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MDMA (Ecstasy)

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Background. *3,4-Methylenedioxymethamphetamine (MDMA or Ecstasy) is a synthetic amphetamine analogue that is recreationally used to obtain a psychological effect of enhanced affiliative emotional response. Its use in Western countries appears to be increasing, particularly among young individuals.*
Methods. *Pertinent basic and clinical literature is critically reviewed.*
Results. *A significant body of literature suggests that the patterns of MDMA use differ from traditional drugs of abuse, with relatively uncommon dependence and escalation of dosage. Nonetheless, MDMA is also neurotoxic with significant deleterious effects on serotonergic neurons, memory, and mood. Despite this, there is a dearth of treatment strategies for both acute intoxication and consequences of longer term use.*
Conclusions. *MDMA is an important drug of abuse that has a wide range of adverse consequences.*

Keywords 3,4-Methylenedioxymethamphetamine, Ecstasy, MDMA

INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA, commonly known as "ecstasy") is a synthetic amphetamine analogue that was originally synthesized in 1914 (1). During the 1960s and 1970s, recreational use of MDMA took root (2), in part fueled by reports of the use of MDMA as a psychotherapeutic adjunct (3). In 1985, the Drug Enforcement Administration (DEA) placed MDMA on Schedule I of controlled substances (4).

The publicity that followed the scheduling of MDMA only served to increase its popularity, particularly on college campuses (5). Recognition of this trend led the National Institute of Drug Abuse (NIDA) to begin formal collection of epidemiologic data in 1989 in the form of the Monitoring the Future Study. Recently, the use of MDMA has increased and its pattern of use has changed. These factors have heightened public awareness of the drug and paradoxically led to an increase in use and adverse consequences. Emerging evidence supports the hypothesis that repeated and extensive MDMA is a neurotoxin in humans with long-lived sequelae on cognition, memory, and emotions.

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Epidemiology

Despite its existence for nearly 90 years, the recreational use of MDMA appears to have had its origins in the 1960s (6). At that time MDMA use was generally confined to small groups on college campuses (6,7), and in 1977 about 2.8% of United States college students reported using MDMA (8). While college is frequently the first time people begin use of MDMA (9,10), use in high school students is becoming more common. In 1998 4.4% of 10^{th} graders and 5.6% of 12^{th} graders had used MDMA at least once (11). In a survey of 14,000 college students at 119 American colleges by the Harvard School of Public Health College Alcohol Study, there was a 69% increase in use between 1997 and 1999 (from 2.8% to 4.7%) (8). At ten high-use schools with a 1997 rate of 4.7%, the rate increased to 10.6% by the year 2000 (8). Over the same time the use of marijuana did not significantly change (38.5% in 1977 and 37.6% in 2000) (8). MDMA is the only illicit drug to see continued increase in use. In a survey of a large New England college performed in 1969, 1978, 1989, and 1999, all drug use peaked in 1978 and dropped thereafter, but MDMA use has continued to increase (6). The increasing popularity of MDMA is not just an American phenomenon, but is seen in both Australia (12) and Europe (13,14), where in some countries it is second only to marijuana use (15).

A change in the pattern of use accompanied the increase in MDMA popularity. Specifically, users initially preferred small groups in private settings (7,16–18), but with the onset of the rave phenomenon in the 1990s MDMA became common in large gatherings in public warehouses or dance clubs. Preferred dosage increased from 75 to 150 mg with an occasional booster of 50 to 100 mg (7,16–18), to 100 to 750 mg and as high as 1250 mg per night (19,20). Concomitant drug use of alcohol, marijuana, and opiates is also more common in raves (8,21,22). MDMA users are less likely to see the drug as harmful (23). It is important to remember that MDMA manufacture is unregulated and quality control is an additional safety issue. The introduction of testing services that ensure that Ecstasy pills contain only MDMA (e.g., DanceSafe kits available commercially) has removed an additional deterrent to some 20% of rave attendees (24).

While MDMA has been advocated as an adjunct to psychotherapy (25–27), no controlled studies of its use have been performed. In one open study, all of 29 subjects who received 75–250 mg reported positive changes in attitude and emotion (26). Twenty-two reported enhanced psychotherapeutic insight and 21 patients in couples treatment reported increased closeness and communication with their partner (26). All experienced adverse consequences similar to those reported by recreational users. Large doses of MDMA have been found to be neurotoxic in human studies (28–30), but low doses are actively being explored in controlled studies of psychotherapy (31).

A typical MDMA user is a college student (6,7). In a survey of 14,000 college students in 119 American colleges, MDMA users were more likely to use marijuana, smoke cigarettes, engage in binge alcohol consumption, and have multiple sex partners (8). But they were not academic underachievers (8). In a study of 132 pregnant MDMA users compared with 122 non-users, MDMA-using women were younger (23.2 vs. 31.2 years old, $P < 0.0001$), experienced more unplanned pregnancies (84.2% vs. 54.3%, $P < 0.05$), and were more likely to be single parents (57% vs. 18.3%, $P < 0.001$) (32). Over half abused alcohol (66.4% vs. 37.3%, $P < 0.001$) (32). Over a third reported some psychiatric problem, but only 6.5% had a psychiatric diagnosis.

Metabolism and Pharmacokinetics

MDMA is usually present in two optical isomers with the dextrorotary form, S-(+)-MDMA being more potent in the central nervous system (CNS) (33). MDMA is metabolized to MDA (which is sometimes used recreationally), 4-hydroxy-3-methoxymethamphetamine (HMMA), and 3,4-dihydroxymethamphetamine (HHMA) (34,35,36). The combination of MDMA and HHMA accounts for 58% of total drug in the urine (37). MDA accounts for less than 5% to 28% of MDMA (34,38,39).

