

**Listing and Summary of Ecstasy Medical Articles  
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***Illicit drug-related harm during the Sydney 2000 Olympic Games: implications for public health surveillance and action.***, Indig D, Thackway S, Jorm L, Salmon A, Owen T., *Addiction* 2003 Jan;98(1):97-102.

**AIMS:** To describe presentations to emergency departments during the Sydney 2000 Olympic Games for conditions related to the use of illicit drugs; to discuss the implications of such presentations for surveillance and public health action at similar events in the future. **DESIGN:** Identification of target presentations in sentinel emergency departments; entry of data into a purpose-built database; and daily electronic transfer of data for central collation and analysis. **SETTING:** Fifteen sentinel emergency departments in the greater Sydney metropolitan area for a 38-day period spanning the Sydney 2000 Olympic Games. **PARTICIPANTS:** Four hundred and twenty-four presentations to sentinel emergency departments with conditions related to illicit drug use. **MEASUREMENTS:** Patient's age, sex, country and region of residence, location of emergency department, types of illicit drugs involved and departure status. **FINDINGS:** The mean daily number of presentations for adverse events due to illicit drug use was significantly higher (13.3 versus 8.8 presentations,  $t = 2.2$ ,  $P = 0.04$ ) in the 2-week Olympic Games period than in the lead-up to the Games, culminating in a large peak following the closing ceremony. There was also a significant increase (5.1 versus 1.7 presentations,  $t = 2.8$ ,  $P = 0.007$ ) in the mean daily number of presentations related to use of ecstasy or amphetamines, whereas no change was noted in presentations related to heroin use. Over half (52%) of presentations occurred at two emergency departments in areas known as being 'hot-spots' for illicit drug use. **CONCLUSIONS:** Enhanced surveillance of adverse events following illicit drug use, possibly targeting known 'hot-spots', should be considered for future mass events. Advance preparation of preventive strategies, such as 'party-safe' messages, will enable rapid response to unusual patterns of illicit drug-related harm during future mass events.

***Acute liver failure following the use of ecstasy (MDMA)***, [Article in German], Lange-Brock N, Berg T, Muller AR, Fliege H, Neuhaus P, Wiedenmann B, Klapp BF, Monnikes H., *Z Gastroenterol* 2002 Aug;40(8):581-6. The use of "ecstasy" (Methylenedioxymethamphetamine) as a recreational drug is increasing in Europe since the 1980's. Aside intended psychological effects the use of ecstasy can be followed by symptoms of intoxication; complications include toxic hepatic damage up to acute hepatic failure. This case-report is about a 17-year old female patient who regularly used "ecstasy" over a six-month period. Two days after the last use of "ecstasy", she reported to her general practitioner with nausea, vomiting, abdominal pain and jaundice. Within 10 days the patient developed acute liver failure. With criteria for liver transplantation fulfilled she was listed for orthotopic liver transplantation of high urgency which was carried out only one day later. Histological examination of the explanted liver showed evidence for a toxic fulminant hepatitis. After transplantation the patient made a full recovery and was released from hospital on day 26 after transplantation. At the first control after six months the patient was in good physical and nutritional condition, serological parameters were normal and ultrasound examination of the transplanted liver was unremarkable. The ethiopathology of "ecstasy"-induced hepatotoxicity, which can occur dose-independently with a symptom-free period from days to weeks after ingestion is not yet fully understood. Possible mechanisms of hepatic damage include influence of MDMA on body temperature regulation, harmful effects of the substance or further components of the "ecstasy"-tablets on the liver cell or a genetic vulnerability of some individuals against amphetamines and amphetamine derivatives. There are no parameters existing which could predict the course and severity of "ecstasy"-induced hepatopathy. Especially in young patients with symptoms of hepatic damage frequent controls of clinical status and relevant laboratory parameters are of great importance. Patient transfer to a specialised centre should follow as early as possible; at the latest, when coagulopathy occurs.

***Mental disorders in ecstasy users: a prospective-longitudinal investigation.***, Lieb R, Schuetz CG, Pfister H, von Sydow K, Wittchen H., *Drug Alcohol Depend* 2002 Oct 1;68(2):195-207.

**OBJECTIVES:** To investigate the relationship between ecstasy use and mental disorders in a representative sample of adolescents and young adults. **METHOD:** Data for this investigation were drawn from the Early Developmental Stages of Psychopathology (EDSP) study, an epidemiological-longitudinal study in which 14-24 year-olds were examined prospectively over a period of about 4 years. Results are based on N=2462 participants who completed

whole study period and for whom drug use behavior could be determined. RESULTS: (1). Ecstasy users, compared with non-users, were at significantly increased risk of DSM-IV substance related disorders, including alcohol use disorders (52.6 vs. 15.6%; OR=5.6, 95% CI=3.8-8.1). Further, ecstasy users also had a higher risk of alcohol use disorders, when compared with users of other illicit substances (52.6 vs. 40.3%; OR=1.7, 95% CI=1.1-2.4). (2). Ecstasy users had significantly higher rates for almost all DSM-IV mental disorders examined when compared with non-users (any non-substance use disorder: 68.7 vs. 44.5%; OR=3.1, 95% CI=2.1-4.4) and compared with users of other illicit drugs (any non substance use disorder: 68.7 vs. 55.5%; OR=1.8, 95% CI=1.2-2.6). (3). Ecstasy users also reported significantly higher rates of prescription medicine use, though they did not use more medical services than non-drug users. (4). Analyses of temporal patterns of ecstasy use and disorder onset revealed that the first use of ecstasy was secondary to the onset of DSM-IV mental disorders in the majority of cases. Still, subjects with mental disorders at baseline also showed a significantly increased risk for initiation of ecstasy use during the 4-year follow-up period. CONCLUSIONS: Care should be taken in cross sectional studies in interpreting mental disorder signs and symptoms merely as a consequence of ecstasy use, as ecstasy use might be associated with the use of multiple substances, and onset of mental disorder is more likely to precede rather than to follow use of ecstasy and related substances.

***Attentional processes in abstinent methylenedioxyamphetamine (ecstasy) users.***

**Zakzanis KK, Young DA, Radkoshnoud NF.,** Appl Neuropsychol 2002;9(2):84-91.

In recent years, methylenedioxyamphetamine (MDMA or ecstasy) has gained great popularity among young adults. Although human research in abstinent users has focused primarily on memory function, little attention has been given to other neuropsychological functions that may have some bearing on memory performance, such as attention. Hence, the purpose of this study was to examine the effects of MDMA on attentional processes. Accordingly, 24 MDMA users and 30 matched normal controls were tested on the Wechsler Abbreviated Scale of Intelligence (WASI) and the Test of Everyday Attention (TEA). We found MDMA users to show generally no significant difference on attention tasks compared with controls with the exception of a single TEA subtest. More interestingly, we found some preliminary evidence to indicate that dosage, in terms of the number of tablets used, may be related to impairment on specific component attentional tasks. This finding brings to light the important relationship between poor attentional processes and drug-taking behaviors and their reciprocal relationship.

***Assessing the temporal relationship between race and ecstasy use among high school seniors., Yacoubian GS Jr.,*** J Drug Educ 2002;32(3):213-25.

Previous research has suggested that the use of ecstasy is primarily a white phenomenon. To date, however, these studies have all been conducted at single points in time. No research has examined the temporal relationship between race and the use of ecstasy. In the current study, data collected from 10,088 high school seniors surveyed through the Monitoring the Future (MTF) study between 1996 and 1999 are analyzed. Chi-square statistics are used to explore the temporal relationship between race and the use of ecstasy during this time frame. Statistically significant relationships between race and ecstasy use are discerned. Policy implications are assessed in light of the findings.

***Subarachnoid haemorrhage with "Ecstasy" abuse in a young adult., Auer J, Berent R, Weber T, Lassnig E, Eber B.,*** Neurol Sci 2002 Oct;23(4):199-201,

Abuse of the drugs like amphetamine, cocaine and "Ecstasy" may be complicated by intracerebral, subdural or subarachnoid haemorrhage. Contrary to historical opinion, drug-related intracranial haemorrhage (ICH) is frequently related to an underlying vascular malformation. We report the case of an 18-year-old man with a history of Ecstasy abuse preceding the onset of severe occipital headache. Cerebral computed tomography revealed right-sided subarachnoid haemorrhage and cerebral angiography showed right-sided middle cerebral artery aneurysm of 1 cm diameter. The patient was treated surgically with aneurysm clipping. Three weeks after onset of intracranial haemorrhage, neurological examination demonstrated normal findings. A history of severe headache immediately after using amphetamine, Ecstasy, or cocaine should alert doctors to the possibility of intracerebral haemorrhage. Arteriography should be part of the evaluation of most young patients with stroke or non-traumatic ICH.

***The effects and consequences of selected club drugs., Freese TE, Miotto K, Reback CJ.,*** J Subst Abuse Treat 2002 Sep;23(2):151-6.

Ecstasy (MDMA), gamma-hydroxybutyrate (GHB), ketamine, and methamphetamine are 4 examples of club drugs that are increasing in popularity. Although the pharmacological classifications of these drugs vary, MDMA has

Structural similarities to both amphetamine and the hallucinogen mescaline. Ketamine and GHB are anesthetic agents and methamphetamine is a long-acting psychostimulant. Medical visits for club drug-related toxicity have sharply increased across the country. This article provides a brief review of the literature on club drugs. Copyright 2002 Elsevier Science Inc.

***Ecstasy and drug consumption patterns: a Canadian rave population study.*, Gross SR, Barrett SP, Shestowsky JS, Pihl RO., Can.J.Psychiatry 2002 Aug;47(6):546-51.**

**OBJECTIVE:** This study investigates the drug consumption patterns of a sample of rave attendees in the city of Montreal, Quebec, and seeks to identify the prevalence of 3,4-methylenedioxymethamphetamine (MDMA) and other drug use in this population. **METHOD:** We administered a self-report questionnaire to 210 respondents. For various licit and illicit substances, participants reported their age of first use, number of lifetime uses, and usage in the previous 30 days. **RESULTS:** We found a significant rank order for the sequence of first use: 1) alcohol, 2) nicotine, 3) cannabis, 4) LSD, 5) psilocybin, 6) amphetamine, 7) cocaine, 8) MDMA, 9) gamma-hydroxybutyrate (GHB), 10) ephedrine, 11) ketamine. Alcohol and cannabis were the most commonly used substances, both in cumulative number of lifetime uses and in usage in the preceding 30 days. MDMA and amphetamine were also notable as the next 2 most popular drugs for use in the preceding 30 days and in terms of those who had tried the drugs at least once. We identified a progressive rank order of experimentation, with early alcohol or cannabis use (or both) associated with the early use of all other drugs tried by more than 25% of the sample. We found MDMA and amphetamine use to be prevalent, as was general experimentation with all drugs studied, other than heroin. **CONCLUSION:** Drug consumption levels were substantial in this "rave" population, particularly with respect to recent use of MDMA, amphetamine, cannabis, and alcohol. Results also indicate that the sequence of drug experimentation in this population follows an identifiable pattern.

***MDMA ('Ecstasy') and Other Club Drugs'. The New Epidemic.*, Koesters SC, Rogers PD, Rajasingham CR., *Pediatr Clin North Am* 2002 Apr;49(2):415-33.**

Unfortunately, perceptions that the club drugs can be safe endure. Some groups, such as the Multidisciplinary Association for Psychedelic Study, continue to lobby for the legalization of MDMA for research purposes [76]. DanceSafe is an organization that seeks to educate the "nonaddicted" user to decrease the risks [82]. The DanceSafe Web site offers tips on the safe use of MDMA, such as attention to hydration status and ambient temperature. It also offers free testing of tablets submitted by mail and sells home testing kits to determine the content of pills sold as "ecstasy." Although much remains unknown about the long-term consequences of MDMA and the club drugs, there are clearly enough short-term dangers to prompt more aggressive education and surveillance for its use. Scare tactics and exaggerations often are ignored [53], while Web sites full of anecdotal or incomplete information may lead the unaware user to increased use [113]. Organizations such as DanceSafe imply that proper education decreases addiction and that only uneducated users or addicts suffer the life-altering consequences of drug use. The fallacy in the mission of educating "nonaddicted" users is evident. Peer-based education, with a focus on both the short-term dangers and long-term consequences, may be a more effective approach [9]. Both new and established drugs of abuse continue to plague teens and young adults. Pediatric, family practice, and Med-Peds physicians, and pediatric pharmacologists need to remain vigilant about patterns and trends of drug abuse. MDMA and the other "club drugs" are not benign. Their effects target the brain, alter neurochemistry, and possibly cause irreversible structural damage. What may seem like a harmless drug in a weekend dance club has the potential for major public health problems in years to come [109]. Effective education and timely intervention may prevent these addictive drugs from becoming a way of life, a lifestyle that may have a literal "dead end."

