

Ecstasy

ECSTASY is the street name generally applied to 3,4-methylenedioxymethamphetamine or MDMA. However, other drugs are sold as ecstasy, and ecstasy tablets often contain a range of drugs (including amphetamine, various amphetamine derivatives, caffeine, aspirin, paracetamol, or ketamine) in addition to, or in place of MDMA (Wolff et al., 1995).

Ecstasy is usually sold as a tablet or capsule. The tablets are typically identified by a symbol impressed on the surface. This leads users to refer to them as 'white doves', 'love hearts', etc. Other common street names are 'E', 'Eccy', 'Adam' and 'XTC'.

PHARMACOLOGY

MDMA initially enhances the extracellular brain concentrations of serotonin but eventually serotonin becomes depleted. MDMA also induces a rapid and substantial elevation of dopamine. Serotonin has a role in regulation of aggression, mood, sexual activity, sleep, sensitivity to pain, memory and body temperature (Schloss & Williams, 1998). Dopamine plays a role in the control of movement, cognition, motivation and reward (Rawson, 1999). It is probably the mechanism underlying the stimulant properties of MDMA (Daws et al., 2000).

MDMA is well absorbed from the gastrointestinal tract (Mas et al., 1999). Effects become apparent about 20 minutes after administration and last about 4 hours. Dose and blood concentration relationship may not be linear (de la Torre et al., 2000), and small increases in dose may produce disproportionate increases in effect, possibly contributing to toxicity. Some of the metabolic products of MDMA are themselves bioactive and may also contribute to toxicity (Mas et al., 1999).

MDMA is metabolised in the liver. Some people have low activity of CYP2D6, one of the enzymes involved (Tucker et al., 1994). It has been suggested (but not validated) that, due to reduced metabolism, these individuals are at greater risk of MDMA toxicity (O'Donohoe et al., 1998; Schwab et al., 1999).

Drug interactions may influence MDMA toxicity by altering elimination of MDMA from the body, or through an additive effect. Reported cases of adverse reactions involving ecstasy in combination with fluoxetine (Bingham et al., 1998; Coore, 1996) and ritonavir (Henry & Hill, 1998) support this as a possibility.

PATTERNS OF USE

In the 2001 Australian National Drug Strategy Household Survey, lifetime use of ecstasy or other designer drugs was reported by 6.1% of people aged 14 and over, while 2.9% reported using ecstasy in the previous 12 months (AIHW, 2002). The current trend is one of increasing prevalence of use.

Ecstasy is almost exclusively taken in a social setting (McKetin et al., 1999; Topp et al., 1997b) usually as part of youth culture centred on dance music. Use of ecstasy by friends is a significant factor in initiation and continuation of ecstasy use.

The quantity of active ingredient in one tablet is usually in the range 75–100 mg. Normally one or two tablets are taken at a time but there are reports of greater doses being used, especially by experienced users (Topp et al., 1997b).

Ecstasy is mainly taken orally, but there may be a trend of increasing use by injection (Humeniuk, 2000; Topp et al., 1997b). Most users appear able to regulate their use of ecstasy but some progress to problematic use (Topp et al., 1997b). Whether such problematic use constitutes dependence is an area of debate (Jansen, 1999; Topp et al., 1997a).

PHYSICAL AND PSYCHOSOCIAL COMPLICATIONS

MDMA produces immediate positive psychological effects of euphoria, increased energy, and a feeling of closeness to others, and (less commonly) negative psychological effects of paranoia, anxiety and depression.

Physical Effects of Ecstasy

The incidence of serious acute adverse events arising from ecstasy use is low. It is the unpredictable nature of those adverse events and the risk of mortality and substantial morbidity in young people that make the health consequences of ecstasy significant.

Table 7–1 lists the short- and long-term physical effects of ecstasy.

Hyperthermia

The most significant adverse effect of ecstasy use is hyperthermia. It can quickly become life threatening. The degree of hyperthermia is predictive of mortality.