Maximum plasma MDMA concentrations occur two to four hours after oral dose. Peak plasma concentrations were 130.9 ng/mL after 75 mg and 236.4 ng/mL after 125 mg (40). Half-life is between 7.7 to 8.6 hours (40). The more active S-(+)-MDMA isomer is metabolized faster (35,40) and more extensively (35,41) than the levorotary form so that its half-life is some 30% shorter (35,39,41).

Pharmacology

MDMA causes release of serotonin (42,43) and dopamine (44–46) from nerve endings with concomitant inhibition of serotonin reuptake (47). MDMA has a very low affinity for post-synaptic serotonin receptors (48,49). There is also a dose-related increase in cortical acetylcholine (Ach) release (50), but It is believed that serotonin mediates most of the psychological effects of MDMA.

MDMA is toxic to serotonergic neurons in lower (rats [51–57], mice [51], guinea pigs [52]) and higher (e.g., monkeys [56–63]) mammals. In humans, cerebrospinal fluid (CSF) 5-HIAA levels are reduced in MDMA users (64). This is more pronounced in women than in men (64). N-acetyl aspartate (NAA, a marker of cellular health), measured with magnetic resonance spectroscopy, was significantly reduced in the frontal cortex, but not in the parietal or occipital cortex of 15 MDMA users compared to 12 age-matched controls (65,66). The severity of frontal cortical neuronal loss was significantly related to the extent of previous MDMA use. On magnetic resonance imaging (MRI), MDMA users had significant reductions in cortical gray volume (67). MDMA use is associated with a reduction of binding of the serotonin transporter-specific radioligand, (^{11}C)-McN5652 (68). The extent of MDMA use correlated with the severity of serotonin transporter loss (68). Similar results were reported with single photon emission computed tomography (SPECT) (69), particularly in female heavy users of MDMA (70,71). In subjects abstinent from MDMA for over one year, recovery to normal levels was evident in one study (71).

Damage to dopaminergic neurons is more controversial. A recent paper claiming severe dopamine neuron loss (72), was retracted by the authors (73) after they recognized that one of their MDMA vials actually contained methamphetamine.

Acute Positive Psychological Effects

Unlike many drugs of abuse, which are frequently used in private, MDMA is almost always used in the company of other people. Most MDMA users report several positive mood and emotional effects, particularly in their relation to others such as greater capacity for empathy, communication and understanding (30). Experienced and MDMA-naïve subjects also report euphoria, increased self esteem, high physical and

emotional energy, heightened sensual awareness, relaxation, and dissociation (16,30,74,75). Compared to amphetamine 40 mg, MDMA 125 mg induced-euphoria was greater (76). Both MDMA and meta-chlorophenylpeperazine (mCPP), a serotonin releasing agent, produced euphoria to a similar degree (77).

One of the most common reasons individuals give for using Ecstasy is its effect on sexual drive. Ninety percent of users report an increase in sexual desire and satisfaction (77). Orgasm is delayed but more intense (78). However, erection can be impaired in up to 40% of men (78).

Acute Adverse Psychological Effects

Alteration of perception (17,74,76) may be reported as dysphorogenic. MDMA-naïve subjects reported anxiety, mild depersonalization or derealization, moderate thought disorder, and poor coordination (74). Experienced MDMA users given MDMA under controlled conditions reported frequent impaired decision making ability (40%) and decreased mathematics performance (30%) (16). In a study of 29 subjects given MDMA as an adjunct for psychotherapy, all reported some adverse event ranging from fatigue to worsening of panic attacks (29). Twelve cases of acute psychosis have been associated with MDMA use, but in most cases there was concomitant substance use (79–81). In one case with six months follow-up, psychotic symptoms were still evident (79). Impulsive, aggressive, or irrational behaviors have been associated with MDMA use (82–86). These may be related to MDMA use, to associated factors that increase the likelihood of impulsive behaviors in MDMA users, or to concomitant drug use (8,25,85). While driving is not impaired, increased reckless driving has been found to follow MDMA used alone (87).

Physical Consequences of MDMA Use

Nausea, vomiting, anorexia, hypertension, palpitations, diaphoresis, headaches, difficulty walking, muscle aches and tension, hot and cold flashes, urinary urgency, nystagmus, blurred vision, insomnia, and dry mouth may all be related to the sympathomimetic and serotonergic properties of MDMA (7,12,16,18,26,88). The common complaints of trismus and bruxism may be mediated by serotonin activation of the $5HT_{1B}$ receptors of the trigeminal motor nuclei (77).

All experienced MDMA users reported muscle tension (usually in the form of trismus), diaphoresis, blurred vision, and ataxia were all common (16,17,74). Hyperreflexia (16), tachycardia, and hypertension occur with slightly less frequency (75). These motor abnormalities have been related to driving impairment in at least 18 incidents (but usually used in conjunction with other drugs) (87,89). Five involved collisions (89), and two resulted in death (84,90).

Clinical Manifestations of Long-term MDMA Toxicity

Neurotoxicity. Excessive MDMA use is associated with greater self-report depression, obsessive and compulsive behaviors, anxiety, somatization, and loss of libido (91,92). MDMA users also have problems with memory, attention, reasoning, impulse control, and sleep abnormalities (70,93,94–108). Memory dysfunction persists for one year despite recovery of serotoninergic abnormalities on SPECT (70). In a prospective study of MDMA users there was a progressive decline of both immediate and delayed recall with ongoing use (103).

All subjects exposed to MDMA, regardless of dose or frequency of use, had decreased verbal fluency, decreased immediate prose recall, and decreased delayed prose recall, but no change in visual recall (101). There is evidence that the severity of these problems is related to dose (101). The occipital cortex appears to be relatively spared, and $5\text{-}HT_{2A}$ receptor density may even be upregulated (27,109).