***The health effects of ecstasy: a literature review.*, Gowing LR, Henry-Edwards SM, Irvine RJ, Ali RL. *Drug Alcohol Rev* 2002 Mar;21(1):53-63.**

Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is the third most used illicit drug, after cannabis and amphetamines. There has been considerable interest in the adverse effects of use, with particular attention given to a small number of deaths related to ecstasy use, and the neurotoxic effects of MDMA. This paper reviews case reports of adverse effects attributed to ecstasy use, and the findings of animal and human studies, so as to identify the health effects of ecstasy use, and factors contributing to their occurrence. The incidence of serious acute adverse events related to ecstasy is low. It is the unpredictability of those adverse events and the risk of mortality and substantial morbidity that makes the health consequences of ecstasy significant. Hyperthermia and hyponatraemia are the most significant acute adverse effects, and can occur even when MDMA is the only drug used. Ecstasy users

One should be aware of the importance of controlling body temperature and fluid intake, early signs of adverse effects, and the need to seek medical assistance promptly. Neurotoxicity is potentially the most significant long-term effect of ecstasy. The clinical implications of neurotoxicity are uncertain at this time, but short-term memory impairment may be significant.

***Changes in cardiovascular responsiveness and cardiotoxicity elicited during binge administration of Ecstasy.***, Badon LA, Hicks A, Lord K, Ogden BA, Meleg-Smith S, Varner KJ., J Pharmacol Exp Ther 2002 Sep;302(3):898-907.

The recreational use of 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy) is often characterized by a repeated pattern of frequent drug administrations (binge) followed by a period of abstinence. Radiotelemetry was used to characterize the cardiovascular responses elicited during three MDMA binges (3 or 9 mg/kg b.i.d. for 4 days), each of which was separated by a 10-day MDMA-free period. The heart rate and mean arterial pressure (MAP) responses elicited by 3-mg/kg doses of MDMA were consistent within and between the three binges. In the first binge the 9-mg/kg doses of MDMA increased MAP and produced a biphasic (decrease/increase) heart rate response. The bradycardia elicited by MDMA in the first binge (-75 bpm) was enhanced in the second and third binges (-186 and -287 bpm, respectively). Significant hypotension accompanied the increased bradycardic responses. Atropine abolished the hypotension and significantly attenuated the bradycardic responses. The MAP and heart rate responses elicited by sodium nitroprusside, acetylcholine, phenylephrine, and serotonin (5-HT) were evaluated before each binge and 10 days after the last binge. The hypotension, but not the tachycardia elicited by sodium nitroprusside was attenuated by the repeated administration of MDMA. The responses to phenylephrine, acetylcholine, and 5-HT were unaltered after MDMA. The hearts of treated rats contained foci of inflammatory infiltrates (lymphocytes and macrophages), some of which contained necrotic cells and/or disrupted cytoarchitecture. MDMA produced cardiac arrhythmias in some rats. These results indicate that the binge administration of MDMA can significantly alter cardiovascular and cardiovascular reflex function and produce cardiac toxicity.

***Hyponatraemic states following 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') ingestion.***, Hartung TK, Schofield E, Short AI, Parr MJ, Henry JA., Respiratory Unit, Ninewells Hospital, Dundee, UK.

BACKGROUND: Life-threatening and fatal hyponatraemic complications following ecstasy use have previously been documented. Aim: To define clinical features of hyponatraemia following the ingestion of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). DESIGN: Retrospective case series. METHODS: All enquiries to the London centre of the National Poisons Information Service (NPIS) between December 1993 and March 1996 were screened for cases of MDMA use associated with hyponatraemia (serum sodium <130 mmol/l). History of fluid consumption, presenting features and subsequent clinical course were recorded. RESULTS: Seventeen patients, aged 15-26 years, were identified. Serum sodium levels ranged between 107 mmol/l and 128 mmol/l. In six patients, biochemical results were consistent with inappropriate secretion of antidiuretic hormone (SIADH). Analytical confirmation of MDMA ingestion was obtained in 10 patients. Ten patients were known to have ingested a large amount of non-alcoholic or alcoholic fluid. The clinical pattern was remarkably uniform, with initial vomiting and disturbed behaviour, followed in 11 patients by seizures. Drowsiness, a mute state and disorientation were observed for up to 3 days. Two patients died; 14 made a complete recovery. DISCUSSION: MDMA can cause life-threatening hyponatraemic encephalopathy when accompanied by excessive fluid ingestion. The mechanism involves inappropriate secretion of antidiuretic hormone.

***4-MTA: a new synthetic drug on the dance scene.***, Winstock AR, Wolff K, Ramsey J., Drug Alcohol Depend 2002 Jul 1;67(2):111-5.

4-MTA (p-methylthioamphetamine) is a new synthetic sulphur derivative of amphetamine that has been associated with six deaths since it was first identified in Europe in 1997. Sold as 'ecstasy' or 'Flatliners', the drug like MDMA is a potent serotonin releaser. Using a self-nominated sampling methodology we accessed over 1000 dance drug users through a magazine survey. Ten percent of respondents thought that they had used 4-MTA. Those with experience of 4-MTA tended to come from a sub-population of heavy 'ecstasy'-users. Responses to the effects of the drug were mixed, although about a quarter of those who believed that they had tried 4-MTA thought that they would use it again.

**E**ronic neurotoxic damage in ecstasy (MDMA) users. *Review of the current state of research.*, [Article in German], **Gouzoulis-Mayfrank E, Daumann J, Sass H.**, *Nervenarzt* 2002 May;73(5):405-21.

The popular dance drug ecstasy (3,4-methylenedioxymethamphetamine, or MDMA, and some analogues) causes selective and persistent neurotoxic damage of the central serotonergic system in laboratory animals. Serotonin plays a role in numerous functional systems in the CNS. Consequently, various abnormalities including psychiatric, vegetative, neuroendocrine, and cognitive disorders might be expected in humans following damage of the central serotonergic system. In recent years, the questions of possible functional disorders following ecstasy-induced neurotoxicity were addressed in several cross-sectional studies with drug users. In this review we summarize and evaluate the quality of design of these studies. Despite large methodological problems, evidence accumulates in favor of persisting brain damage in ecstasy users resulting in subtle cognitive deterioration. Findings of relatively low memory performance associated with heavy ecstasy use are highly consistent across different studies and user populations. In addition, low performance in tests of higher executive function were reported in some but not all studies. The important questions about progression, persistence, or reversibility of damage after long periods of abstinence have to be addressed in future studies with longitudinal design.

**Ecstasy-induced psychotic disorder: six-month follow-up study.**, **Landabaso MA, Iraurgi I, Jimenez-Lerma JM, Calle R, Sanz J, Gutierrez-Fraile M.**, *Eur Addict Res* 2002 Jun;8(3):133-40.

**OBJECTIVE:** To describe the psychiatric symptoms manifested by persons diagnosed for the first time as having ecstasy-induced psychotic disorder and to explore the evolution of their symptoms over a 6-month period.

**DESIGN:** Observational study with a 6-month follow-up. **METHOD:** The subjects studied were 32 ecstasy consumers who were treated at two drug-dependency outpatient centers for hallucinatory-delusional manifestations and who were diagnosed as having ecstasy-induced psychotic disorder according to DSM-IV criteria. For the assessment of the intensity of the syndrome and its follow-up, the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impression (CGI) were used at the outset and after 1, 3 and 6 months. All subjects received treatment with olanzapine. **RESULTS:** The treatment program was completed by 96.9% of the patients. At the baseline assessment, a high incidence of symptoms of a severe psychiatric disorder was observed. From the first month the psychotic symptoms (BPRS) were considerably reduced with treatment, with the most severe positive symptoms remitting in the first 3 months. The three assessment indicators (BPRS, HDRS and CGI) showed a statistically significant clinical reduction over the 6 months of the assessment period. Furthermore, no relevant side effects were noted. **CONCLUSIONS:** In its initial manifestations, a drug-induced psychotic syndrome includes marked symptoms meeting the criteria of a severe psychotic disorder, with the presence of considerable positive and negative symptoms. Olanzapine has been shown to be very effective in these situations and its use is suggested as first-choice therapy. Copyright 2002 S. Karger AG, Basel

**Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and gamma-hydroxybutyrate.**, **Smith KM, Larive LL, Romanelli F.**, *Am J Health Syst Pharm* 2002 Jun 1;59(11):1067-76.

The abuse of methylenedioxymethamphetamine (MDMA), flunitrazepam, ketamine hydrochloride, and gamma-hydroxybutyrate (GHB) is discussed. Club drugs are chemical substances used recreationally in social settings. Use is increasingly frequent among young people, especially during all-night dance parties. All four agents have been classified as controlled substances. MDMA ("ecstasy") is available as a tablet, a capsule, and a powder; formulations may contain many adulterants. MDMA increases the release of neurotransmitters. The desired effects are euphoria, a feeling of intimacy, altered visual perception, enhanced libido, and increased energy. The most common adverse effects are agitation, anxiety, tachycardia, and hypertension. More serious adverse effects include arrhythmias, hyperthermia, and rhabdomyolysis. Flunitrazepam is a potent benzodiazepine. At higher doses, the drug can cause lack of muscle control and loss of consciousness. Other adverse effects are hypotension, dizziness, confusion, and occasional aggression. Ketamine is a dissociative anesthetic used primarily in veterinary practice. It may be injected, swallowed, snorted, or smoked. Like phencyclidine, ketamine interacts with the N-methyl-D-aspartate channel. Analgesic effects occur at lower doses and amnesic effects at higher doses. Cardiovascular and respiratory toxicity may occur, as well as confusion, hostility, and delirium. GHB, a naturally occurring fatty acid derivative of gamma-aminobutyric acid, was introduced as a dietary supplement. Increasing doses progressively produce amnesia, drowsiness, dizziness, euphoria, seizures, coma, and death. Flunitrazepam, ketamine, and GHB have been used to facilitate sexual assault. Supportive care is indicated for most cases of club drug intoxication. The increasing abuse of MDMA, flunitrazepam, ketamine hydrochloride, and GHB, particularly by young people in

Equal settings such as clubs, should put health care professionals on guard to recognize and manage serious reactions.

***Is there a temporal correlation between substance abuse and psychosis in adolescents?***

[Article in German], Holtmann M, Becker K, Hartmann M, Schmidt MH., Z Kinder Jugendpsychiatr Psychother 2002 May;30(2):97-103.

OBJECTIVES: The temporal relationship between substance abuse and symptoms of psychosis in adolescent patients was examined. METHODS: The hospital records of all adolescent inpatients admitted to the Central Institute of Mental Health in Mannheim during the period from 1976-1997 with a first-time diagnosis of psychosis were examined retrospectively for evidence of co-morbid substance abuse. RESULTS: In 18 of a total of 165 psychotic patients, co-morbid substance abuse was present, whose frequency rose after 1988, with a renewed increase since 1996. Two of the 18 adolescents began taking drugs only after the appearance of the first symptoms of psychosis, in 13 others the abuse was already well established, while for the final three patients the onset of psychotic symptoms and substance abuse was congruent, occurring within the same month. A close temporal correlation between symptoms of psychosis and substance abuse was established for amphetamines (including ecstasy), LSD and excessive abuse of cannabis. CONCLUSIONS: Substance abuse constitutes a risk factor for the development of psychoses without, however, necessarily being a direct trigger of psychosis.

***Persisting Continuous Visual Perception Disorder in a Chronic MDMA ('Ecstasy') User.*** Passie T, Schneider U, Emrich HM. Department of Clinical Psychiatry and Psychotherapy, Medical School Hannover (Germany), Aust N Z J Psychiatry 2002 Feb;36(2):266-7. No abstract available.

***How Strong Is The Evidence That Brain Serotonin Neurons Are Damaged In Human Users Of Ecstasy?*** Kish SJ., Pharmacol Biochem Behav 2002 Apr;71(4):845-55.

Understanding the diverse functions of serotonin in the human brain can be obtained through examination of subjects having a lower than normal number of brain serotonin neurons. Behavioral abnormalities consistent with brain serotonergic damage have been reported in some polydrug users who also use the neurotoxin ecstasy (methylenedioxymethamphetamine, MDMA). This review evaluates the evidence from neuroimaging studies that brain serotonergic damage is a feature of human users of ecstasy. To date, neuroimaging studies designed to establish whether levels of brain serotonin neurons are lower than normal in ecstasy users have employed radioligands that bind to one component of the serotonin neuron, the serotonin transporter (SERT). Because these studies are methodologically flawed in terms of reliability or validity of the SERT measurement and appear to have employed polydrug users, no definitive information is yet available on the question of ecstasy toxicity to human brain serotonin neurons. Until these issues are resolved, it cannot be assumed that ecstasy exposure represents a chronic serotonin deficiency condition.

***Recreational Ecstasy/MDMA, The Serotonin Syndrome, and Serotonergic Neurotoxicity.*** Parrott AC., Pharmacol Biochem Behav 2002 Apr;71(4):837-44.