It is typically accompanied by a number of clinical problems, including:

- seizures
- disseminated intravascular coagulation
- rhabdomyolysis
- renal and liver impairment which may be induced or exacerbated by the hyperthermia (Green et al., 1995)

Clinical signs and symptoms are consistent with malfunction of normal temperature control and water balance. MDMA can produce hyperthermia in quiet surroundings, but in the setting of 'raves' or dance parties, toxicity appears to be enhanced. It is probably a combination of:

- the direct effects of MDMA
- high ambient temperature
- sustained physical activity; and
- inadequate fluid replacement

All impair temperature regulation (Green et al., 1995; Henry et al., 1992).

Hyponatraemia ('water intoxication')

Ecstasy use has also been associated with hyponatraemia. Cases are marked by:

- features of confusion
- reduced consciousness; and
- in some cases, seizures or convulsions

In general symptoms resolve as sodium levels are normalised, with full recovery achieved within a few days. However, fatalities have been reported, apparently due to cerebral oedema associated with excess fluid.

In most cases of hyponatraemia, copious amounts of water were consumed. This may be a response to a sensation of thirst induced by MDMA. Alternatively, behavioural disturbance, including stereotyped repetitive actions such as water consumption, may arise from MDMA ingestion (White et al., 1997). The administration of MDMA is associated with inappropriate release of anti-diuretic hormone, arginine vasopressin (Henry et al., 1998). This would reduce

Table 7-1
Physical effects of ecstasy

| Short-term effects | Long-term effects |
|--|---|
| <ul style="list-style-type: none"> • pupil dilation • increased jaw tension and grinding of teeth • loss of appetite • dry mouth • tachycardia • hot and cold flushes • sweaty palms • hyperthermia • hyponatraemia or 'water intoxication' | <ul style="list-style-type: none"> • insomnia • depression • headaches • muscle stiffness |

urine formation and the body's capacity to excrete excess fluid.

First reports of hyponatraemia occurred after dance club owners encouraged users to take dance breaks in a cool room and drink water. This advice is still sound for prevention of hyperthermia, but:

- an upper limit of 500 ml per hour is considered the amount able to be handled by the body

Drug screening undertaken in cases of acute adverse effects commonly indicate the presence of a range of drugs in addition to MDMA. However, the reporting of cases of hyperthermia or disturbances of salt or water balance where MDMA was the only drug detected, demonstrate that MDMA alone can produce adverse effects. Given that hyperthermia and disturbances of salt or water balance generally occur when MDMA is used in nightclub or dance party settings, these data also suggest that the acute adverse effects of MDMA arise primarily from the way it is used.

Dose–response relationship

The dose of MDMA is not predictive of severity of outcome (Gowing et al., 2002). In the absence of a dose–response relationship, it has been suggested that some form of metabolic myopathy or individual variability in metabolism of MDMA may underlie adverse effects. However, instances of muscle abnormality or impaired MDMA metabolism have not been identified in any cases of severe reactions and there appears to be a mix of first time and experienced MDMA users affected, making this explanation unlikely, or at least uncommon.

Severe reactions might be due to contaminants in the preparation taken. However, reports of affected persons taking from the same supply as others, who did not experience severe reactions, means that contaminants are an unlikely explanation (Hall, 1997). The combination of

dose, setting and individual behaviour most likely determines outcome.

Liver damage

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 (Jones & Simpson, 1999). Most reported cases resolved spontaneously over weeks to months, but a minority progressed to full liver failure requiring transplantation, with some cases being fatal.

It appears that those who resume ecstasy use after recovery are at risk of recurrence of liver damage and development of chronic hepatitis (Andreu et al., 1998). The mechanism of ecstasy-related liver damage is uncertain and, relative to other causes, ecstasy use remains a minor contributor to the incidence of liver failure (Andreu et al., 1998; Jones & Simpson, 1999).

Neurotoxicity

Animal studies show administration of MDMA produces damage to serotonin axons in the brain (McCann et al., 2000). Brain imaging techniques have found persisting abnormalities in brain morphology in ex-users of ecstasy, even with moderate use (Gamma et al., 2000; Kish et al., 2000; Reneman et al., 2000). Psychological tests in current and former ecstasy users compared to non-using controls have consistently found impairment in short-term memory function in ecstasy users (Gouzoulis-Mayfrank et al., 2000; Parrott et al., 2000; Rodgers 2000; Wareing et al., 2000).