Somatic Toxicity. There are many somatic toxic events that have been associated with MDMA use. These include thrombotic or hemorrhagic strokes (119–114), leukoencephalopathy (115), myocardial infarction (116) and arrhythmias (82,117), and pneumothorax (118). It is likely that these are either idiosyncratic or related to impurities from the manufacturing process. Certainly, the cases of hepatotoxicty (117,119–125) and aplastic anemia (126,127) most likely occur secondary to contaminants. In a drug sampling study performed in the Netherlands only 75% of "ecstasy" pills actually contained MDMA (128). About one third of the pills contained amphetamine or other derivatives (128). The study did not examine the presence of other contaminants.

Deaths associated with MDMA use have been increasing over the last decade (129,130). There have also been several cases of severe illness or death due to electrolyte and fluid abnormalities (131–139) or multiple organ failure or a serotonin syndrome (140)-like illness (117,141–148). Some of these may be explained by the fact that subjects using MDMA may experience an increase in body temperature, which is worse in hot ambient temperatures (149). When associated with the hot, crowded environments frequently encountered in raves, dehydration and its consequences are likely (150). A similar phenomenon occurs in animals where crowding increases amphetamine toxicity in animals (a phenomenon labeled aggregation toxicity) (151,152).

Treatment

It is uncommon for MDMA users to present seeking treatment for their "ecstasy" use. Consequently, there are no clear guidelines for treatment. The abuse potential of MDMA is clear. Primates will self-administer MDMA (134,135). If an animal is trained to discriminate amphetamine from saline, MDMA easily substitutes for amphetamine (136,137). And animals treated with MDMA have increased cocaine

self-administration to twice the rate of saline treated controls (138). Intracranial self-administration of MDMA increases the perceived reward of an electrical stimulus to the medial forebrain bundle (139). These data suggest that if MDMA has abuse potential and may facilitate the abuse of other substances.

Serotonin reuptake inhibiting antidepressants may offer a possible treatment for subjects who present with an MDMA addiction. In rats, preadministration of fluoxetine 10 mg/kg given prior to or concurrent with MDMA 15 mg/kg protects against MDMA-induced serotonergic toxicity (140). MDMA-induced behavioral disturbance in rats (in animal models of anxiety and depression) are reversed with subsequent administration of fluoxetine at 6 mg/kg/day (160). Interestingly, paroxetine counters some of the immune system-related changes seen with acute administration of MDMA in humans (reduced CD4 cells, increased cytokines but reduced responsiveness to cytokines, and reduced responsiveness of lymphocytes to mitogens) (161). Citalopram preadministration to healthy volunteers (40 mg intravenously) prior to MDMA 1.5 mg/kg orally blocks the increased pulse and blood pressure induced by MDMA, but does not block the hyperthermia (150). Olanzapine or clozapine coadministration with MDMA in rabbits and rats does block the hyperthermia (162). Nantenine is a naturally occurring plant alkaloid that has been shown to block the behavioral and physiological effects of MDMA in mice (163). Its safety and efficacy has not been documented in humans. There are no specific treatment recommendations for either helping curb MDMA abuse or countering its consequences. Exploring the use of paroxetine and the atypical antipsychotic drugs, olanzapine and clozapine, in human MDMA toxicity is indicated.

SUMMARY

MDMA use is common in college students and appears to be increasing. The patterns of MDMA use differs from the use of other habit-forming drugs in that MDMA is usually used in large, social situations. However, MDMA use is associated with use and abuse of other drugs. Furthermore, MDMA induces several neuropsychiatric complications that range from depressed mood to memory difficulties. While MDMA is frequently used to enhance sexual pleasure, its long-term use frequently leads to sexual dysfunction. A wide range of infrequent but dangerous medical complications have been reported to occur as a consequence of MDMA use. No clear treatment strategy is available, but serotonin reuptake inhibiting antidepressants may play a useful role.