The ring-substituted amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) or "Ecstasy" is widely used a recreational drug. It stimulates the release and inhibits the reuptake of serotonin (5-HT) and other neurotransmitters such as dopamine to a lesser extent. The acute boost in monoamine activity can generate feelings of elation, emotional closeness, and sensory pleasure. In the hot and crowded conditions of raves/dances, mild versions of the serotonin syndrome often develop, when hyperthermia, mental confusion, and hyperkinesia predominate. Rest in a cooler environment generally reverses these problems, although they can develop into medical emergencies, which occasionally prove fatal. This acute serotonergic overactivity is exacerbated by the high ambient temperatures, overcrowding (aggregate toxicity), and use of other stimulant drugs. The on-drug experience is generally followed by negative moods, with 80--90% of weekend Ecstasy users reporting 'midweek blues', due probably to monoaminergic depletion. Single doses of MDMA can cause serotonergic nerve damage in laboratory animals, with repeated doses causing extensive loss of distal axon terminals. Huether's explanatory model for this 5-HT neurotoxicity will be briefly described. There is an increasing body of evidence for equivalent neuropsychobiological damage in humans. Abstinent regular Ecstasy users often show: reduced cerebrospinal 5-HIAA, reduced density of 5-HT transporters, blunted response to a fenfluramine challenge, memory problems, higher cognitive deficits, various psychiatric disorders, altered appetite, and loss of sexual interest. Functional deficits may remain long after drug use has ceased and are consistent with serotonergic axonal loss in higher brain regions.



***Pneumomediastinum as a Complication of Recreational Ecstasy Use.***, [Article in French] **Le Floch AS, Lapostolle F, Danhiez F, Adnet F.**, Ann Fr Anesth Reanim 2002 Jan;21(1):35-7.

Ecstasy recreational use dramatically increased during the last decade in France. Multiple complications associated with ecstasy consumption have been reported. We describe an exceptional case of pneumomediastinum related to ecstasy recreational use. The patient was a 19-year old patient whose medical history was significant for asthma and was a moderate tobacco smoker. He reported regular ecstasy recreational use. He presented at the emergency unit for chest pain and cough, 48 hours after the ingestion of three tablets of ecstasy and the inhalation of three other tablets. Blood pressure was 90/60 mmHg, pulse rate was 120 per minute, respiratory rate was 32 per minute and pulse oximetry was 93%. Neck emphysema was noted. Chest radiograph and scanner diagnosed pneumomediastinum. Outcome was favorable with symptomatic treatment and the patient was discharged home eight days later. Pneumomediastinum is an exceptional complication after ecstasy recreational use. Physician should be aware of the risk of such event.

***Pneumomediastinum Following Ecstasy (methylenedioxyamphetamine, MDMA) Ingestion In Two People At The Same 'Rave'.***, **Rejali D, Glen P, Odom N.**, J Laryngol Otol 2002 Jan;116(1):75-6.

Ecstasy is a class A controlled drug often consumed by the young population for recreational purposes. Documented complications of its use include hyperpyrexia, disseminated intravascular coagulation (DIC), renal failure and rhabdomyolysis. We report on two patients who developed pneumomediastinum after Ecstasy abuse. Both patients obtained and consumed the drug at the same establishment and presented to the same hospital within half an hour. The possible pathogenesis of this complication are discussed and the literature reviewed. Pneumomediastinum should be recognized as a possible complication of Ecstasy use. Conservative management is appropriate.

***"Ecstasy"-Induced Hepatitis In An Active Duty Soldier***", **Hwang I, Daniels AM, Holtzmuller KC.**, Mil Med 2002 Feb;167(2):155-6.

3,4-Methylenedioxymethamphetamine, or "Ecstasy," is a drug commonly used at "rave" parties to heighten energy and intimacy. Although its complications have been well described in Europe, including less common side effects such as hepatic failure and rhabdomyolysis, physicians in the United States have less experience with this drug because of the shorter duration of its use in this country. We present a case of an active duty soldier who was admitted for acute hepatitis secondary to Ecstasy ingestion and describe its proposed pathophysiology. We believe that with the increased use of Ecstasy in the United States, especially among younger patients, including soldiers, military physicians will need to be more familiar with this potentially deadly drug.

***Characteristics of Pregnant Women Who Use Ecstasy (3, 4-methylenedioxyamphetamine).***, **Ho E, Karimi-Tabesh L, Koren G.**, Neurotoxicol Teratol 2001 Nov-Dec;23(6):561-7.

To determine the characteristics of pregnant women who use Ecstasy (3,4-methylenedioxyamphetamine, MDMA), and to identify reproductive risk factors associated with this group of women. Prospective, observational study. Pregnant women who have contacted the Motherisk Alcohol and Substance Use Helpline at The Hospital for Sick Children, in Toronto, about exposure to drugs, chemicals, infection or radiation. All inquiries from December 1998 to October 2000 concerning pregnant women who reported use of MDMA, and control cases of women not exposed to MDMA selected within the same week of the MDMA callers. Age, maternal demographics, pregnancy characteristics, patterns of alcohol, tobacco, and illicit drug use, psychological/emotional status, sexually transmitted disease, MDMA method and pattern of use, and adverse drug reactions after ingestion of MDMA. The 132 pregnant women who used MDMA were significantly younger (mean 23.2 vs. 31.2 years,  $P<.0001$ ), and had more unplanned pregnancies compared to 122 pregnant nonusers (84.2% vs. 54.3%,  $P<.05$ ). MDMA users were also more likely to be single (57.0% vs. 18.3%,  $P<.001$ ), and to be White (82.2% vs. 56.0%,  $P<.05$ ). Comparably more MDMA users smoked cigarettes (53.8% vs. 19.7%,  $P<.0001$ ), drank alcohol (66.4% vs. 37.3%,  $P<.0001$ ), and had significantly more episodes of binge drinking during pregnancy (mean 2.12 vs. 0.05,  $P<.001$ ). Illicit drugs such as cocaine, marijuana, methamphetamine, ketamine, gamma-hydroxy butyrate, and psilocybin were used more frequently among the MDMA sample. Over a third of MDMA users reported psychiatric/emotional problems, including 6.5% with a clinically diagnosed condition that was being treated with medication and/or counseling. Pregnant women who use MDMA tend to be young, single, and report psychological morbidity, and have a clustering of risk factors that may compromise the pregnancy and fetus. Smoking, heavy alcohol intake, and polydrug use, combined with a higher than expected rate of unplanned pregnancies, increases the risk of fetal

Exposure to potentially harmful substances. It is important to account for the range of confounding risk factors among women who use MDMA in order to define possible direct effects of MDMA in pregnancy

***Ecstasy Use: Cognitive Deficits Related To Dosage Rather Than Self-Reported Problematic Use Of The Drug., Fox HC, Parrott AC, Turner JJ.*** J Psychopharmacol 2001 Dec;15(4):273-81.

Previous research has shown drug-free Ecstasy users to demonstrate selective cognitive impairment. However, there seems to be a degree of individual variation in the occurrence of such deficits. The present study aimed to assess whether these cognitive deficits are related to an awareness of problematic Ecstasy use, or to past drug dosage. Twenty regular Ecstasy users who reported experiencing Ecstasy-related problems were compared with 20 Ecstasy users who had not reported any previous problems. The two groups displayed similar past histories in relation to a range of illicit drugs, and were divided into low, medium and high users. The controls comprised 20 illicit recreational drug users who had never taken Ecstasy. Executive task measures comprised the Tower of London (TOL), the Wisconsin Card Sorting Task (WCST) and spatial working memory. Immediate and delayed word recall, matched verbal recognition and recall and simple reaction time were also included. Both Ecstasy groups performed significantly worse than controls on two executive measures: TOL planning time and spatial working memory score. There were no differences in cognitive impairment between the Ecstasy users who complained of problems and those who did not. In both groups, decrement on executive tasks was demonstrated as a function of previous drug dose. The study confirms that heavy Ecstasy polydrug use may culminate in selective executive deficits. It also demonstrates that two differently self-perceived Ecstasy groups showed similar cognitive impairment, despite only one group complaining of problems. Because all Ecstasy participants also consumed a range of other illicit drugs, the results are reflective of Ecstasy polydrug use in individuals who use Ecstasy as a drug of preference.

***Ecstasy: Dangers And Controversies., Pham JV, Puzantian T.*** Pharmacotherapy 2001 Dec;21(12):1561-5.

Ecstasy is a recreational drug that is increasing in popularity, particularly in young adolescents. Its appeal involves its euphoric effects and a feeling of empathy for others (hence the nickname "hug drug"). This appeal may be furthered by a misleading and anecdotal perception of safety. Cases of adverse effects, toxic reactions, and fatalities are increasingly being reported in the medical literature, as well as in the popular press. Adverse effects include hyperthermia, seizures, cardiac abnormalities, and hyponatremia. Long-term Ecstasy use may result in serotonin terminal degeneration and depletion, which may result in psychiatric and cognitive sequelae. Controversy surrounds the legalization of Ecstasy for medicinal purposes.

***A Comprehensive Review of MDMA and GHB: Two Common Club Drugs., Teter CJ, Guthrie SK.*** Pharmacotherapy 2001 Dec;21(12):1486-513.

"Club drugs" have become alarmingly popular. The use of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) and gamma-hydroxybutyrate (GHB), in particular, has increased dramatically from 1997-1999. The pharmacokinetics of MDMA and GHB appear to be nonlinear, making it difficult to estimate a dose-response relationship. The drug MDMA is an amphetamine analog with sympathomimetic properties, whereas GHB is a gamma-aminobutyric acid analog with sedative properties. Symptoms of an MDMA toxic reaction include tachycardia, sweating, and hyperthermia. Occasional severe sequelae include disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure. Treatment includes lowering the body temperature and maintaining adequate hydration. Symptoms of GHB intoxication include coma, respiratory depression, unusual movements, confusion, amnesia, and vomiting. Treatment includes cardiac and respiratory support. Because of the popularity of these agents and their potentially dangerous effects, health care professionals must be familiar with these substances and the treatment options for patients who present with symptoms of a toxic reaction.

***Increasing MDMA Use Among College Students: Results of a National Survey., Strote J, Lee JE, Wechsler H.*** J Adolesc Health 2002 Jan;30(1):64-72.

PURPOSE: To examine the prevalence and changing patterns of ecstasy use among college students, and to determine characteristics, associated behaviors, and interests of ecstasy users. METHODS: The study analyzes data regarding ecstasy use and related behaviors from the 1997 and 1999 Harvard School of Public Health College Alcohol Study. This is a survey of a nationally representative sample of over 14,000 college students at 119 U.S. four-year colleges. Changes in self-reported annual ecstasy use were examined, and lifestyle and high-risk behaviors associated with Ecstasy use were identified. Data were analyzed using 2 x 2 Chi-square tests and multiple

istic regression fitted by the generalized estimating equations (GEE). RESULTS: The prevalence of past year ecstasy use rose from 2.8% to 4.7% between 1997 and 1999, an increase of 69%. This increase was observed across nearly all subgroups of student and college type. A smaller sample of ten colleges revealed that the increase continued in 2000. Ecstasy users were more likely to use marijuana, engage in binge drinking, smoke cigarettes, have multiple sexual partners, consider arts and parties as important, religion as less important, spend more times socializing with friends, and spend less times studying. Unlike other illicit drug users, ecstasy users were not academic underachievers and their satisfaction with education was not different from that of non-ecstasy users. CONCLUSION: Ecstasy use is a high-risk behavior among college students which has increased rapidly in the past decade.

***Ecstasy (MDMA): Are The Psychological Problems Associated With Its Use Reversed By Prolonged Abstinence?***, Morgan MJ, McFie L, Fleetwood H, Robinson JA., Psychopharmacology (Berl) 2002 Jan;159(3):294-303.

RATIONALE: Chronic, regular recreational use of ecstasy (MDMA) is associated with psychopathology, elevated behavioural impulsivity and persistent impairment of memory performance. OBJECTIVE: The aim of the present study was to investigate which of these sequelae persist after at least 6 months of abstinence from ecstasy.

METHODS: Four groups of participants were compared: 18 current regular recreational ecstasy users, 15 ex-regular ecstasy users who had abstained from using the drug for an average of 2 years, 16 polydrug users who had never taken ecstasy and 15 drug-naïve controls. RESULTS: There were no significant group differences in age, education level, or pre-morbid intelligence and, generally, the use of illicit drugs other than ecstasy was not significantly different among the three drug-using groups. Both current and ex-ecstasy users exhibited elevated psychopathology and behavioural impulsivity compared with polydrug users and drug-naïve controls, but current ecstasy users exhibited a broader range of psychopathology than ex-users. Both groups of ecstasy users also exhibited impaired working memory and verbal recall performance compared with drug-naïve controls, but only ex-users exhibited impaired verbal recall relative to polydrug users. Regression analysis indicated that psychopathology was primarily predicted by the extent of previous consumption of cannabis rather than ecstasy, whereas the majority of the cognitive deficits were only predicted by the extent of previous ecstasy use.