These studies constitute mounting evidence of ecstasy having a neurotoxic effect.

Psychological Effects and Complications

Depression, or low mood, and concentration and/or memory problems are commonly reported in the week following ecstasy use (Curran, 2000). Cases of persistent depression, panic disorders, 'flashbacks' and delusions have been related to ecstasy use (Benazzi & Mazzoli, 1991; Cohen & Cocores, 1997).

The risk of psychiatric sequelae is probably greater when:

- other drugs, particularly cannabis, are used in addition to ecstasy
- ecstasy is used repeatedly and at high doses over a period of months
- there is a family or personal history of psychiatric disorders (Schifano et al., 1998)

MANAGEMENT AND INTERVENTION STRATEGIES

Strategies for Different Levels of Use

Acute adverse effects

Reassurance, observation and monitoring for several hours in a subdued environment until symptoms subside, is appropriate in most ecstasy intoxication cases (Williams et al., 1998).

Hyperthermia and hyponatraemia are the most significant complications necessitating intervention. In both conditions the treatment response needs to be rapid and intense to avert significant morbidity and mortality. In the case of hyperthermia, the patient may deteriorate rapidly towards multiple organ failure, requiring intensive support of cardiovascular, respiratory and renal systems (Hall, 1997). This requires admission to an intensive care unit.

Many cases of ecstasy-induced liver damage will resolve without intervention, and simply require monitoring. However, patients developing jaundice, or with evidence of hepatic failure, require specialist care.

It is also important to educate users about the importance of controlling body temperature and fluid intake, early signs of adverse effects, and the need to seek medical assistance promptly.

Treatment for Ecstasy Use

Those who use ecstasy more frequently (monthly to weekly) and/or use larger amounts, and those who use by injection are likely to be at increased risk of harm and hence constitute targets for intervention.

Pharmacological interventions

There is currently very little information on pharmacological interventions for ecstasy users. Selective serotonin reuptake inhibitors (SSRIs), if taken concurrently with MDMA, have been shown to block usual subjective effects of MDMA (Stein & Rink, 1999). However, administration of SSRIs (e.g. fluoxetine, citalopram) subsequent to MDMA may potentiate the effects of released serotonin, worsening any adverse effects (Green et al., 1995) and limiting their value as a treatment agent.

Non-pharmacological interventions



See Chapter 13
Psychosocial Interventions

Non-pharmacological interventions (also see Chapter 13) which have demonstrated most efficacy in treating psychostimulant users are:

- relapse prevention
- cue exposure/response prevention
- multifaceted behavioural therapy

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Contingency management approaches may also be of value.

Attracting users into treatment and intervening prior to development of problematic use is a priority. An approach well suited to these purposes is early and brief intervention (Barry, 1999), administered opportunistically when possible ecstasy use is identified.