REFERENCES

1. Merck E: Verfahren zur darstellung von alkyloxyaryl-dialyloxyarylund alkylenedioxy-arylaminopropanen bzw. deren am stickstoffmonalkylieten derivaten. German Patent # 273,350. 1914
2. Hardman HF, Haavik CO, Seevers MH: Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals. *Toxicol Appl Pharmacol* 1973; 25:299–309.
3. Shulgin AT, Nichols DE: Characterization of three new psychomimetics. In Stillman R, Willette R (eds.): *The Psychopharmacology of Hallucinogens*. New York: Pergamon Press. 1978: 74–83.
4. Lawn JC: Schedules of controlled substances: Scheduling of 3,4-methylenedioxymethamphetamine (MDMA) into Schedule I of the Controlled Substances Act. *Fed Register* 1986; 51:36552–36560
5. Peroutka SJ: Incidence of recreational use of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") on an undergraduate campus. *N Engl J Med* 1987; 317:1542–1543
6. Pope HG Jr, Ionescu-Pioggia M, Pope KW: Drug use and life style among college undergraduates: A 30-year longitudinal study. *Am J Psychiatry* 2001; 158:1519–1521
7. Peroutka SJ, Newman H, Harris H: Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacol* 1988; 1:273–277
8. Strote J, Lee JE, Wechsler H: Increasing MDMA use among college students: Results of a national survey. *J Adolesc Health* 2002; 30:64–72
9. Cuomo MJ, Dyment PG, Gammino VM: Increasing use of "ecstasy" (MDMA) and other hallucinogens on a college campus. *J Am College Health* 1994; 42:272–274
10. Randell T: Rave scene, ecstasy use, leap Atlantic. *J Am Med Assoc* 1992; 268:1506
11. Johnston LD, O'Malley PM, Bachman JG: *National survey results on drug use from the Monitoring the Future Study, 1975–1998. Volume I. Secondary school students*. NIH Publication No. 99–4660. Washington, DC; U.S. Department of Health and Human Services. 1999
12. Topp L, Hando J, Dillon P, et al.: Ecstasy use in Australia: Patterns of use and associated harm. *Drug Alcohol Depend* 1999; 55:105–115
13. Cregg MT, Traqcey JA: Ecstasy abuse in Ireland. *Irish Med J* 1993; 86:118–120
14. Christophersen AS: Amphetamine designer drugs—An overview and epidemiology. *Toxicol Lett* 2000; 112–113:127–131
15. Landry MJ: MDMA: A review of epidemiolgic data. *J Psychoactive Drugs* 2002; 34:163–169
16. Downing J: The psychological and physiological effects of MDMA on normal volunteers. *J Psychoactive Drugs* 1986; 18:335–340
17. Siegel RK: MDMA: Nonmedical use and intoxication. *J Psychoactive Drugs* 1986; 18:349–354
18. Liester MB, Grob CS, Bravo GL, et al.: Phenomenology and sequelae of 3,4-methylenedioxymethamphetamine use. *J Nervous Mental Dis* 1992; 180:345–352
19. Brown ER, Jarvie DR, Simpson D: Use of drugs at "raves." *Scott Med J* 1995; 40:168–171
20. Forsyth AJ: Places and patterns of drug use in the Scottish dance scene. *Addiction* 1996; 91:511–521
21. Gervin M, Hughes R, Bamford L, et al.: Heroin smoking by "chasing the dragon" in young opiate users in Ireland: Stability and associations with use to "come down" of "Ecstasy." *J Sub Abuse Treat* 2001; 20:297–300
22. Gerhard H: Party-drugs: Sociocultural and individual background and risks. *Int J Clin Pharmacol Therap* 2001; 39:362–366
23. Yacoubian GS Jr, Boyle C, Harding CA, et al.: It's a rave new world: Estimating the prevalence and perceived harm of ecstasy and other drug use among club rave attendees. *J Drug Educ* 2003; 33:187–196

24. Dundes L: DanceSafe and ecstasy: Protection or promotion? *J Health Soc Policy* 2003; 17:19–37
25. Shulgin AT, Nichols DE: Characterization of three new psychomimetics. In Stillman R, Willette R (Eds.): *The psychopharmacology of hallucinogens*. New York: Pergamon Press, 1978: 74–83
26. Greer G, Tolbert P: Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs* 1986; 18:319–327
27. Greer GR, Tolbert P: A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs* 1998; 30:371–379
28. Reneman L, Majoie CB, Flick H, et al.: Reduced N-acetylaspartate levels in the frontal cortex of 3,4-methylenedioxymethamphetamine (Ecstasy) users: Preliminary results. *Am J Neuroradiol* 2002; 23:231–237
29. McCann UD, Szabo Z, Scheffel U, et al.: Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998; 352:1433–1437
30. Semple DM, Ebmeier KP, Glabus MF, et al.: Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *Br J Psychiatry* 1999; 175:63–69
31. Doblin R: A clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): Partnering with the FDA. *J Psychoactive Drugs* 2002; 34:185–194
32. Ho E, Karimi-Tabesh L, Koren G: Characteristics of pregnant women who use ecstasy (3,4-methylenedioxymethamphetamine). *Neurotoxicol Teratol* 2001; 23:561–567
33. Anderson GM, Braun G, Braun U, et al.: *Absolute configuration and psychomimetic phenylalkylamines*. NIDA Research Monograph 22. Rockville, MD, 1978