CONCLUSIONS: Selective impairments of neuropsychological performance associated with regular ecstasy use are not reversed by prolonged abstinence. This is consistent with evidence that ecstasy has potent and selective neurotoxic effects on brain serotonergic systems in humans.

***3,4-Methylenedioxymethamphetamine (Ecstasy) and Alcohol Interactions in Humans: Psychomotor Performance, Subjective Effects, and Pharmacokinetics.***, Hernandez-Lopez C, Farre M, Roset PN, Menoyo E, Pizarro N, Ortuno J, Torrens M, Cami J, de La Torre R., J Pharmacol Exp Ther 2002 Jan;300(1):236-44

3,4-Methylenedioxymethamphetamine (MDMA) is frequently consumed in association with alcohol. The effect of this combination in humans has not been previously investigated. Nine male healthy volunteers received single oral doses of 100 mg of MDMA plus 0.8 g/kg ethanol, 100 mg of MDMA, 0.8 g/kg of ethanol, and placebo in a double blind, double dummy, randomized crossover trial. Measurements included psychomotor performance, subjective effects, and pharmacokinetics. Plasma concentrations of MDMA showed a 13% increase after the use of alcohol, whereas plasma concentrations of alcohol showed a 9 to 15% decrease after MDMA administration. The MDMA-alcohol combination induced longer lasting euphoria and well being than MDMA or alcohol alone. MDMA reversed the subjective sedation induced by alcohol but did not reduce drunkenness feelings. MDMA did not reverse the actions of alcohol on psychomotor abilities. Combined use of MDMA and alcohol causes dissociation between subjective and objective sedation. Subjects may feel euphoric and less sedated and might have the feeling of doing better, but actual performance ability continues to be impaired by the effect of alcohol. Confirmation of these findings in further studies will be highly relevant in terms of road safety.

***Amnesic Syndrome and Severe Ataxia Following the Recreational Use of 3,4-methylene-dioxymethamphetamine (MDMA, 'Ecstasy') and other Substances.***, Kopelman MD, Reed LJ, Marsden P, Mayes AR, Jaldow E, Laing H, Isaac C., Neurocase 2001;7(5):423-432.

A 26-year-old woman suffered disseminated intravascular coagulation (DIC) and a brief respiratory arrest following recreational use of 3,4-methylene-dioxymethamphetamine (MDMA; 'ecstasy'), together with amyl nitrate, lysergic acid (LSD), cannabis and alcohol. She was left with residual cognitive and physical deficits, particularly severe anterograde memory disorder, mental slowness, severe ataxia and dysarthria. Follow-up

Investigations have shown that these have persisted, although there has been some improvement in verbal recognition memory and in social functioning. Magnetic resonance imaging and quantified positron emission tomography investigations have revealed: (i) severe cerebellar atrophy and hypometabolism accounting for the ataxia and dysarthria; (ii) thalamic, retrosplenial and left medial temporal hypometabolism to which the anterograde amnesia can be attributed; and (iii) some degree of fronto-temporal-parietal hypometabolism, possibly accounting for the cognitive slowness. The putative relationship of these abnormalities to the direct and indirect effects of MDMA toxicity, hypoxia and ischaemia is considered.

***Personality dimensions and psychopathological profiles of Ecstasy users.* Dughiero G, Schifano F, Forza G., Hum Psychopharmacol 2001 Dec;16(8):635-639.**

Only limited information is available with respect to personality traits and the psychopathological characteristics of Ecstasy users. To shed some light on the issue, we compared a group of 43 Ecstasy consumers (made up of both 'experimenters', those who took  $\leq 27.5$  tablets in their lifetime, and 'abusers', those who took larger amounts of the drug) with a composite control group of 77 subjects (made up of drug-free people, cannabis users and users of illicit drugs other than Ecstasy). Three instruments were used: the Questionnaire for the Assessment of the Use of Entactogenic Drugs (to assess modalities and characteristics of Ecstasy use); the Cloninger Tridimensional Personality Questionnaire (which measures harm avoidance, reward dependence and novelty seeking) and the SCL-90 (which measures 10 different psychiatric variables). The Ecstasy consumer group subjects showed higher novelty seeking scores than the controls ( $p < 0.001$ ), and Ecstasy experimenters showed lower harm avoidance scores than the abusers ( $p = 0.029$ ), but values of both reward dependence and harm avoidance dimensions were associated with sex. On the SCL-90, Ecstasy users showed higher scores than the controls on the obsession-compulsion ( $p = 0.004$ ), phobic anxiety ( $p = 0.037$ ), psychoticism ( $p = 0.005$ ) and sleep disturbances ( $p = 0.046$ ) subscales. However, many of the SCL-90 subscale results were associated with sex, and only the psychoticism values seemed to suggest a clinical condition. The main finding of this study is that high novelty seeking scores are characteristic of Ecstasy consumers: The propensity to look selectively for novelties could possibly act as a predisposing factor for Ecstasy abuse itself. Copyright 2001 John Wiley & Sons, Ltd.

***Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria.* Cottler LB, Womack SB, Compton WM, Ben-Abdallah A., Hum Psychopharmacol 2001 Dec;16(8):599-606.**

As part of an ongoing National Institute on Drug Abuse study on the reliability of DSM substance use disorders, 173 adolescents and young adults have been interviewed to date with the CIDI-Substance Abuse Module (SAM) to determine use and abuse of and dependence on 'club drugs' and other substances. Respondents are recruited from a substance abuse program, high school ads, college dorm flyers, the internet and chain referral. Retest interviews after 5 days determined the reliability of responses. Ecstasy use was reported by 52 respondents (30%); of these users 52% were female and 23% were non-white. Nearly all users (94%) reported recent Ecstasy use. Among Ecstasy users, 'continuing to use despite knowledge of physical or psychological harm' was the most prevalent dependence criterion (63%), with excellent retest agreement ( $\kappa = 0.66$ ). Withdrawal (59%) and tolerance (35%) were also commonly reported dependence criteria. Hazardous use was the most commonly reported abuse symptom. Most surprising were the rates of Ecstasy use disorders: 43% met DSM-IV criteria for dependence; 34% met criteria for abuse; only 23% met neither. This is the first effort to assess the reliability of Ecstasy abuse and dependence, and the first to determine abuse and dependence using criteria specific to Ecstasy. The importance of additional studies and the relevance of such work to DSM-V are discussed. Copyright 2001 John Wiley & Sons, Ltd.

***3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and driving impairment.* Logan BK, Couper FJ., J Forensic Sci 2001 Nov;46(6):1426-33.**

3,4-Methylenedioxymethamphetamine, or MDMA, is increasing in popularity in the United States as a drug of abuse. It has stimulant and empathogenic mood altering properties with the potential to affect psychomotor skills and impact driving. This report reviews the literature relating to the relevant psychomotor effects of the drug, the relationship between dose and blood concentrations, and studies and case reports on specific effects of the drug on driving. The latter reports include both laboratory driving simulator studies and anecdotal reports, and case series. We also report details of eighteen cases of apparent MDMA impaired driving, including six drivers whose blood

Found positive for MDMA alone. Most subjects displayed muscle twitching and body tremors, dilated pupils, slow pupillary reaction to light, elevated pulse and blood pressure, lack of balance and coordination, and most were perspiring profusely. Five of the six subjects were given field sobriety tests (one leg stand, walk and turn test), and all five performed poorly. There was no clear correlation between the blood concentration of MDMA and the specific demeanor of the subject. These findings are consistent with other reports, and lead to the conclusion that MDMA use is not consistent with safe driving, and that impairment of various types may persist for a considerable time after last use.

***Executive function in abstinent MDMA ('ecstasy') users., Zakzanis KK, Young DA., Med Sci Monit 2001 Nov-Dec;7(6):1292-8.***

**BACKGROUND:** Methylenedioxyamphetamine (MDMA, or 'Ecstasy') is a growingly popular recreational drug of abuse that is known to damage brain serotonergic neurons in animals and possibly humans. Few functional consequences of MDMA-induced serotonin neurotoxicity have been identified, either in animals or humans. This study sought to determine whether individuals with a history of MDMA use showed evidence of executive dysfunction.**MATERIAL AND METHODS:** Two groups of young individuals were compared: 24 abstinent MDMA users who had taken MDMA at least once and 24 controls who had never taken MDMA. Each MDMA user completed a questionnaire regarding the characteristics of their MDMA use and all participants completed a questionnaire regarding other recreational drug experience. The Behavioural Assessment of the Dysexecutive Syndrome (BADS) was used to measure executive function in all participants.**RESULTS:** Evidence of impairment was found on two subtests of the BADS and in terms of a Total Profile Score. In addition, several significant product moment correlations were found suggesting that increases in MDMA consumption may relate to more pronounced impairment in executive function.**CONCLUSIONS:** Accordingly, MDMA use may be associated with deficits in executive function.

***Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxyamphetamine (MDMA or 'ecstasy'): preliminary findings., Reneman L, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeten GJ, Booij J., Arch Gen Psychiatry 2001 Oct;58(10):901-6***

**BACKGROUND:** Although the popular drug 3,4-methylenedioxyamphetamine (MDMA or "ecstasy") has been shown to damage brain serotonin (5-HT) neurons in animals, the fate and functional consequences of 5-HT neurons after MDMA injury are not known in humans. We investigated the long-term effects of MDMA use on cortical 5-HT neurons in humans and memory function, because brain 5-HT has been implicated in memory function. **METHODS:** Twenty-two recent MDMA users, 16 ex-MDMA users who had stopped using MDMA for more than 1 year, and 13 control subjects. The effects of MDMA use on cortical 5-HT neurons was studied by means of single-photon emission computed tomography with iodine 123-labeled 2beta-carbomethoxy-3beta-(4-iodophenyl) tropane ([<sup>123</sup>I]beta-CIT) by quantification of brain 5-HT transporter densities. Verbal memory performance was assessed with the Rey Auditory Verbal Learning Test. **RESULTS:** Mean cortical [<sup>123</sup>I]beta-CIT-labeled 5-HT transporter density was significantly lower in recent MDMA users than in controls (1.17 vs. 1.28 [-9%]) but not in ex-MDMA users (1.24 vs. 1.28 [-3%]). Recent and ex-MDMA users recalled significantly fewer words than did controls on the immediate recall (47.0 and 48.0 vs 60.0, respectively; P =.001) as well as the delayed recall (9.8 and 10.1 vs. 13.1, respectively; P =.003). Greater use of MDMA was associated with greater impairment in immediate verbal memory. However, memory performance was not associated with [<sup>123</sup>I]beta-CIT binding to cortical 5-HT transporters or duration of abstinence from MDMA. **CONCLUSION:** The present study suggests that, while the neurotoxic effects of MDMA on 5-HT neurons in the human cortex may be reversible, the effects of MDMA on memory function may be long-lasting.

***Heroin smoking by "chasing the dragon" in young opiate users in Ireland: stability and associations with use to "come down" off "Ecstasy"., Gervin M, Hughes R, Bamford L, Smyth BP, Keenan E., J Subst Abuse Treat 2001 Jun;20(4):297-300.***

We explored the frequency of commencing opiate use by "chasing the dragon" to "come down" off Ecstasy and the stability of heroin smoking in young opiate takers by assessing 102 subjects in Dublin using a semistructured interview. Ninety-two subjects had used Ecstasy. Of these, 68 reported "chasing" to "come down" off Ecstasy at

One point in their history and were found to have used Ecstasy more frequently and in larger amounts. Thirty-six reported that their first experience of using opiates was to "come down" off Ecstasy, 28 citing this as their main reason for commencement. Eighty-six of the 102 commenced opiates by "chasing" heroin, 61 of whom progressed to injecting after a mean of 2.9 years. This was associated with starting illicit drug use earlier, starting heroin earlier, and a history of using Ecstasy. Implications for service planners in developing responses to illicit drug use among adolescents are discussed.

***Three Cases of Fatal Paramethoxyamphetamine Overdose., Martin TL.,*** J Anal Toxicol., 2001 Oct 25(7):649-51. Two recent cases of death due to paramethoxyamphetamine (PMA), a methoxylated phenylethylamine derivative, are described and compared with a previous PMA death that occurred in this province in 1985. The deceased were 18 or 19 years of age and were reported to have ingested either methylenedioxyamphetamine (MDMA, Ecstasy) or methylenedioxyamphetamine (MDA) prior to their deaths. Concentrations of PMA were measured in both peripheral and heart blood samples using gas chromatography equipped with a nitrogen-phosphorus detector. PMA results in the most recent cases were 0.6 mg/L and 1.3 mg/L in the peripheral blood samples, and corresponding heart blood samples were 0.7 mg/L and 2.3 mg/L, respectively. In the 1985 case, the femoral blood concentration was 0.6 mg/L, and the heart blood concentration was 0.8 mg/L. Significant differences between heart and peripheral blood concentrations were observed in two of the three cases, which may indicate the potential for postmortem redistribution of PMA.

***Fatalities Caused by the MDMA-related Drug Paramethoxyamphetamine (PMA)., Kraner JC, McCoy DJ, Evans MA, Evans LE, Sweeney BJ,*** J Anal Toxicol., 2001 Oct;25(7):645-648.