REFERENCES

- AIHW (Australian Institute of Health & Welfare) 2002, *2001 National Drug Strategy Household Survey: First Results*, Drug Statistics Series No. 9, AIHW cat. no. PHE 35, AIHW, Canberra.
- Andreu, V., Mas, A., Bruguera, M. et al. 1998, 'Ecstasy: a common cause of severe acute hepatotoxicity', *Journal of Hepatology*, vol. 29, no. 3, pp. 394–397.
- Barry, K.L. 1999, *Brief Interventions and Brief Therapies for Substance Abuse*, Treatment Improvement Protocol (TIP) Series No. 34, US Department of Health and Human Services, Rockville, Maryland.
- Benazzi, F. & Mazzoli, M. 1991, 'Psychiatric illness associated with "ecstasy"', *Lancet*, vol. 338, no. 1520.
- Bingham, C., Beaman, M., Nicholls, A.J. & Anthony, P.P. 1998, 'Necrotizing renal vasculopathy resulting in chronic renal failure after ingestion of methamphetamine and 3,4-methylenedioxymethamphetamine ('ecstasy')', *Nephrology Dialysis Transplant*, vol. 13, no. 10, pp. 2654–2655.
- Cohen, R.S. & Cocores, J. 1997, 'Neuropsychiatric manifestations following the use of 3,4-methylenedioxymethamphetamine (MDMA: "Ecstasy")', *Progress in Neuropsychopharmacol Biological Psychiatry*, vol. 21, no. 4, pp. 727–734.
- Coore, J.R. 1996, 'A fatal trip with ecstasy: a case of 3,4-methylenedioxymethamphetamine/3,4-methylenedioxyamphetamine toxicity', *J R Soc Med*, vol. 89, no. 1, 51P–52P.
- Curran, H.V. 2000, 'Is MDMA ('Ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research', *Neuropsychobiology*, vol. 42, no.1, pp. 34–41.
- Daws, L., Irvine, R.J., Callaghan, P.D., Toop, P.N., White, J.M. & Bochner, F. 2000, 'Differential behavioural and neurochemical effects of para-methoxyamphetamine and 3,4-methylenedioxymethamphetamine in the rat', *Progress in Neuropsychopharmacol Biological Psychiatry*, vol. 24, pp. 955–977.
- de la Torre, R., Farre, M., Ortuno, J. et al. 2000, 'Non-linear pharmacokinetics of MDMA ('ecstasy') in humans', *British Journal of Clinical Pharmacology*, vol. 49, no. 2, pp. 104–109.
- Gamma, A., Frei, E., Lehmann, D., Pascual-Marqui, R.D., Hell, D. & Vollenweider, F.X. 2000, 'Mood state and brain electric activity in ecstasy users', *Neuroreport*, vol. 11, no. 1, pp. 157–162.
- Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., et al. 2000, 'Impaired cognitive performance in drug free users of recreational ecstasy (MDMA)', *Journal of Neurosurgery & Psychiatry*, vol. 68, no. 6, pp. 719–725.

- Gowing, L.R., Henry-Edwards, S.M., Irvine, R.J. & Ali, R.L. 2002, 'The health effects of "ecstasy": a literature review', *Drug & Alcohol Review*, vol. 21, no. 1, pp. 53–63.
- Green, A.R., Cross, A.J. & Goodwin, G.M. 1995, 'Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or 'Ecstasy')', *Psychopharmacology*, vol. 119, pp. 247–260.
- Hall, A.P. 1997, ' "Ecstasy" and the anaesthetist', *British Journal of Anaesthesia*, vol. 79, no. 6, pp. 697–698.
- Henry, J.A., Fallon, J.K., Kicman, A.T., Hutt, A.J., Cowan, D.A. & Forsling, M. 1998, 'Low-dose MDMA ("ecstasy") induces vasopressin secretion', *Lancet*, vol. 351, no. 9118, p. 1784.
- Henry, J.A. & Hill, I.R. 1998, 'Fatal interaction between ritonavir and MDMA', *Lancet*, vol. 352, no. 9142, pp. 1751–1752.
- Henry, J.A., Jeffreys, K.J. & Dawling, S. 1992, 'Toxicity and deaths from 3,4-methylenedioxymethamphetamine ('ecstasy')', *Lancet*, vol. 340, pp. 384–387.
- Humeniuk, R. 2000, *South Australian Drug Trends 1999. Findings from the Illicit Drug Reporting System*, NDARC Technical Report No. 88, National Drug and Alcohol Research Centre, Sydney.
- Jansen, K.L. 1999, 'Ecstasy (MDMA) dependence', *Drug & Alcohol Dependence*, vol. 53, no. 2, pp. 121–124.
- Jones, A.L. & Simpson, K.J. 1999, 'Review article: mechanisms and management of hepatotoxicity in ecstasy (MDMA) and amphetamine intoxications', *Alimentary Pharmacology & Therapeutics*, vol. 13, no. 2, pp. 129–133.
- Kish, S.J., Furukawa, Y., Ang, L., Vorce, S.P. & Kalasinsky, K.S. 2000, 'Striatal serotonin is depleted in brain of a human MDMA (Ecstasy) user', *Neurology*, vol. 55, no. 2, pp. 294–296.
- McCann, U.D., Eligulashvili, V. & Ricaurte, G.A. 2000, '(+/-)-3,4-Methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: clinical studies', *Neuropsychobiology*, vol. 42, no. 1, pp. 11–16.
- McKetin, R., Darke, S., Hayes, A. & Rumbold, G. 1999, *Drug Trends 1998. A Comparison of Drug Use and Trends in Three Australian States: Findings from the Illicit Drug Reporting System (IDRS)*, NDARC Monograph No. 41, National Drug and Alcohol Research Centre, Sydney.
- Mas, M., Farre, M., de la Torre, R. et al. 1999, 'Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans', *Journal of Pharmacology & Experimental Therapeutics*, vol. 290, no. 1, pp. 136–145.
- O'Donohoe, A., O'Flynn, K., Shields, K., Hawi, Z. & Gill, M. 1998, 'MDMA toxicity: no evidence for a major influence of metabolic genotype at CYP2D6', *Addiction Biology*, vol. 3, pp. 309–314.