34. Helmlin H-J, Bracher K, Bourquin D, et al.: Analysis of 3,4-methylenedioxyamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS. *J Analytical Toxicol* 1996; 20:432–440
35. Fallon JK, Kicman AT, Henry JA, et al.: Stereospecific analysis and enantiomeric disposition of 3,4-methylenedioxymethamphetamine (Ecstasy) in humans. *Clin Chem* 1999; 45:1058–1069
36. Maurer HH, Bickeboeller-Friedrich J, Kraemer T, et al.: Toxcicokinetics and analytical toxicology of amphetamine-derived designer drugs ("Ecstasy"). *Toxicol Lett* 2000; 112–113:133–142
37. Segura M, Ortuno J, Farre M, et al.: 3,4-Dihydroxymethamphetamine (HHMA): A major in vivo 3,4-methylenedioxymethamphetamine (MDMA) metabolite in humans. *Chem Res Toxicol* 2001; 14:1203–1208
38. de la Torre R, Farre M, Ortuno J, et al.: Non-linear pharmacokinetics of MDMA ("ecstasy") in humans. *Br J Clin Pharmacol* 2000; 49:104–109
39. Verebey K, Alrazi J, Jaffe JU: The complications of "ecstasy" (MDMA). *J Am Med Assoc* 1988; 259:1649–1650
40. Mas M, Farre M, de la Torre R, et al.: Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. *J Pharmacol Exp Therap* 1999; 290:136–145
41. Pacifici R, Farre M, Pichini S, et al.: Sweat testing of MDMA with the Drugwipe analytical device: A controlled study with two volunteers. *J Analyt Toxicol* 2001; 25:144–146
42. Johnson MP, Hoffman AH, Nichols DE: Effects of the enantiomers of MDA, MDMA and related analogues on [^{3}H]-serotonin and [^{3}H]-dopamine release from superfused rat brain slices. *Eur J Pharmacol* 1986; 132:269–276
43. McKenna DJ, Peroutka SJ: Neurochemistry and neurotoxicity of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *J Neurochem* 1990; 54:14–22
44. Yamamoto BK, Spanos LJ: The acute effects of methylenedioxymethamphetamine on dopamine release in the awake-behaving rat. *Eur J Pharmacol* 1988; 148:195–203
45. Hiramatsu M, Cho AK: Enantiomeric differences in the effects of 3,4-methylenedioxymethamphetamine on extracellular monoamines and metabolites in the striatum of freely-moving rats. *Neuropharmacol* 1990; 29:269–275
46. Nash JF, Meltzer HY, Gudelsky GA: Effect of 3,4-methylenedioxymethamphetamine accumulation in the striatum and nucleus accumbens. *J Neurochem* 1990; 54:1062–1067
47. Steele TD, Nichols DE, Yim GKW: Stereochemical effects of 3,4-methylenedioxymethamphetamine (MDMA) and related amphetamine derivatives on inhibition of uptake of [^{3}H]-monoamines into synaptosomes from different regions of rat brain. *Biochem Pharmacol* 1987; 36:2297–2303
48. Lyon RA, Glennon RA, Titeler M: 3,4-methylenedioxymethamphetamine (MDMA): Stereoselective interactions at brain 5-HT$_1$ and 5-HT$_2$ receptors. *Psychopharmacol* 1986; 88:525–526
49. Bettaglia G, Brooks BP, Kulsakdinum C, et al.: Pharmacologic profile of MDMA (3,4-methylenedioxymethaphetamine) at various brain recognition sites. *Eur J Pharmacol* 1988; 149:159–163
50. Acquas E, Marrocu P, Pisanu A, et al.: Intravenous administration of ecstasy (3,4-methylenedioxymethamphetamine) ebhances cortical and striatal acetylcholine release in vivo. *Eur J Pharmacol* 2001; 418:207–211
51. Stone DM, Stahl DC, Hanson GR, et al.: The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methlenedioxyamphetamine (MDA) on monaminergic systems in the rat brain. *Eur J Pharmacol* 1986; 128:41–48
52. Schmidt CJ, Wu L, Lovenberg W: Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analog. *Eur J Pharmacol* 1986; 124:175–178
53. Schmidt CJ: Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *J Pharmacol Exp Ther* 1987; 240:1–7
54. Commins DL, Vosmer G, Virus RM, et al.: Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther* 1987; 241:338–345
55. O'Hearn EG, Battaglia G, DeSouza EB, et al.: Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of sertotonergic axon terminals in forebrain: Immunocytochemical evidence for neurotoxicity. *J Neurosci* 1988; 8:2788–2803
56. Slikker W, Ali SF, Scallet C, et al.: Neurochemical and neurohistological alterations in the rat and monkey produced by orally administered methylenedioxymethamphetamine (MDMA). *Toxicol Appl Pharmacol* 1988; 94:448–457
57. Slikker W Jr, Holson RR, Ali SF, et al.: Behavioral and neurochemical effects of orally administered MDMA in the rodent and nonhuman primate. *Neurotoxicol* 1989; 10:529–549
58. Ricaurte GA, DeLanney LE, Irwin I, et al.: Toxic effects of MDMA on central serotonergic neurons in the primate: Importance of route and frequency of drug administration. *Brain Res* 1988; 446:165–168
59. Ricaurte GA, Katz JL, Martello MB: Lasting effects of (+–)-3,4-methylenedioxymethamphetamine (MDMA) on central