The past several years have seen a marked increase in the recreational use of 3,4-methylenedioxyamphetamine (MDMA) or "Ecstasy". MDMA use is especially common among young people participating in dance parties called "raves". Paramethoxyamphetamine (PMA) exhibits both structural and pharmacological similarity to MDMA. It may, however, be a more potent central stimulant, particularly in its effects on serotonergic transmission. Several fatalities from PMA have been reported in Australia, and here we report three recent fatalities that occurred in the midwestern United States in which each of the decedents believed that they were ingesting MDMA. Symptoms observed included agitation and bruxism, progressing to severe hyperthermia, convulsions, and hemorrhage. Blood was screened for drugs of abuse by enzyme immunoassay with the presence of amphetamines indicated in each case. Confirmation and quantitation for amphetamines was performed by gas chromatography-mass spectrometry. The deceased, two males ages 19 and 24 and a female age 18, had postmortem blood PMA concentrations of 1.07, 0.60, and 1.90 mg/L, respectively. PMA is not a contaminant of MDMA, and no MDMA was found in any of these cases. The primary metabolite of PMA is produced by O-demethylation to 4-hydroxyamphetamine, a reaction catalyzed by cytochrome P450 2D6. This enzyme is noted to be genetically polymorphic. Those with the "slow metabolizer" phenotype may be likely to have higher peak blood concentrations of PMA. Whether any of the decedents described herein were of the slow metabolizer phenotype is not known. Several groups have advocated the onsite use of the Marquis Test for the purpose of pill screening in efforts to distinguish PMA from MDMA. A dark purple is consistent with MDMA, whereas PMA imparts no color change in this test. PMA is often in the form of a white pill with a Mitsubishi symbol on one side. This design has been identified in at least one of these fatalities.

***Ecstasy Pill Testing: Harm Minimization Gone Too Far?, Winstock AR, Wolff K, Ramsey J.,*** Addiction 2001 Aug;96(8):1139-48.

Harm reduction has become the focus of public health initiatives and therapeutic intervention in the management of dependent drug use over the last 20 years. The last decade has seen such approaches being extended to recreational drug use. Most harm reduction initiatives have aimed to inform users about risks and ways of minimizing risk. The concept of providing illicit drug users with quality assessment of their chosen drug is one possible harm reduction intervention that until recently has received little attention. In response to well-publicized 'ecstasy'-related deaths organizations in some European countries and the United States have chosen to provide a 'pill testing service' for users. There are two broad categories of pill testing offered. Simple colour reagent test kits (Marquis Reagent and colour charts) form the most widely used on-site pill testing method. Less frequently, but more accurately, laboratory personnel with access to sophisticated chromatographic equipment (high performance liquid chromatography (HPLC) or gas chromatography-mass spectrometry (GC-MS)) may provide analysis of a pill. Pill testing kits have been advocated as a 'tool to protect yourself against the polluted XTC market'. We refute this line

Reasoning. Of the different tests only techniques such as GC-MS can identify satisfactorily the psychoactive constituents present in ecstasy pills. Colour tests based on an interpretation of a colour response in the presence of a drug are, at best, subjective. Pill testing of any description does not guarantee safety, or protect the consumer against individual responses to pills. At best it gives an artificial 'shine of safety' to a group of diverse drugs that remain both illicit and potentially harmful. Other simpler harm reduction mechanisms are likely to be more effective.

***The Pharmacology and Toxicology of "Ecstasy" (MDMA) and Related Drugs., Kalant H., CMAJ 2001 Oct 2;165(7):917-28.***

"Ecstasy" (MDMA) and related drugs are amphetamine derivatives that also have some of the pharmacological properties of mescaline. They have become popular with participants in "raves," because they enhance energy, endurance, sociability and sexual arousal. This vogue among teenagers and young adults, together with the widespread belief that "ecstasy" is a safe drug, has led to a thriving illicit traffic in it. But these drugs also have serious toxic effects, both acute and chronic, that resemble those previously seen with other amphetamines and are caused by an excess of the same sympathomimetic actions for which the drugs are valued by the users. Neurotoxicity to the serotonergic system in the brain can also cause permanent physical and psychiatric problems. A detailed review of the literature has revealed over 87 "ecstasy"-related fatalities, caused by hyperpyrexia, rhabdomyolysis, intravascular coagulopathy, hepatic necrosis, cardiac arrhythmias, cerebrovascular accidents, and drug-related accidents or suicide. The toxic or even fatal dose range overlaps the range of recreational dosage. The available evidence does not yet permit an accurate assessment of the size of the problem presented by the use of these drugs.

***Electrophysiological Evidence of Serotonergic Impairment in Long-term MDMA ("Ecstasy") Users., Croft RJ, Klugman A, Baldeweg T, Gruzelier JH., Am J Psychiatry, 2001 Oct;158(10):1687-92.***

"Ecstasy," or 3,4-methylenedioxymethamphetamine (MDMA), causes long-term impairment to the serotonin (5-HT) system in rats, dogs, and nonhuman primates. 5-HT dysfunction has also been observed in human recreational users of the drug, but whether 5-HT dysfunction in humans is caused by MDMA has not been established, since dysfunction may have preceded MDMA exposure. This ambiguity about causation is particularly important in MDMA research, because 5-HT deficiency is a predictor of risky behavior. METHOD: The 5-HT function of 22 long-term MDMA users was compared to that of 20 drug-naïve comparison subjects and 19 cannabis users. 5-HT function was assessed with the intensity dependence paradigm, a tool that measures 5-HT-related attenuation of neural response to auditory stimuli (measured with EEG). RESULTS: Long-term MDMA users exhibited 5-HT dysfunction, relative to both cannabis users and drug-naïve comparison subjects. This dysfunction was related to total MDMA consumption (after removing the effect of frequency of use) but not to frequency of use (after removing the effect of total consumption). CONCLUSIONS: These data show that 5-HT dysfunction occurs in MDMA users, is related to users' MDMA consumption, and is independent of cannabis use. The results do not suggest that self-medication explains this relationship, because the deficit was related to total MDMA consumption but not frequency of consumption. The results are thus consistent with the thesis that MDMA consumption causes 5-HT impairment in humans.

***Former Chronic Methylenedioxymethamphetamine (MDMA or ecstasy) Users Report Mild Depressive Symptoms., MacInnes N, Handley SL, Harding GF., J Psychopharmacol, 2001 Sep;15(3):181-6.***

Previous work has indicated recreational use of methylenedioxymethamphetamine (MDMA or ecstasy) is associated with elevated scores on self-report measures of depression. We sought to examine the long-term effects of consumption on depression in a group of individuals who had consumed large quantities of the drug in the past, but were now leading relatively drug free lives. Respondents to this study (n = 29) had consumed an average of 1.5 ecstasy tablets in the last month, 8.4 in the last 6 months and 23.3 in the last 12 months. The estimated total consumed was 527 tablets, indicating that these respondents were indeed former chronic users of the drug. None of the respondents had consumed ecstasy in the last 14 days. Levels of depression (Beck's Depression Inventory) were significantly (p < 0.01) elevated compared to a matched non-drug using control group. Within the group of former chronic users, these levels of depression were not significantly affected by current use of alcohol, cannabis or amphetamine, but were positively correlated with an external locus of control (p < 0.05), infrequent but severe- (p < 0.05) and frequent but mild- (p < 0.005) self-report measures of life stress. Multiple regression indicated that levels of frequent but mild life stress (p < 0.005) and the quantity of ecstasy tablets respondents consumed over a 12-h period (p < 0.05) were the only variables that were significant predictors of self-reported levels of depression. The

Results of this study indicate that former chronic ecstasy users report higher levels of depression than their matched controls.

***Effects of Ecstasy (MDMA) on the Brain in Abstinent Users: Initial Observations with Diffusion and Perfusion MR Imaging., Reneman L, Majoie CB, Habraken JB, den Heeten GJ.,*** Radiology 2001 Sep;220(3):611-7.

To evaluate the effects of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) on the human brain by using diffusion and perfusion magnetic resonance (MR) imaging. Eight abstinent ecstasy users and six ecstasy nonusers underwent diffusion and perfusion MR imaging. Apparent diffusion coefficient and relative cerebral volume maps were reconstructed. Differences in apparent diffusion coefficient values and relative cerebral volume ratios between the groups were analyzed with the Mann-Whitney-Wilcoxon test. The relationship between apparent diffusion coefficient and relative cerebral volume and the extent of previous ecstasy use was investigated with Spearman rank correlation. RESULTS: Apparent diffusion coefficient values ( $0.84$  vs  $0.65 \times 10^{-5}$  cm<sup>2</sup>/sec,  $P < .025$ ) and relative cerebral volume ratios ( $1.22$  vs  $1.01$ ,  $P < .025$ ) were significantly higher in the globus pallidus of ecstasy users compared with nonusers, respectively. Increases in pallidal relative cerebral volume were positively correlated with the extent of previous use of ecstasy ( $\rho = 0.73$ ,  $P < .04$ ). CONCLUSION: Ecstasy use is associated with tissue changes in the globus pallidus. These findings are in agreement with findings in case reports, suggesting that the globus pallidus is particularly sensitive to the effects of ecstasy.

***Understanding Reasons for Drug Use Amongst Young People: A Functional Perspective., Boys A, Marsden J, Strang J.,*** Health Educ Res, 2001 Aug;16(4):457-69.

This study uses a functional perspective to examine the reasons young people cite for using psychoactive substances. The study sample comprised 364 young poly-drug users recruited using snowball-sampling methods. Data on life-time and recent frequency and intensity of use for alcohol, cannabis, amphetamines, ecstasy, LSD and cocaine are presented. A majority of the participants had used at least one of these six drugs to fulfil 11 of 18 measured substance use functions. The most popular functions for use were using to: relax (96.7%), become intoxicated (96.4%), keep awake at night while socializing (95.9%), enhance an activity (88.5%) and alleviate depressed mood (86.8%). Substance use functions were found to differ by age and gender. Recognition of the functions fulfilled by substance use should help health educators and prevention strategists to make health messages about drugs more relevant and appropriate to general and specific audiences. Targeting substances that are perceived to fulfil similar functions and addressing issues concerning the substitution of one substance for another may also strengthen education and prevention efforts.

***Drugs and the Dance Music Scene: A Survey of Current Drug Use Patterns Among a Sample of Dance Music Enthusiasts in the UK., Winstock AR, Griffiths P, Stewart D.,*** Drug Alcohol Depend 2001 Sep 1;64(1):9-17.

This study explores the utility of a self-completion survey method to quickly and cheaply generate information on patterns and trends among regular "recreational" drug consumers. Data is reported here from 1151 subjects accessed through a dance music publication. In keeping with previous studies of drug use within the dance scene polysubstance use was the norm. Many of those reporting use of "ecstasy" were regularly using multiple tablets often consumed in combination with other substances thus exposing themselves to serious health risks, in particular the risk of dose related neurotoxic effects. Seventy percent were drinking alcohol at hazardous levels. Subjects' patterns of drug purchasing also put them at risk of severe criminal sanction. Data supported evidence that cocaine use had become increasing popular in the UK, but contrasted with some commentators' views that ecstasy use was in decline. The utility of this method and how the results should be interpreted is discussed, as are the data's implications for harm and risk reduction activities.

***Fatal Brain Edema After Ingestion of Ecstasy and Benzylpiperazine., Balmelli C, Kupferschmidt H, Rentsch K, Schneemann M.,*** Dtsch Med Wochenschr, 2001 Jul 13;126(28-29):809-11. [Article in German]

A 23-year-old woman was hospitalized with headache, malaise and somnolence 11 hours after ingestion of A2 (benzylpiperazine), 7 hours after ingestion of ecstasy (MDMA), and large volume of fluids. On admission she had bradycardia (heart rate 48/min), hypertension (blood pressure 154/95 mm Hg), and reduced consciousness with diminished tendon reflexes and non-reacting pupils (Glasgow Coma Score 6). INVESTIGATIONS: Serum sodium was markedly decreased (115 mmol/l [normal 135-145]) with low plasma osmolality (246 mosm/kg [normal 280-300]). Other laboratory findings were within normal limits. TREATMENT AND COURSE: The patient had severe hypervolaemic hypotonic hyponatraemia. 40 minutes after admission she seized twice and was intubated. Brain CT

En showed massive cerebral oedema with beginning tonsillar herniation. Serum sodium concentration returned to normal within 38 hours, but the patient deteriorated neurologically with increasing tonsillar herniation detected in a second brain CT scan. The patient died 57 hours after admission. CONCLUSION: 13 cases of MDMA-associated severe hyponatraemia are reported. Intake of fluids after MDMA ingestion may lead to potentially fatal hypervolaemic hypotonic hyponatraemia with cerebral oedema. Symptoms appear about 8 hours (range 4-18) after MDMA ingestion. Even low doses of MDMA and fluids may lead to a serious outcome. The only risk factor is female gender. Measurement of serum sodium and brain CT scan is recommended in all patients with altered mental status after MDMA consumption.