- Parrott, A.C., Sisk, E. & Turner, J.J. 2000, 'Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users', *Drug & Alcohol Dependence*, vol. 60, no. 1, pp. 105–110.
- Rawson, R.A. 1999, *Treatment for Stimulant Use Disorders*, Treatment Improvement Protocol (TIP) Series No. 33, Department of Health and Human Services, Rockville, Maryland, USA.
- Reneman, L., Booij, J., Schmand, B., van den Brink, W. & Gunning, B. 2000, 'Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin neurotransmission', *Psychopharmacology (Berl)*, vol. 148, no. 3, pp. 322–324.
- Rodgers, J. 2000, 'Cognitive performance amongst recreational users of "ecstasy" ', *Psychopharmacology (Berl)*, vol.151, no. 1, pp. 19–24.
- Schifano, F., Di Furia, L., Forza, G., Minicuci, N. & Bricolo, R. 1998 'MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients', *Drug & Alcohol Dependence*, vol. 52, no. 1, pp. 85–90.
- Schloss, P. & Williams, D.C. 1998, 'The serotonin transporter: a primary target for antidepressant drugs', *Journal of Psychopharmacology*, vol. 12, no.2, pp. 115–121.
- Schwab, M., Seyringer, E., Brauer, R.B., Hellinger, A. & Griese, E.U. 1999, 'Fatal MDMA intoxication', *Lancet*, vol. 353, no. 9152, pp. 593–594.
- Stein, D. J. & Rink, J. 1999, 'Effects of "Ecstasy" blocked by serotonin reuptake inhibitors', *Journal of Clinical Psychiatry*, vol. 60, no. 7, p. 485.
- Topp, L., Hall, W. & Hando, J. 1997a, *Is There a Dependence Syndrome for Ecstasy?* NDARC Technical Report No. 51, National Drug and Alcohol Research Centre, Sydney.
- Topp, L., Hando, J., Degenhardt, L., Dillon, P., Roche, A. & Solowij, N. 1997b, *Ecstasy Use in Australia*, NDARC Monograph No. 39, National Drug and Alcohol Research Centre, Sydney.
- Tucker, G.T., Lennard, M.S., Ellis, S.W. et al. 1994, 'The demethylation of methylenedioxymethamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6)', *Biochemical Pharmacology*, vol.47, no. 7, pp. 1151–1156.
- Wareing, M., Fisk, J.E. & Murphy, P.N. 2000, 'Working memory deficits in current and previous users of MDMA ('ecstasy')', *British Journal of Psychology*, vol. 91, no. 2, pp. 181–188.
- White, J. M., Bochner, F. & Irvine, R. J. 1997, 'The agony of "ecstasy" ', *Medical Journal of Australia*, vol. 166, no. 3, pp. 117–118.
- Williams, H., Dratcu, L., Taylor, R., Roberts, M. & Oyefeso, A. 1998, ' "Saturday night fever": ecstasy related problems in a London accident and emergency department', *Journal of Accident & Emergency Medicine*, vol. 15, no. 5, pp. 322–326.
- Wolff, K., Hay, A.W., Sherlock, K. & Conner, M. 1995, 'Contents of "ecstasy" ', *Lancet*, vol. 346, no. 8982, pp. 1100–1101.

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