological changes of heatstroke were seen. Hyperpyrexia in users of ecstasy at raves and similar dances has been the main cause of death in the UK, but other mechanisms are implicated. After the deaths from heatstroke, advice was given that dancers should take time out from dancing (going to a 'chill-out' area) and drink plenty of fluid. These deaths were associated with both MDMA and MDEA use. Deaths at raves may be due in part to the phenomenon of 'aggregation toxicity'. When laboratory animals are housed together, rather than on their own, amphetamine toxicity is increased. A similar function may occur with MDMA and could account for the increase in deaths with people grouped together[6].

The development of complications following ecstasy use is unpredictable. The range of MDMA found in fatal cases has varied from trace amounts to 4.2 mg/L. MDEA is found in similar concentrations. Most people who use ecstasy experience no complications. One individual reported by Henry *et al.*[15] apparently took forty-two ecstasy tablets at home and had no symptoms other than a 'hangover', with tachycardia and hypertension; the recorded plasma MDMA was 7.72 mg/L.

Many cases also involve other drugs, particularly amphetamines (which are commonly encountered in ecstasy). Although users will only take ecstasy at dances—and consume little alcohol, which interferes with the enjoyment of ecstasy—some will 'come down' from their ecstasy high by using other drugs including heroin, benzodiazepines and alcohol.

In addition to fatal heatstroke, reported complications include convulsions, cardiac arrhythmias, renal failure, pneumomediastinum, aplastic anaemia, cerebral infarction, cerebral haemorrhage and cerebral venous sinus thrombosis[21–27].

Water intoxication

In 1993 water intoxication in ecstasy users began to be reported[11,28–29]. Apparently the advice to take copious fluid was doing harm. One of the main complaints of ecstasy users is a dry mouth. MDMA also promotes repetitive behaviour. People dancing to repetitive beating music say that it enables them to coordinate their movements with the dancing. However, when drinking fluid, continuous swigging at a bottle may cause excessive fluid intake without the person appreciating how much fluid is being consumed. If the fluid is plain water, it does not replace the salts lost in the sweating that follows vigorous dancing. Another factor, inappropriate secretion of antidiuretic hormone, was suggested in one case. A subsequent study showed that, when given to healthy well hydrated volunteers, MDMA causes an increase in secretion of antidiuretic hormone[30]. Water intoxication appears to be a consequence of a pharmacological action of MDMA, combined with excessive fluid intake. A fatal case of water intoxication has also been reported from Australia[31].

Liver damage

Among the first deaths in the UK, liver damage was recognized. It seemed to be a function of hyperpyrexia and attendant problems of shock and disseminated intravascular coagulation. However, there have also been reports of ecstasy causing hepatitis and fulminant liver failure independently of hyperpyrexia[32 35]. A report from King's College Hospital, London, described eight cases of acute liver failure following ecstasy use, and reviewed the other reported cases of liver damage[36]. Two patients had hyperthermia and developed disseminated intravascular coagulation and rhabdomyolysis. Four patients had hyperacute liver failure without hyperthermia and two presented with abdominal pain and jaundice. These latter two patients, who recovered without requiring transplantation, had lobular hepatitis with cholestasis. Of thirteen previously reported patients, two had a history of hyperthermia, two acute liver failure without hyperthermia and the other nine cases were drug related hepatitis. These latter cases of hepatitis are not related to other actions of MDMA and seem to be an idiosyncratic reaction.

NEUROPSYCHIATRIC SEQUELAE

In assessing whether a psychostimulant causes or contributes to psychological or psychiatric disorders one must always bear in mind the possibility of a separate underlying disorder. Furthermore, as has been pointed out by Jansen, polydrug use is more common than single drug misuse[37]. Nevertheless, amphetamines are well recognized to cause psychiatric disorders and MDMA has also been reported to be associated with disorders of the mind. Poor concentration and attention, and memory impairment along with sleep disturbance, have been identified. Flashbacks, hallucinations, depersonalization and derealization may occur. In some users who take large quantities of drugs such as MDMA, LSD and ketamine a state may occur in which there is a high level of mental imagery without a perceptual disorder. Jansen has termed this the Pandora's box syndrome or busy-head syndrome[37]. Jansen states that, although this condition is not serious and should not prevent normal activity it may alter concentration and attention. Midweek 'blues' are a common finding in ecstasy users after weekend use[10].

Depression occurs in some users, and also panic attacks and anxiety. Psychosis has been reported, and is well recognized in amphetamine users. These complaints are not surprising in view of the role of serotonin in depression. An examination of regular users showed subnormal concentrations of 5-hydroxyindoleacetic acid (5-HIAA) in their cerebrospinal fluid[38]. 5-HIAA is the major metabolite of serotonin. In female MDMA users there was also a depletion in homovanillic acid, the main metabolite of dopamine. These data suggest serotoninergic neuron damage. Animal studies provide further evidence[39]. When non-human primates were given MDMA at a dose of 2.5 mg/kg there was a 44% depletion of these neurons. The comparable dose in rats was 10–20 mg/kg. When 3.5 mg/kg was given to monkeys there was 78% depletion, and 90% depletion with a dose of 5 mg/kg. These data suggest that the brains of primates are more sensitive than those of rats. McCann *et al.*[40] studied serotonin transporter binding in the living brains of fifteen MDMA users who were abstinent at the time, and found decreases (compared with controls) that were related to extent of MDMA use. The threshold for neurotoxicity may be low; with 80–140 mg of MDMA in each tablet and most users taking only one tablet, the usual dose will be 1–2 mg/kg.

CONCLUSIONS

The UK has now seen over a decade of ecstasy use. Deaths from heatstroke, water intoxication, liver failure and cardiac disease have been encountered. As well as the physical effects of ecstasy, there is increasing evidence for psychological disorders. Some anecdotal evidence suggests that the harm reduction message has helped to reduce acute deaths. Although many users will point to the low risk of ecstasy in relation to the number of users, the data from animal studies raise serious questions about long-term neurotoxicity. There may be a hidden cost of ecstasy use in suicides and accidents, but convincing evidence of long-term physical damage is still lacking. The report of deaths in South Australia from the use of paramethoxyamphetamine indicates that drug culture continues to change and the medical profession should be aware of this evolution.[41].

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