***Heroin Smoking by "Chasing the Dragon" in Young Opiate Users in Ireland: Stability and Associations with Use to "Come Down" Off "Ecstasy". Gervin M, Hughes R, Bamford L, Smyth BP, Keenan E., : J Subst Abuse Treat., 2001 Jun 20(4):297-300.***

We explored the frequency of commencing opiate use by "chasing the dragon" to "come down" off Ecstasy and the stability of heroin smoking in young opiate takers by assessing 102 subjects in Dublin using a semistructured interview. Ninety-two subjects had used Ecstasy. Of these, 68 reported "chasing" to "come down" off Ecstasy at some point in their history and were found to have used Ecstasy more frequently and in larger amounts. Thirty-six reported that their first experience of using opiates was to "come down" off Ecstasy, 28 citing this as their main reason for commencement. Eighty-six of the 102 commenced opiates by "chasing" heroin, 61 of whom progressed to injecting after a mean of 2.9 years. This was associated with starting illicit drug use earlier, starting heroin earlier, and a history of using Ecstasy. Implications for service planners in developing responses to illicit drug use among adolescents are discussed.

***Ecstasy Induced Acute Myocardial Infarction., Qasim A, Townend J, Davies MK., Heart, 2001 Jun;85(6):E10.***  
A 23 year old man presented with a clinical history and ECG compatible with acute myocardial infarction, having taken a single tablet of ecstasy (3,4-methylenedioxymetamphetamine) 18 hours previously. He was treated with aspirin and thrombolytic therapy; however, cardiac catheterisation showed angiographically normal coronary arteries and left ventricular function. Sympathomimetic drugs are freely available and widely abused in Britain, but there is little evidence of the mechanisms or management of cardiac complications. In such cases the use of standard treatment for acute myocardial infarction is recommended with agents such as glyceryl trinitrate and phentolamine to reduce coronary artery spasm. Early coronary angiography may help to determine the relative contribution of spasm, thrombus, and underlying atherosclerotic disease.

***Poisoning With the Recreational Drug Paramethoxyamphetamine ("Death")., Ling LH, Marchant C, Buckley NA, Prior M, Irvine RJ., Med J Aust., 2001 May 7;174(9):453-5.***

To describe the clinical features of paramethoxyamphetamine (PMA; "death") poisoning and to compare these with those of people with self-reported "ecstasy" poisoning. DESIGN: Retrospective casenote review. 22 patients who presented to the Emergency Department of the Royal Adelaide Hospital (RAH), a major metropolitan teaching hospital, between 1 January 1996 and 31 December 1998 with PMA poisoning identified through urine drug screens; and 61 patients with self-reported ecstasy poisoning between 1 September 1997 and 31 December 1998 found through the hospital databases. RESULTS: Patients with PMA poisoning presented with tachycardia (64%), hyperthermia (temperature > 37.5 degrees C; 36%), coma (41%), seizures (32%), arrhythmias (23%), and QRS intervals > or = 100 ms (50%) with greater frequency and often greater severity than those with self-reported ecstasy poisoning. Two patients with PMA poisoning presented with severe hypoglycaemia (blood glucose level, < 1.5 mmol/L) accompanied by hyperkalaemia (K<sup>+</sup> concentration, > 7.5 mmol/L). CONCLUSIONS: At our hospital, PMA poisonings accounted for most of the severe reactions among people who believed they had taken ecstasy. Hypoglycaemia and hyperkalaemia may be specific to PMA poisoning. PMA toxicity should be suspected with severe or atypical reactions to "ecstasy", and confirmed by chromatographic urine drug screens.

***Recreational Use of 3,4-methylenedioxymethamphetamine (MDMA) or "Ecstasy": Evidence for Cognitive Impairment, Bhattachary S and Powell JH., Psychol.Med., 2001 May, 31(4); 647-658.***

It has recently been shown that 3, 4- methylenedioxymethamphetamine (MDMA) or Ecstasy causes long lasting alterations to brain structure and function in animals, and there is mounting evidence that recreational users of the drug show impairments in some aspects of cognitive functioning including memory for verbal information. The

Present study investigates possible effects on other cognitive functions and explores the temporal course of development and resolution of these impairments by comparing novice, regular and abstaining users with a matched group of non-users. Eighty participants categorized as non-users, novice users, regular users or currently abstinent users of MDMA were assessed on tests of verbal IQ, reversed digit span, immediate and delayed recall of a prose passage and of a complex geometric figure and verbal fluency. **RESULTS:** The four groups were well-matched for verbal IQ and on demographic variables. They differed in frequency of cannabis use over the last month, but this did not correlate with any cognitive test scores. All three groups of MDMA users showed significantly poorer verbal fluency and immediate and delayed prose recall than non-users. Days since last use and total lifetime consumption of MDMA made separate contributions to the variance in the recall scores, accounting jointly for almost half of the variance in delayed recall. By contrast, the groups did not differ on either visual recall or reversed digit span. **CONCLUSIONS:** The observed deficits provide further evidence of impairments of verbal but not visual memory in MDMA users, and indicate that the deficits are not attributable either to differences in general reasoning ability or to impairments of working memory. The data further suggest that the observed impairments may be attributable to a combination of reversible acute effects of MDMA resolving over a period of 2-3 weeks and more long-term changes associated with extent of lifetime consumption.

**Fatal Ecstasy Intoxication., Nielsen S, Lundemose JB, Simonsen MS, Dragsholt C., Ugeskr Laeger 2001 Apr 16;163(16):2253-2255. [Article in Danish]**

A case of full-blown, lethal MDMA intoxication, owing to abuse of ecstasy is described. The increasing popularity of ecstasy among young, otherwise healthy, people prompts health care providers to recognise better the symptoms of systemic intoxication in order to initiate early treatment, such as rehydration, cooling in cases of hyperthermia, seizure treatment, correction of cardiac arrhythmia, and metabolic and electrolyte abnormalities.

**Memory Impairment in Abstinent (MDMA (Ecstasy) Users: A Longitudinal Investigation. Zakzanis KK and Young DA, Neurology, 2001 Apr, 56(7): 966-969.**

To examine the neurotoxic potential of continued MDMA (Ecstasy) use in humans and its functional consequences over the course of 1 year, 15 MDMA users participated in a longitudinal study in which they completed a brief neuropsychological test battery composed mainly of retrospective and prospective memory tasks. Subjects were abstinent for 2 weeks on initial and 1-year testing. Continued use of MDMA was associated with progressive decline in terms of immediate and delayed recall.

**The Many Faces of Ecstasy. Doyon S., Curr.Opin.Pediatr, 2001 Apr, 13(2): 170-176.**

References to the word ecstasy in popular culture can mean different things to different individuals. The most common form of ecstasy (methylenedioxymethamphetamine (MDMA)), is an amphetamine with some hallucinogenic properties at high doses. It is directly neurotoxic to the human brain and has been linked to a number of deaths worldwide. Deaths result from hyperthermia, hyponatremia, or cerebral edema. (Liquid Ecstasy-GHB) A naturally occurring metabolite of gamma-aminobutyric acid, gammahydroxybutyrate (GHB) is a potential central nervous system depressant. Although GHB is a Schedule I drug, analogs remain widely available for consumption. Acute intoxication with GHB or its analogs leads to coma and respiratory depression. Chronic use of GHB or its analogues is associated with a withdrawal syndrome characterized by autonomic excitation. Herbal ecstasy refers to ephedrine-containing preparations. Acute and chronic overdoses of herbal ecstasy have been linked to hypertension, tachydysrhythmias, myocardial infarctions, cerebrovascular accidents and deaths. There is no regulation of the ephedrine content of available herbal ecstasy products.

**Gender Differences in the Subjective Effects of MDMA. Liechti ME et.al., Psychopharmacology, 2001 Mar, 154(2): 161-168.**

3,4-methylenedioxymethamphetamine (MDMA) mainly releases serotonin (5-HT). MDMA is contained in the recreational drug Ecstasy. 5-HT is known to play an important role in mood and anxiety disorders, for which there is a female preponderance. To date, there are no systematic data on gender differences in the subjective effects of MDMA. The present work analyzed the pooled data from three controlled studies on the psychological and physiological effects of MDMA in healthy volunteers with no or minimal MDMA experience. A particular focus of the analyses were possible gender differences. A total of 74 subjects (54 male, 20 female) participated in all three studies. MDMA in oral doses ranging from 70-150 mg (1.35-1.8 mg/kg) was administered under double-blind placebo-controlled conditions. Subjective peak changes were assessed by standardized psychometric rating

Files. Physiological measures were blood pressure, heart rate, and peripheral body temperature. Adverse drug effects were assessed during the experimental session and after 24 h. RESULTS: Psychoactive effects of MDMA were more intense in women than in men. Women especially had higher scores for MDMA-induced perceptual changes, thought disturbances, and fear of loss of body control. The dose of MDMA positively correlated with the intensity of perceptual changes in women. Acute adverse effects and sequelae were also more frequent in female than in male subjects. In contrast, men showed higher increases in blood pressure than woman. CONCLUSION: the fact that equal doses of MDMA per kilogram of body weight produce stronger responses in women compared to men is consistent with an increased susceptibility of women to the 5-HT releasing effects of MDMA. Our results also indicate that increasing doses of MDMA produce more hallucinogen-like perceptual alterations, particularly in women.

***An "Accidental" Acute Psychosis with Ecstasy Use. Vaiva G., et.al., J.Psychoactive Drugs, 2001 Jan-Mar, 33(1): 95-98.***

Over the last 10 years, Europe has witnessed the development of the ecstasy phenomenon; this term is used to describe several products sharing more or less the same effects. The most widely used and hence the most well known is 3,4-MDMA, but MDA, MDEA, and MBDB and even 2CB or nexus are available. The psychopathological consequences of MDMA use in man are relatively poorly understood. The case reported here involves an acute psychotic episode with residual symptoms after six months, with a sudden onset at least 12 hours after taking alcohol and ecstasy without realizing it, in an individual with no previous psychopathology other than a moderate anxiety disorder. Twelve cases of acute psychotic episodes after taking ecstasy have been reported in the literature; two after taking the drug on two occasions and one after a single use. No authors have examined the previous mental state or possible previous psychopathology with any precision. The present subject had not displayed any previous psychotic behavior when tested with a proven standardized interview technique; this was confirmed by his peers and his family. He did, however, show signs of social phobia. Although the personality of an individual is a factor in taking a drug, and probably in the quality of the psychotropic effects experienced, a host of arguments favor the appearance of psychotic symptoms de novo, which were probably related to direct toxicity by MDMA and/or its metabolites on the serotonergic neurons.

***Monitoring Synthetic Drug Markets, Trends, and Public Health. Spruit IP., Subst.Use Misuse, 2001 Jan, 36(1-2):23-47. (Netherlands)***

The Drugs Information and Monitoring System (DIMS) in The Netherlands is a toxicoepidemiologic monitor of drug markets that was established in 1992. Its main focuses are to identify the compounds of synthetic drugs, describe prevalence and trends, and identify health risks. Here we discuss the insights gained in the Ecstasy market, based on the weekly testing of more than 100 drug samples, and key information of synthetic drug users delivering drug samples and personnel participating in the DIMS network. Pills used as Ecstasy may contain a wide variety of compounds. The percentage of samples containing MDMA increased slowly reaching almost 75% in 1996, but decreasing sharply in 1997. Amphetamines ("speed" and "ice") and experimental varieties were found in at least one-third of the pills. Origins and effects of this development are discussed, as well as the risk assessment. In 1998, the percentage of MDMA pills increased more than ever before, indicating among other things that consumers prefer the conventional product. However, the use of "speed" and other drugs may also be stimulated by the decrease in 1997 of the percentage of MDMA pills. With more new types of drugs likely in the next century, a monitor such as DIMS provides important surveillance and data for public health and prevention aims.

***New Drug of Abuse, Graeme KA, Emerg Med Clin North Am, 2000 Nov; 18(4); 625-36.***

Newer club drugs of abuse are frequently used in the settings of raves and the popularity of these agents requires emergency physicians to become familiar with the clinical presentations and management of the toxicity induced by these agents.

***Ecstasy, Shannon M, Pediatr Emerg Care, 2000 Oct; 16(5); 377-80.***

Ecstasy in overdose has major toxicity, producing several different life-threatening manifestations. Hepatotoxicity and hyponatremia are common but poorly understood consequences of MDMA overdose. The drug can produce long-term, if not permanent, neurologic sequelae by destruction of serotonergic neurons. Chronic Ecstasy use can result in psychosis, depression, and suicidal ideation.

**Human Pharmacology of 3,4-Methylenedioxymethamphetamine Psychomotor Performance and Subjective Effects.** Cami J, et al., *J. Clin Psychopharmacol*, Aug2000 20(4): 455-66.