serotonergic neurons in nonhuman primates: Neurochemical observations. *J Pharmacol Exp Ther* 1992; 261:616–622
60. Insel TR, Battaglia G, Johannessen JN, et al.: 3,4-methylenedioxymethamphetamine ("ecstasy") selectively destroys brain serotonin terminals in rhesus monkeys. *J Pharmacol Exp Ther* 1989; 249:713–720
61. Wilson MA, Ricaurte GA, Molliver ME: Distinct morphological classes of serotonergic axons in primates exhibit differential vulnerability to the psychotropic drug 3,4-methylenedioxymethamphetamine. *Neurosci* 1989; 28:121–137
62. Fischer CA, Hatzidimitriou G, Katz JL, et al.: Reorganization of ascending serotonin axon projections in animals previously exposed to the recreational drug 3,4-methylenedioxymethamphetamine *J Neurosci* 1995; 15:5476–5485
63. Hatzidimitriou G, McCann UD, Ricaurte GA: Abnormal serotonin innervation in the forebrain of monkeys exposed to MDMA seven years previously: Factors influencing abnormal recovery. *J Neurosci* 1999; 19:5096–5107
64. McCann UD, Ridenour A, Shaham Y, et al.: Brain serotonergic neurotoxicity after MDMA ("ecstasy"): A controlled study in humans. *Neuropsychopharmacol* 1994; 10:129–138
65. Reneman L, Majoie CB, Schmand B, et al.: Prefrontal N-acetylaspartate is strongly associated with memory performance in (abstinent) ecstasy users: preliminary report. *Biol Psychiatry* 2001; 50:550–554
66. Reneman L, Majoie CB, Flick H, et al.: Reduced N-acetylaspartate levels in the frontal cortex of 3,4-methylenedioxymethamphetamine (ecstasy) users: preliminary results. *Am J Neuroradiol* 2002; 23:231–237
67. Cowan RL, Lyoo IK, Sung SM, et al.: Reduced cortical gray matter density in human MDMA (Ecstasy) users: a voxel-based morphometry study. *Drug Alcohol Depend* 2003; 72:225–235
68. McCann UD, Szabo Z, Scheffel U, et al.: Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998; 352:1433–1437
69. Semple DM, Ebmeier KP, Glabus MF, et al.: Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *Br J Psychiatry* 1999; 175:63–69
70. Reneman L, Lavalaye J, Schmand B, et al.: Cortical serotonin transporter density and berbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): Preliminary findings. *Arch Gen Psychiatry* 2001; 58:907–908
71. Reneman L, Booij J, de Bruin K, et al.: Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet* 2001; 358:1864–1869
72. Ricaurte GA, Yuan J, Hatzidimitriou G, et al.: Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy'"). *Science* 2002; 297:2260–2263
73. Ricaurte GA, Yuan J, Hatzidimitriou G, et al.: Retraction of Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy'"). *Science* 2002; 297:2260–2263. *Science* 2003; 301:1479
74. Vollenweider FX, Gamma A, Liechti M, et al.: Psychological and cardiovascular effects and short-term sequelae of MDMA ("Ecstasy") in MDMA-naïve healthy volunteers. *Neuropsychopharmacol* 1998; 19:241–251
75. Grab CS, Poland RE, Chang L, et al.: Psychobiologic effects of 3,4-methylendioxymethamphetamine in humans: Methodological considerations and preliminary observations. *Behav Brain Res* 1996; 73:103–107
76. Mas M, Farre M, de la Torre R, et al.: Cardiovacular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. *J Pharmacol Exp Ther* 1999; 290:136–145
77. Tancer ME, Johanson CE: The subjective effects of MDMA and mCPP in moderate MDMA users. *Drug Alc Depend* 2001; 65:97–101
78. Zemishlany Z, Aizenberg D, Weizman A: Subjective effects of MDMA ('Ecstasy') on human sexual function. *Eur Psychiatry: J Assoc Eur Psychiatrists* 2001; 16:127–130
79. Vaiva G, Boss V, Bailly D, et al.: An "accidental" acute psychosis with ecstasy use. *J Psychoactive Drugs* 2001; 33:95–98
80. Creighton FJ, Black DL, Hyde CE: 'Ecstasy' psychosis and flashbacks. *Br J Psychiatry* 1991; 159:713–715
81. Cox DE: "Rave" to the grave. *Forensic Sci Int* 1993; 60:5–6
82. Dowling GP, McDonough ET, Bost RD: 'Eve' and 'Ecstasy.' A report of five deaths associated with the use of MDEA and MDMA. *J Am Med Assoc* 1987; 257:1615–1617
83. Cadier MA, Clarke JA: Ecstasy and Whizz at a rave resulting in a major burn plus complications. *Burns* 1993; 19:239–240
84. Hooft PJ, Van der Voorde HP: Reckless behavior related to the use of 3,4-methylenedioxymethamphetamine (ecstasy): Apropos of fatal accident during car surfing. *Int J Legal Med* 1994; 106:328–329
85. Bond AJ, Verheyden SL, Wingrove J, et al.: Angry cognitive bias, trait aggression and impulsivity in substance users. *Psychopharmacol (Berl)* 2004; 17:331–339
86. Curran HV, Verheyden SL: Altered response to tryptophan supplementation after long-term abstention from MDMA (ecstasy) is highly correlated with human memory function. *Psychopharmacol (Berl)* 2003; 169:91–103
87. Brookhuis KA, De Waard D, Samyn N: Effects of MDMA (ecstasy), and multiple drugs use on (simulated) driving performance and traffic safety. *Psychopharmacol (Berl)* 2004; in press
88. Solowij N, Hall W, Lee N: Recreational MDMA use in Sydney: A profile of 'Ecstasy' users and their experiences with the drug. *Br J Addiction* 1992; 87:1161–1172
89. Logan BK, Couper FJ: 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and driving impairment. *J Forensic Sci* 2001; 46:1426–1433
90. Cifasi J, Long C: Traffic fatality related to the use of methylenedioxymethamphetamine. *J Forensic Sci* 1996; 41:1082–1084
91. MacInnes N, Handley SL, Harding GF: Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms. *J Psychopharmacol* 2001; 15:181–186
92. Parrott AC, Milani RM, Parmar R, et al.: Recreational ecstasy/MDMA and other drug users from the UK and Italy: psychiatric symptoms and psychobiological problems. *Psychopharmacol* 2001; 159:77
93. Verkes RJ, Gijsman HJ, Pieters RC, et al.: Cognitive performance and serotonergic function in users of ecstasy. *Psychopharamacol* 2001; 153:186–202
94. Krystal JH, Price LH: Chronic 3,4-methylenedimethoxymethamphetamine (MDMA) use: Effects on mood and neuropsychological function? *Am J Drug Alcohol Abuse* 1992; 18:331–341
95. Allen RP, McCann UD, Ricourte GA: Persistent effects of +/–3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") on human sleep. *Sleep* 1993; 16:560–564
96. McGuire P: Long term psychiatric and cognitive effects of MDMA use. *Tox Lett* 2000; 112–113:153–156