MDMA is of increasing use among youth because of its apparent entactogenic properties, such as euphoria, friendliness, closeness, and empathy. Experimental studies have shown MDMA to be neurotoxic. Data on pharmacologic actions of MDMA in humans are limited. A randomized, double blinded, crossover, controlled trial to assess psychomotor performance and subjective effects in eight healthy male volunteer. MDMA was given in the same range of doses used for drug purposes (75 and 125 mg). The short-term administration of MDMA produced marked euphoria, a slight impairment in the performance of psychomotor tasks, and mild changes in body perceptions without hallucinations. These data support the abuse liability of MDMA.

**Toxicity of Drug Abuse - Amphetamine Designer Drugs: Mental Effects and Consequences of Single Dose Use.** Morland J; *Toxicol Lett*; 2000 Mar 15; 112-113; 147-152

MDMA interferes with serotonin and catecholamine transporters in the central nervous system to increase monoamine synaptic levels and thereby mediate the majority of its central nervous effects. These range from wanted effects like euphoria, central nervous stimulation, and feeling of closeness to mild hallucinations, impairment of cognition and coordination and further to serious reactions like agitation, disturbed and bizarre behavior, and possibly psychosis. The full picture of the consequences of these transitory changes is not known. It has been assumed that the risk of being involved in fatalities and accidents during the state of MDMA influence is increased, but this possible risk increase has so far not been determined. Observations of the prevalence of MDMA involvement in cases of reckless driving and the MDMA blood concentrations measured indicate a risk increase comparable to that observed after use of amphetamines. Parrot and Lasky (1998, *Psychopharmacology* 139, 261-8) study three groups of MDMA users, 2 days after ingestion, MDMA-users felt significantly more depressed, abnormal, unsociable, unpleasant, and less well-tempered than the controls. Cognitive performance on both vocal recall and visual scanning tasks was significantly reduced on MDMA compared to controls. Memory recall was also significantly impaired in "drug-free" MDMA users, with regular MDMA users displaying the worst memory scores at every test session. 20% of the respondent MDMA users reported difficulties in concentration, dizziness or vertigo, visual hallucinations and drowsiness. 20 psychiatrists reported high frequency of possible detrimental effects associated with previous MDMA use noted as altered time perception and cognitive changes. A series of negative effects report by subjects participating in the studies, included disorientation, blurred vision, difficulties in walking, brief short term memory loss, confusion, difficulties with multiplication and impaired judgment. "Beneficial aspects" of drug use were talkativeness, open-minded, closeness to others, and happiness. 48 MDMA cases during a 15-month period consumed between one-half to two ecstasy tablets before the adverse event brought them to a London Emergency Room. The most common clinical features were feelings of being "strange, unwell, dizzy, collapsed, loss of consciousness, nausea, vomiting and panic, anxiety, restlessness. There were six severe episodes of delirium, seizures, coma. The use of MDMA is accompanied by marked neurobiological changes in the central nervous system, particularly linked to serotonin and catecholamine transmission. A series of possible adverse acute mental and behavioral effects have been observed in people shortly after single dose use of MDMA. More serious complications of such effects have also been reported.

**Ecstasy - Long Term Effects on the Human Central Nervous System Revealed by Positron Emission Tomography.** Obrocki J, et al, Br. J., *Psychiatry*; 1999 Aug; 175; 186-8.

By comparison with a control group, the glucose metabolic uptake of the ecstasy user group was altered within the amygdala, hippocampus, and Brodmann's area. The results suggest the possibility that ecstasy use has lasting effects on central neuronal activity in humans.

**MDMA and MDEA Misuse: An Immunohistochemical Study on Three Fatal Cases.** Fineschi V. et al., *Forensic Sci Int*, 1999 Sep 30; 379(378): 65-74.

Three fatal cases of MDMA/MDEA misuse were examined. These were white males, 19 and 20 years of age, in which postmortem toxicology showed the presence of MDMA in one case, MDEA in another case, and both drugs in a third case. The clinical data were analyzed and immunohistochemical investigations. A complete immunohistochemical study has made it possible to demonstrate rhabdomyolysis and myoglobinuria with alterations of the organs typical of a DIC. Clinical, histopathological and toxicological data suggests that severe or fatal complications following ecstasy ingestion could be related to idiosyncratic response. Case 1: Male, 19 years, was seen ingesting numerous tablets of ecstasy in a discotheque for the entire duration of the party until early morning. Late the following morning he began to experience respiratory difficulty, uncoordinated movements,

Generalized hypertonia, and hyperpyrexia (40.6C). He was diagnosed with disseminated intravascular coagulation. He suffered a cardiac arrest unresponsive to cardiopulmonary resuscitation. Toxicological analysis of body fluids showed presence of MDMA and MDA (metabolite of MDMA). Case 2: Male 20 years, went with some friends to a discotheque, where he remained for some hours and where he was seen to ingest numerous tablets of ecstasy. When he returned home around 0200, he told his mother that he felt feverish. The armpit temperature was established at 40C and he immediately went to bed. At 1200 he was found dead, his pillow soaked in blood. Toxicological analysis of body fluids showed presence of MDMA, MDA, and MDEA. Case 3: Male, 19 years was found unconscious near a discotheque and taken to ER and transferred to the ICU. Clinical course worsened, diffuse subcutaneous petechiae appeared, the patient sustained convulsion and hypotensive. Patient pronounced dead approximately 28 hours after having been found at the discotheque. Toxicological analysis of body fluids showed presence of MDEA.

**3,4-Methylenedioxy Analogues of Amphetamine: Defining the Risks to Humans. Hegadoren KM, Baker GB, and Bourin M. *Neurosci Biobehav Rev* 1999 Mar;23(4):539-553.**

Analogues of amphetamines (MDMA-Ecstasy/Adam; MDA-Love, and MDE-Eve) are drugs that produce feeling of euphoria and energy, and a desire to socialize, which go far to explain their current popularity as “rave drugs”. In addition to these positive effects, the drugs are relatively inexpensive to purchase and have the reputation of being safe compared to other drugs. Yet there is mounting evidence that these drugs do not deserve this reputation of being safe. The article reviews the risks associated with analogue drug abuse, behavioral and cognitive effects, toxicity, psychopathology, neurotoxicity, abuse potential, and the potential for drug-drug interactions associated with acute and chronic use. British newspapers abound with horror stories about young adults being hospitalized or dying after ingestion of these drugs, prompting one physician to dub the combination of MDMA and rave dancing as the “the dance of death.” The most common reported after effects of MDA, MDMA, and MDEA are drowsiness, muscle aches and general fatigue, depression lasting 1-2 days, difficulty in concentration, paranoia and short-lived anxiety and irritability. The after-effects increase with successive doses, while the positive subjective effects diminish. It is difficult to collect accurate information regarding the numbers of deaths that can be ascribed directly to the ingestion of these drugs due to the presence in many of the cases of other combined drug abuse. While it is important to recognize that the number of deaths related to these drugs is relatively small when the frequency of use is considered, the lack of apparent relationship between dose and toxicity and the seriousness of the clinical presentation even when the patient survives suggests that these drugs do not deserve the “harmless” label and that educational programs are needed. Educational materials must accurately set out the risks these drugs represent to adolescents and young adults if they are to be believed. We need to move away from the scare tactics associated with some of the media coverage and provide reasoned information from which individuals make informed choices about the use of MDA, MDMA, and MDEA and can recognize warning signs that require immediate medical attention both in themselves and their follow “ravers”.

***Hyponatraemia and Seizures After Ecstasy Use.* Holmes S B, Banerjee AK, and Alexander WD., *Postgrad. Med. J.*, 1999 Jan; 75(879):32-3**

A patient presented to our unit with seizures and profound hyponatraemia after ingestion of a single tablet of ecstasy. No other drugs were taken. Rapid elevation of serum corticosterone and prolactin levels occurs through a 5-HT receptor-mediated mechanism. 5-HT release caused increased antidiuretic hormone secretion in some controlled studies on animals. Other theories have been suggested for the pathogenesis of the hyponatremia. Hyperthermia and sweating, known consequences of ecstasy ingestion and vigorous dancing, result in sodium loss which, coupled with excessive water intake, leads to hyponatraemia. Evidence of water intoxication has been detected both in vivo and post-mortum. However, the mechanism may be more complex, and multifactorial in origin. The toxic effects of ecstasy are due directly to the parent compound and not to impurities within the tablet. The seizures proved resistant to therapy and ventilation on the intensive care unit was required. Resolution of the seizures occurred on correction of the metabolic abnormalities. The pathogenesis of seizures and hyponatraemia (low blood sodium levels) after ecstasy use is discussed. Ecstasy use should be considered in any young patient presenting with unexplained seizures and attention should be directed towards electrolyte (plasma salt) levels, particularly sodium. Learning Points: (1) Seizures following ecstasy use may not respond to therapy with anticonvulsants and benzodiazepines. (2) Ecstasy ingestion may result in hyponatraemia which is exacerbated by water intoxication. (3) Unrestricted water intake should not be recommended following ecstasy use. (4) Patients may present with seizures and hyponatraemia without other features of ecstasy toxicity.

**Recreational use of Ecstasy (MDMA) is Associated with Elevated Impulsivity. Morgan MJ. Neuropsychopharmacology 1998 Oct;19(4);252-64.**

Recent evidence suggests MDMA produces long-term reduction in serotonin. Serotonin is implicated in the regulation of mood, anxiety, aggression, impulsivity, and cognition. The combined data from two studies indicated that ecstasy users exhibited elevated impulsivity on both self-report and behavioral measures, and that those who had taken the most ecstasy had the most elevated trait impulsiveness scores. These findings are consistent with previous evidence that elevated levels of impulsivity in humans are associated with reduced levels of serotonergic function. Combined data from the study presented in this article indicates that recreational ecstasy users committed significantly more errors in the MFF20 (Cairns and Cammock 1978) than polydrug control subjects, who had similar drug histories but had never taken illicit drugs, all of whom were of similar age, height, gender, education, and estimated premorbid IQ. By definition, some of the elevated trait impulsiveness, observed in the groups of participants who had used illicit drugs probably reflects a pre-existing predisposition that may have led to subsequent use of illicit drugs. However, it is also possible that some of the elevation of trait impulsiveness, particularly the additional elevation associated with heavy past consumption of ecstasy, may be attributable to the neurotoxic effects of ecstasy on brain 5-HT systems, because, as noted, reductions in serotonergic function have consistently been associated with elevated levels of impulsive behavior. A number of ecstasy users volunteered information indicated that their reduced ability to concentrate, impaired memory, and slowed mental processing were a direct consequence of taking ecstasy, as was their increased susceptibility to anxiety, depression, aggression, irritability, and mood swings.

**Death by Ecstasy: The Serotonin Syndrome? Mueller PD., et al., Annals of Emergency Medicine, 1998 Sept, Part I, 32(3), pg 377-380.**

Serotonin syndrome, a condition in which there is central serotonin receptor hyperstimulation has been described since the 1950s. Classic findings of severe serotonin syndrome include hypothermia, mental status changes, autonomic instability, and altered muscle tone or rigidity. A number of medications have been implicated in the induction of serotonin syndrome, including those that reduce metabolism (ie, monoamine oxidase inhibitors), increase production (ie L-tryptophan), or inhibit uptake of serotonin (ie, Fluoxetine, clomipramine, meperidine, dextromethorphan, pentazocine, fenfluramine). MDMA has been shown in animal models to cause massive release of serotonin from pre synaptic vesicles and inhibit its uptake. The following case illustrates that MDMA can induce a toxidrome consistent with severe serotonin syndrome. A 20 year old woman was brought to the emergency department unresponsive and cyanotic. She had ingested 2 tablets of MDMA within the previous 4 hours. She had a negative past medical history, was taking no medications, and had not been previously treated with any antidepressants or other prescription medications. History of previous use of MDMA or other illicit drugs was not available. Toxicological analysis of blood and urine indicated the presence of MDMA. No other toxic substances were present except acetaminophen, barbiturate and benzodiazepine used during treatment in the hospital. Initial anxiety, nausea, tachycardia, and elevated blood pressure are followed by relaxation, euphoria, and feelings of enhanced emotional insight. Tolerance to the psychoactive properties of MDMA develops rapidly with loss of the ability to evolve the desired response with repeated doses within several hours; instead, sympathomimetic effects predominate resulting in anxiety, dysphoria and paranoia. There have been multiple case reports in the medical literature of MDMA-induced morbidity and mortality that fit the diagnostic criteria for serotonin syndrome. This is being increasingly recognized in the medical literature. The Poison Information Services in London has also summarized severe complications and fatalities associated with MDMA use, many of which fit the diagnostic criteria for severe serotonin syndrome. Most cases of toxicity appear to be idiosyncratic and are not associated with massive overdose. Since MDMA has only about one tenth the stimulant effect of amphetamine on the central nervous system, excessive sympathetic stimulation by MDMA seems unlikely in these cases.