97. Reneman L, Booij J, Schmand B, et al.: Memory disturbances in "Ecstasy" users are correlated with altered brain serotonin neurotransmission. *Psychopharm* 2000; 148:322–324
98. Parrott AC, Lasky J: Ecstasy (MDMA) effects upon mood and cognition: Before, during and after a Saturday night dance. *Psychopharmacol* 1998; 139:261–268
99. McCann UD, Mertl M, Eligulashvili V, et al.: Cognitive performance in (+/–) 3,4-methlenedixoymethamphetamine (MDMA, "ecstasy") users: A controlled study. *Psychopharmacol* 1999; 143:417–425
100. Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, et al.: Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *J Neurol Neurosurg Psychiatry* 2000; 68:719–725
101. Bhattachary S, Powell JH: Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy': Evidence for cognitive impairment. *Psychol Med* 2001; 31:647–658
102. Croft RJ, Mackay AJ, Mills AT, et al.: The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacol* 2001; 153:373–379
103. Zakzanis KK, Young DA: Memory impairment in abstinent MDMA ("Ecstasy") users: A longitudinal investigation. *Neurol* 2001; 56:966–969
104. Gouzoulis-Mayfrank E, Thimm B, Rezk M, et al.: Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27:819–827
105. Jacobsen LK, Menel WE, Pugh KR, et al.: Preliminary evidence of hippocampal dysfunction in adolescent MDMA ("ecstasy") users: Possible relationship to neurotoxic effects. *Psychopharmacol (Berl)* 2004; 173:383–390
106. Verbaten MN: Specific memory deficits in ecstasy users? The results of a meta-analysis. *Hum Psychopharmacol* 2003; 18:281–290
107. Oliveri M, Calvo G: Increased visual cortical excitability in ecstasy users: a transcranial magnetic stimulation study. *J Neurol Neurosurg Psychiatry* 2003; 74:1136–1138
108. Wareing M, Murphy PN, Fisk JE: Visuospatial memory impairments in users of MDMA ("ecstasy"). *Psychopharmacol (Berl)* 2004; 173:391–397
109. Reneman L, Endert E, de Bruin K, et al.: The acute and chronic effects of MDMA ("ecstasy") on cortical 5-HT_{2A} receptors in rat and human brain. *Neuropsychopharmacol* 2002; 26:387–396
110. Harries DP, DeSilva R: 'Ecstasy' and intracerebral haemorrhage. *Scott Med* 1992; 37:476
111. Gledhill JA, Moore DF, Bell D, et al.: Subarachnoid hemorrhage associated with MDMA abuse. *J Neurol Neurosurg Psychiatry* 1993; 56:1036–1037
112. Hughes JC, McCube M, Evans RJ: Intracranial haemorrhage associated with ingestion of "Ecstasy." *Arch Emerg Med* 1993; 10:372–374
113. Manchanda S, Connolly MJ: Cerebral infarction in association with ecstasy abuse. *Postgrad Med J* 1993; 69:874–875
114. Rothwell PM, Grant R: Cerebral venous thrombosis induced by 'ecstasy.' *J Neurol Neurosurg Psychiatry* 1993; 56:1035–1039
115. Bertram M, Egelhoff T, Schwarz S, et al.: Toxic leukoencephalopathy following "ecstasy" ingestion. *J Neurol* 1999; 146:617–618
116. Qasim A, Townend J, Davies MK: Ecstasy induced acute myocardial infarction. *Heart (Br Cardiac Soc)* 2001; 85:E10
117. Henry JA, Jeffreys KJ, Dowling S: Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). *Lancet* 1992; 340:384–387
118. Mazur S, Hitchcock T: Spontaneous pneumomediastinum, pneumothorax and ecstasy abuse. *Emergency Med (Fremantle, Western Australia)* 2001; 13:121–123
119. Shearman JD, Satsangi J, Chapman RWG, et al.: Misuse of Ecstasy. *Br Med J* 1992; 305:309
120. Ijzermans JNM, Tilanus HW, DeMan RA, et al.: Ecstasy and liver transplantation. *Ann Med Interne* 1993; 144:568
121. Khakoo SI, Coles CJ, Armstrong JS, et al.: Hepatotoxicity and accelerated fibrosis following 3,4-methylenedioxymethamphetamine ("Ecstasy") usage. *J Clin Gastroenterology* 1995; 20:244–247
122. Ellis AJ, Wendon JA, Portmann B, et al.: Acute liver damage and ecstasy ingestion. *Gut* 1996; 38:454–458
123. Andreu V, Mas A, Bruguera M, et al.: Ecstasy: A common cause of severe acute hepatotoxicity. *J Hepatol* 1998; 29:394–397
124. DeCarlis L, DeGasperi A, Slim AO, et al.: Liver transplantation of ecstasy-induced fulminant hepatic failure. *Trans Proc* 2001; 33:2743–2744
125. Lawler LP, Abraham S, Fishman EK: 3,4-methylenedioxymethamphetamine (ecstasy)-induced hepatotoxicity: multidetector CT and pathology findings. *J Computer Assis Tomography* 2001; 25:649–652
126. Marsh JC, Abboudi ZH, Gibson FM, et al.: Aplastic anemia following exposure to 3,4-methylenedioxymethamphetamine ('Ecstasy'). *Br J Haematol* 1994; 88:281–285
127. Clark AD, Butt N: Ecstasy-induced very severe aplastic anaemia complicated by invasive pulmonary mucormycosis treated with allogeneic peripheral blood progenitor cell transplant. *Clin Lab Haematol* 1997; 19:279–281
128. Spruit IP: Monitoring synthetic drug markets, trends, and public health. *Substance Use Misuse* 2001; 36:23–47
129. Garcia-Repetto R, Moreno E, Soriano T, et al.: Tissue concentrations of MDMA and its metabolite MDA in three fatal cases of overdose. *Forensic Sci Int* 2003; 135:110–114
130. Schifano F, Oyefesco A, Webb L, et al.: Reviews of deaths related to taking ecstasy, England and Wales, 1997–2000. *Brit Med J* 2003; 326:80–81
131. Maxwell DL, Polkey MI, Henry JA: Hyponatremia and catatonia stupor after taking 'ecstasy.' *Br Med J* 1993; 27:1399
132. Kessel B: Hyponatremia after ingestion of "ecstasy." *Brit Med J* 1994; 308:414
133. Matthai SM, Davidson DC, Sills JA, et al.: Cerebral oedema after ingestion of MDMA ("ecstasy") and unrestricted intake of water. *Br Med J* 1996; 312:1359
134. Hall AP: Hyponatremia, water intoxication and 'ecstasy.' *Intensive Care Med* 1997; 23:1289
135. Ajaelo I, Koenig K, Snoey E: Severe hyponatremia and inappropriate antidiuretic hormone secretion following ecstasy use. *Acad Emerg Med* 1998; 5:839–840
136. Magee C, Staunton H, Tormey W, et al.: Hyponatremia, seizures and stupor associated with ecstasy ingestion in a female. *Ir Med J* 1998; 91:178
137. Holmes SB, Banerjee AK, Alexander WD: Hyponatremia and seizures after ecstasy use. *Postgrad Med J* 1999; 75:32–33
138. O'Connor A, Cluroe A, Couch R, et al.: Death from hyponatremia-induced cerebral oedema associated with MDMA ("Ecstasy") use. *N Z Med J* 1999; 112:255–256

139. Budisavljevic MN, Stewart L, Sahn SA, et al.: Hyponatremia associated with 3,4-methylenedioxymethylamphetamine ("Ecstasy") abuse. *Am J Med Sci* 2003; 326:89–93
140. Sternbach H: The serotonin syndrome. *Am J Psychiatry* 1991; 148:705–713
141. Demirkiran M, Jankovic J, Dean JM: Ecstasy intoxication: An overlap between serotonin syndrome and neuroleptic malignant syndrome. *Clin Neuropsychopharmacol* 1996; 19:157–164
142. Mueller PD, Korey WS: Death by "ecstasy": The serotonin syndrome? *Ann Emerg Med* 1998; 32:377–380
143. Brown C, Osterloh J: Multiple complications from recreational ingestion of MDMA ("Ecstasy"). *J Am Med Assoc* 1987; 258:780–781
144. Chadwick IS, Linsley A, Freemont AJ, et al.: Ecstasy, 3,4-methylenedioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia. *J Roy Soc Med* 1991; 84:37.
145. Campkin NTA, Davies UM: Another death from Ecstasy. *J Royal Soc Med* 1992; 85:61
146. Roberts L, Wright H: Survival following intentional massive overdose of 'Ecstasy.' *J Accidental Emerg Med* 1993; 11:53–54
147. Lehmann ED, Thom CH, Croft DN: Delayed severe rhabdomyalysis after taking ecstasy. *Postgrad Med J* 1995; 71:186–187
148. Coore JR: A fatal trip with ecstasy: A case of 3,4-methylenedioxymethamphetamine/3,4-methylenedioxy-ampthetamine toxicity. *J Royal Soc Med* 1996; 89:51P–52P
149. Green AR, Sanchez V, O'Shea E, et al.: Effect of ambient temperature and a prior neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA) on the hyperthermic response of rats to a single or repeated ('binge' ingestion) low dose of MDMA. *Psychopharmacol (Berl)* 2004; 173:264–269
150. Liechti ME, Vollenweider FX: The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. *J Psychopharmacol* 2000; 14:269–274
151. Chance M: Aggregation as a factor influencing the toxicity of sympathomimetic amines in mice. *J Pharmacol Exp Ther* 1946; 198:214–219
152. Hohn R, Lasagna L: Effects of aggregation and temperature on amphetamine toxicity in mice. *Psychopharmacologia* 1960; 1:210–220
153. Lamb RJ, Griffiths RR: Self-injection of 3,4-methylenedioxymethamphetamine MMDMA) in the baboon. *Psychpharmacol* 1987; 91:268–272
154. Beardsley PM, Balster RL, Harris LS: Self-administration of methylenedioxymethamphetamine (MDMA) by rhesus monkey. *Drug Alcohol Depend* 1986; 18:149–157
155. Glennon RA, Young RY: Further investigations of the discriminative stimulus properties of MDA. *Pharmacol Biochem Behav* 1984; 20:501–505
156. Kamien JB, Johanson CE, Schuster CR, et al.: The effects of (+)-methylenedixoymethamphetamine and (+)-methylenedioxyamphetamine in monkeys trained to discriminate (+)-amphetamine from saline. *Drug Alcohol Depend* 1986; 18:139–147
157. Fletcher PJ, Robinson SR, Slippoy DL: Pre-exposure to (+/–) 3,4-methylenedioxymethamphetamine (MDMA) facilitates acquisition of intravenous cocaine self-sdministration in rats. *Neuropsychopharmacol* 2001; 25:195–203
158. Hubner CB, Bird M, Ressnick S, et al.: The threshold lwering effects of MDMA (ecstasy) on brain-stimulation reward. *Psychopharmacol* 1988; 95:49–51
159. Sanchez V, Camarero J, Esteban B, et al.: The mechanisms involved in the long-lasting neuroprotective effect of fluoxetine against MDMA ('ecstasy')-induced degeneration of 5-HT nerve endings in rat blind. *Br J Pharmacol* 2001; 134:46–57
160. Thompson MR, Li KM, Clemens KJ, et al.: Chronic fluoxetine treatment partly attenuates the long-term anxiety and depressive symptoms induced by MDMA ('Ecstasy') in rats. *Neuropsychopharmacol* 2004; 29:694–704
161. Pacifici R, Pichini S, Zuccaro P, et al.: Paroxetine inhibits acute effects of MDMA on the immune system in humans. *J Pharmacol Exp Ther* 2004; 309:285–292
162. Blessing WW, Seaman B, Pedersen NP, et al.: Clozapine reverses hyperthermia and sympathetically mediated cutaneous vasoconstriction induced by 3,4-methylenedioxymethamphetamine (ecstasy) in rabbits and rats. *J Neurosci* 2003; 23:6385–6391
163. Fantegrossi WE, Kiessel CL, Leach PT, et al.: Nantenine: An antagonist of the behavioral and physiological effects of MDMA in mice. *Psychopharmacol (Berl)* 2004; 173:270–277