**Clinical and Toxicological Aspects of the Use of Ecstasy (Article in Dutch) Pennings EJ, Konijn KZ, deWolff FA., Ned Tijdschr Geneesk 1998 Aug 29;142(35); 1942-6.**

MDMA use in humans has a stimulatory effect and enhances feeling of openness and solidarity. The drug depletes serotonin stores and inhibits serotonin synthesis, and inhibits the reuptake of serotonin into the neuron. This leads to destruction of serotonergic axon terminals in animal brain. Similar events of Ecstasy damage are indicated to occur in the human brain. We strongly advise against the use of MDMA as the long term clinical consequences are not known. In man, life-threatening complications after MDMA use include hypothermia, hyponatremia, and liver

ure. Psychiatric complications include psychosis, depression, panic disorder, and impulsive behavior. The chronic psychosis responds poorly to therapy.

***Cognitive Performance in Recreational Users of MDMA of Ecstasy: Evidence for Memory Deficits., Parrott AC, Lees A, Garham NH, Jones M, WesnesK. J. Psychopharmacol 1998;12(1):79-83.***

Cognitive tasks performance was assessed in three groups of young people: 10 regular users of MDMA who had taken MDMA 10 times or more; 10 novice MDMA users who had taken MDMA one to nine times; and 10 control subjects who had never taken MDMA. A computerized battery of cognitive tasks was undertaken on a day when subjects were drug free. Performance on the response speed and vigilance measures (simple reaction time, choice reaction time, and number vigilance), was similar across the three subgroups. However on immediate word recall and delayed word recall, both groups of MDMA users recalled significantly fewer words than controls. Animal research has shown that MDMA can lead to serotonergic neurodegeneration, particularly in the hippocampus and frontal cortex. Although the study design was far from ideal, these data are consistent with other findings of memory decrements in recreational MDMA users, possibly caused by serotonergic neurotoxicity.

***"Saturday Night Fever": Ecstasy related problems in a London Accident and Emergency Department, Williams H., et al., J. Accid. Emerg Med 1998, 15:332, 322-326.***

Forty eight consecutive MDMA related cases were identified. All were in the 15-30 year age group with the majority presenting in the early hours at weekends and having consumed the drug MDMA at a nightclub. The mean number of tablets consumed was two and almost 40% had taken MDMA before. Poly drug use was common with half of the samples having concurrently taken another illicit substance-most commonly other stimulants (amphetamines and cocaine). A wide range of adverse clinical features was found. The most common symptoms were vague and nonspecific such as feeling strange or unwell, however many patients had collapsed or lost consciousness. The most common signs elicited were related to sympathetic over activity, agitation/disturbed behavior, and increased temperature. The more serious complications of delirium, seizures, and profound unconsciousness (coma) were commoner when MDMA was used in combination with other substances. In a review of 48 cases, in 33% of the cases, MDMA was the only substance used. In nearly 17% of the cases alcohol was also consumed; while, other illicit drugs were used with MDMA in 31% of the cases (12 instances amphetamine, 2 instances cocaine, 3 instances LSD, 5 instances THC, two instances GHB, and 2 instances of other illicit drugs). A combination of MDMA, alcohol, and another drug were reported in nearly 19% of the cases. Another illicit substance was therefore used in combination with MDMA in half the 48 episodes reviewed. Of those case in which the patient used MDMA alone, 81% had high pulse rates, 43% felt unwell, dizzy, weak, or strange; between 30-40% reported one or more of the following - loss of consciousness or collapse, nausea or vomiting, panic, anxiety, restlessness, palpitations dilated pupils, hyperventilation, high blood pressure. Between 10-25% of the individuals reported thirst, visual disturbances, abdominal pain, difficulty breathing, headache, shaking sweating, feeling hot/cold, hypothermia, hallucinating, or other complaints. Similar but slightly higher percentages were recorded in those who were polydrug abusers - used MDMA in addition to another drug.

***Ecstasy and Related Substances-Serum Levels in Impaired Drivers., Moeller MR, Hartung M., J. Anal Toxicol 1997 Nov-Dec; 21(7): 591.***

In 1995 and 1996, the authors were able to prove the presence of Ecstasy and related substances in impaired drivers in 30 cases. The presence of MDMA was shown in 18 cases and MDEA in 17 cases. MDEA alone was found in 5 cases. In all other cases, there was combination of these substances, sometimes with amphetamine. MDA was found in 23 cases. It can be assumed that

MDA is mainly a metabolite of MDMA and MDEA. In 25 of the 30 cases, cannabis was also found indicating polydrug abuse. One subject had also consumed codeine and another one had also ingested bromazepam. Eighteen subjects had a blood alcohol concentration of less than 0.03%

***MDMA - Induced Hyperthermia: A Survivor with an Initial Body Temperature of 42.9-degree C. Mallick A., and Bodeham, J. Accid. Emerg Med, 1997, Sept; 14(5) 336-8.***

A 19-year-old male survived hyperpyrexia (42.9 degrees C; 109 degrees F) following MDMA ingestion of three tablets four hours previously. He collapsed at a local nightclub. He developed convulsions, rhabdomyolysis, metabolic acidosis, and respiratory failure. This was successfully managed by assisted ventilation, aggressive fluid therapy and cooling measures. This is the first report of a survivor with such a severe hyperpyrexia. The use of MDMA has increased in he US, UK, and continental Europe. Severe and sometimes fatal adverse reactions are

Increasingly encountered in various accident and emergency (ACE) departments. These include hypothermia, metabolic derangement, seizures, hypertensive crises, cardiac dysrhythmias, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure, hepatic toxicity, cerebrovascular accidents, and psychiatric disturbances. Survival with a core temperature of greater than 42 C is rare. We attribute the survival of our patient to prompt and rapid control of hyperthermia in the A&E. It would not have been possible to bring down the body temperature within an hour with cooling measures alone. Moreover, external cooling can lead to peripheral vasoconstriction and a raised core temperature. Dehydration was corrected with aggressive 0.9% isotonic fluid therapy over a period of 6 hours with pulmonary artery and central venous pressure monitoring as a guide. There have been reports of three deaths due to dilutional hyponatraemia and acute water intoxication from MDMA ingestion. This may result from drinking excessively large volumes of water throughout the event in rave parties, following the advice from drug misuse agencies, and the release of antidiuretic hormone by MDMA. Urgent estimation of serum sodium is therefore indicated in this situation.

***Ecstasy-Induced Rhabdomyolysis (muscle degeneration) and its Role in the Development of Acute Renal Failure. Cunningham, Intensive Crit Care Nursing 1997, Aug 13(4) 216-23.***

One of the potentially devastating side effects of Ecstasy (MDMA) is rhabdomyolysis. From consideration of the pathophysiology of rhabdomyolysis and its role in the development of acute renal failure, it becomes apparent that preventative measures and prompt treatment can prevent patients developing acute renal failure as a consequence of rhabdomyolysis. The use of drugs by young people has become prominent in the media by cases like that of Leah Betts, who died shortly after her 18<sup>th</sup> birthday following the use of ecstasy. Drug-induced rhabdomyolysis is not uncommon: heroin, methadone and temazepam have all been indicated throughout the literature as causes when a patient has been unconscious for some time allowing a crush injury to develop. The focus of this article is on the effects of ecstasy-induced rhabdomyolysis as ecstasy is a commonly used recreational drug among young people in the 16-25 age group (Brown et al 1995), with a wide variation in social class and occupations. Rhabdomyolysis is a condition seen frequently in some intensive therapy units and is one of the many side-effects of ecstasy use. It is a clinical syndrome of muscle pain, weakness and brown urine due to the breakdown of muscle. A more appropriate term, myoglobinuria, has been used following the classic description of crush syndrome in patients injured during the bombing of London in WWII. Renal failure following rhabdomyolysis is a side-effect of ecstasy use. O'Connel (1994) noted that out of nine documented deaths in Britain due to ecstasy use, five of the patients had rhabdomyolysis among their clinical symptoms; also seven out of 15 recorded cases of hyperpyrexia due to ecstasy, developed rhabdomyolysis. Drug induced rhabdomyolysis complicated by acute renal failure has a 46% mortality rate (Roth et al 1988). There are three ways in which ecstasy may induced rhabdomyolysis by causing damage to muscle cells: (1) hyperpyrexia, (2) increased energy consumption (dancing); (3) crush injury when a patient has been unconscious for some time. Ecstasy- Induced Hyperpyrexia is associated with severe metabolic acidosis, muscle rigidity, disseminated intravascular coagulation and hyperkalemia. Acute renal failure follows when the tissues have been damaged allowing myoglobin to infiltrate the extracellular fluid, eventually leading to damage of the kidney. Ecstasy-Induced Energy Consumption through exercise, for example, dancing, is an important cause of rhabdomyolysis. Exercise by itself or in the presence of any of the many metabolic disturbances that impair energy production can lead to necrosis and rhabdomyolysis (Sweny 1989). Crush Injury is possible when a patient has been unconscious for some time following the ingestion of ecstasy. Damage to compressed muscle groups of the arms, legs, and sacrum are not uncommon. Failure to appreciate the importance of muscle necrosis as the underlying problem in the crush syndrome may have disastrous consequences. Shaw et al (1994) state that there may be a delay in recognizing the signs of muscle compression and necrosis when a patient is first admitted to hospital with a drug overdose.

***Mood and Cognitive Effects of +/-Methylenedioxymethamphetamine (MDMA, Ecstasy): Weekend High Followed by Mid Week Low. Curan HV and Travill RA, Addiction, 1997 Jul 92(7)821-31***

A comparison of 12 participants who reported having taken MDMA with 12 participants who reported having consumed only alcohol. Individuals assessed the following day and again at mid week (day 5). Acute effects of MDMA broadly replicated previous finding. MDMA users rated elevated mood on day 1 but significantly low mood on day 5, at which points some participants scored with the range for clinical depression. In contrast, the alcohol group showed less pronounced changes, with the lowest point being day 2. The MDMA group also showed significant impairments on an attention/working memory task, compared with alcohol users. Conclusions: Weekend use of MDMA may lead to depressed mood mid-week. Possible mechanisms underlying the findings are

discussed in terms of temporary depletion of serotonin, serotonergic neurotoxicity, and psychological aspects of mood change.

***MDMA (Ecstasy) Use: An overview of psychiatric and medical sequelae (in German), Thomasius R, Schmolke M, and Krause D., Fortschr Neurol Psychiatr 1997 Feb; 65(2) 49-61.***

Since the mid-eighties psychiatric complications and consequences of the abuse of MDMA have been reported in at least 48 cases. It is necessary to differentiate between acute psychiatric complications, which subside completely when the level of intoxication comes down, toxic psychoses and long-term psychiatric diseases as a consequence of substance abuse. The latter involve atypical and paranoid psychoses, depressions, panic disorders, depersonalization and behavioral disorders. Convulsive seizures are among the most common problems involving the central nervous system. Furthermore, there have been reports on cerebrovascular accidents and intracranial hemorrhages. Literature reports on at least 53 cases of medical complications in abusers of MDMA, 14 of which came to a lethal end. Research still blatantly lacks prospective epidemiological and clinical studies on a sufficiently large scale to identify different developments of dependency and predictors of harmful and unhealthy consumption.

***Pathology of Deaths Associated with "Ecstasy" and "Eve" Misuse, Milroy CM., et al., Fr.Jor.Path., 1996, 49, pg 149-153.***

The postmortum findings in deaths associated with MDMA and MDEA were studied in seven young white men aged between 20-25 years of age. Striking changes were identified in the liver, which varied from foci of individual cell necrosis to centrilobular necrosis. In one case, there was massive hepatic necrosis. Changes consistent with catecholamine induced myocardial damage were seen in five cases. In the brain, perivascular haemorrhagic and hypoxic changes were identified in four cases. Overall, the changes in four cases were the same as those reported in heat stroke, although only two cases had a documented history of hyperthermia. Of these four cases, all had changes in their liver, three had changes in their brains, and three in their heart. Of the other three cases, one man died of fulminant liver failure, one of water intoxication and one probably from a cardiac arrhythmia associated with myocardial fibrosis. These data suggest that there is more than one mechanism of damage in ring substitute amphetamine misuse, injury being caused by hyperthermia in some cases, but with ring substituted amphetamines also possibly having a toxic effect on the liver and other organs in the absence of hyperthermia.

***Toxicity and Deaths from 3,4-methylenedioxymethamphetamine (Ecstasy), Henry JA., et al., Lancet, 15 Aug 1992, 340, pg 384-387.***

The risk of adverse reactions to MDMA is now widely known in both the US and UK, but the patterns of illness remain varied. The article relates experiences encountered during 1990 and 1991, during which time there were an increase in cases of severe toxicity following the ingestion of small quantities of MDMA. Among 7 fatalities, the pattern of toxicity included fulminant hypothermia, convulsions, disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure. In addition, 7 cases of hepatotoxicity were monitored and suspect that the frequency of this complication is increasing. Also described were 5 subjects involved in road traffic accidents in whom MDMA was identified. The article detailed the level of MDMA and other drugs encountered along with information on circumstances surrounding the ingestion, clinical course of events and outcomes - half of which were fatal.