

Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: Overview of pathophysiology and clinical management. (review).

Hall AP; Henry JA. *British Journal of Anaesthesia* 96(6): 678-685, 2006. (75 refs.)

Since the late 1980s 'Ecstasy' (3,4-methylenedioxymethamphetamine, MDMA) has become established as a popular recreational drug in western Europe. The UK National Criminal Intelligence Service estimates that 0.5-2 million tablets are consumed weekly in Britain. It has been reported that 4.5% of young adults (15-34 yr) in the UK have used MDMA in the previous 12 months. Clinically important toxic effects have been reported, including fatalities. While the phenomenon of hyperpyrexia and multi-organ failure is now relatively well known, other serious effects have become apparent more recently. Patients with acute MDMA toxicity may present to doctors working in Anaesthesia, Intensive Care and Emergency Medicine. A broad knowledge of these pathologies and their treatment is necessary for anyone working in an acute medical specialty. An overview of MDMA pharmacology and acute toxicity will be given followed by a plan for clinical management. Copyright 2006, Oxford University Press.

DOVER and QUVER - New marker combinations to detect and monitor at-risk drinking.

Berner MM; Bentele M; Kriston L; Manz C; Clement HW; Harter M et al. *Alcoholism: Clinical and Experimental Research* 30(8): 1372-1380, 2006. (51 refs.)

At-risk drinking is a common medical problem. "Objective" laboratory tests are widely used, especially in situations where it might be favorable for the patient to dissimulate the existing alcohol problem. In this study, we report a new approach to combine the biological markers % carbohydrate-deficient transferrin (%CDT) and gamma-glutamyltransferase (gamma GT) to increase diagnostic properties to identify patients with at-risk drinking behavior. Fifty-eight general practitioners (GPs) participated in the study at 2 study sites in South-West Germany. Patients filled in a questionnaire that included the Alcohol Use Disorders Identification Test (AUDIT) and gave a blood sample. The GP recorded his assessment about

the presence of an alcohol-related disorder in the patient. Screening results of 1 test center were used as a calculation sample. The results at the other site were used to cross-validate the study outcomes. The markers were combined by 2 methods. The first approach used the AUDIT (QUestionnaire VERified; QUVER), and the second was performed using the clinical judgment of the treating GP (DOctor VERified; DOVER). The formulas were calculated using linear and logistic regression models, respectively. A total of 2,940 patients participated in the study, of whom 2,496 completed data sets that could be used for further analysis. In the receiver-operating characteristics (ROC) curves with the reference standard of an AUDIT ≥ 8 , the area under the curve (AUC) of 78.8% for DOVER and 80.6% (QUVER) are in a higher range than the values for gamma-%CDT (75.4%) or gamma-GT (66.3%) and %CDT (74.3%) and suggest a clear superiority of the proposed marker combinations. Regarding the combinations DOVER and QUVER, the cross-validation results were almost identical, with 78.4/78.8% and 80.6/79.5%, respectively. Our study is to date the largest practice-based trial that examines the value of the markers CDT and gamma-GT and their combinations for the screening of at-risk drinking in general practice under routine conditions. Our ROC analysis clearly demonstrated that the combination of the markers gamma-GT and %CDT under routine conditions with a behaviorally oriented reference standard leads to an improvement of diagnostic performance, more so than the use of single markers. Copyright 2006, Research Society on Alcoholism.

Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers.

Abdel-Latif ME; Pinner J; Clews S; Cooke F; Lui K; Oei J. *Pediatrics* 117(6): E1163-E1169, 2006. (30 refs.)

Objective: The purpose of this research was to assess the effects of breast milk on the severity and outcome of neonatal abstinence syndrome. Methods. We conducted a retrospective chart review of 190 drug-dependent mother and infant pairs. Patients were categorized according to the predominant type of milk

consumed by the infant on the fifth day of life (breast milk: n = 85 or formula: n = 105). The Finnegan's scoring system was used to monitor withdrawal, and medication was commenced if there were 2 scores of ≥ 8 . Results: Mean Finnegan scores were significantly lower in the breast milk group during the first 9 days of life even after stratifying for prematurity and exposure to polydrug and methadone. Significantly fewer infants required withdrawal treatment in the breast milk group. The median time to withdrawal occurred considerably later in breast milk group. In a multivariate analysis controlled for exposure to drugs of high risk of neonatal abstinence syndrome, polydrug, and prematurity, breast milk group was associated with lower need for neonatal abstinence syndrome treatment. Conclusions: Breast milk intake is associated with reduced neonatal abstinence syndrome severity, delayed onset of neonatal abstinence syndrome, and decreased need for pharmacologic treatment, regardless of the gestation and the type of drug exposure. Copyright 2006, American Academy of Pediatrics.

Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet.

Cone EJ. *Drug and Alcohol Dependence* 83(Supplement 1): S31-S39, 2006. (28 refs.)

The magnitude of non-therapeutic use, or misuse of prescription pharmaceuticals now rivals that of illicit drug abuse. Drug and formulation tampering enables misusers to administer higher doses by intended and non-intended routes. Perceived motives appear to be a combination of interests in achieving a faster onset and enhancing psychoactive effects. Narcotic analgesics, stimulants, and depressants are widely sought, examined, and tampered with for recreational use. This review examines tampering methods reported on the Internet for selected pharmaceutical products. The Internet provides broad and varied guidance on tampering methods that are specific to drug classes and unique formulations. Instructions are available on crushing, separating, purifying and chemically altering specific formulations to allow changes in dosage, route of administration, and time course of effects. Many pharmaceutical formulations contain features that serve as "barriers" to tampering. The nature and effectiveness of formulation barriers vary widely with many being overcome by adventurous misusers. Examples of successes and failures in tampering attempts are frequently described on Internet sites that support recreational drug use. Successful tampering methods that have widespread appeal evolve into recipes and become archived on multiple websites.

Examples of tampering methods include: (1) how to separate narcotic drugs (codeine, hydrocodone, oxycodone) from excipients and non-desirable actives (aspirin, acetaminophen, ibuprofen); (2) overcoming time-release formulations (beads, layers, matrices); (3) removal of active drug from high-dose formulations (patches, pills); (4) alteration of dosage forms for alternate routes of administration. The development of successful formulations that inhibit or prevent drug/formulation tampering with drugs of abuse should take into consideration the scope and practice of tampering methods available to recreational drug users on the Internet. Copyright 2006, Elsevier.

NicVAX (TM). Aid to smoking cessation, nicotine vaccine.

Boyd B. *Drugs of the Future* 31(3): 203-205, 2006. (16 refs.)

According to the World Health Organization (WHO), the number of smokers worldwide is about 1.3 billion, and tobacco use is considered to be involved in nearly 5 million deaths each year around the globe. A large proportion of smokers try to quit each year, but fewer than 5% are able to maintain abstinence. The addictive effects of smoking are due, in part, to the nicotine contained in tobacco smoke. When nicotine enters the brain, it stimulates the release of dopamine and other neurotransmitters associated with pleasurable effects. The NicVAX (TM) nicotine conjugate vaccine elicits high titers of nicotine-specific antibodies in experimental animals and humans, which blocks nicotine distribution to the brain. Potential strategies to aid in smoking cessation based on NicVAX (TM) include direct vaccination and passive immunization with nicotine-specific antibodies. NicVAX (TM) has been shown to be safe and well tolerated at doses of up to 400 μg . Copyright 2006, Prous Science, SA.

Parental smoking and the risk of childhood leukemia.

Chang JS; Selvin S; Metayer C; Crouse V; Golembesky A; Buffler PA. *American Journal of Epidemiology* 163(12): 1091-1100, 2006. (52 refs.)

Cigarette smoke has been linked to adult myeloid leukemia; however, the association between parental smoking and childhood leukemia remains unclear. Parental smoking and the risk of childhood leukemia were examined in the Northern California Childhood Leukemia Study, a case-control study, between 1995 and 2002. The present analysis included 327 acute childhood leukemia cases (281 acute lymphoblastic leukemia (ALL) and 46 acute myeloid leukemia (AML)) and 416 controls matched on age, sex, maternal race, and Hispanic ethnicity. Maternal

smoking was not associated with an increased risk of either ALL or AML. Paternal preconception smoking was significantly associated with an increased risk of AML (odds ratio = 3.84, 95% confidence interval: 1.04, 14.17); an increased risk for ALL was suggestive for paternal preconception smoking (odds ratio = 1.32, 95% confidence interval: 0.86, 2.04). Greater risks of ALL were observed compared with the risk associated with paternal preconception smoking alone, when paternal preconception smoking was combined with maternal postnatal smoking (P-interaction = 0.004) or postnatal passive smoking exposure (P-interaction = 0.004). These results strongly suggest that exposure to paternal preconception smoking alone or in combination with postnatal passive smoking may be important in the risk of childhood leukemia. Copyright 2006, Johns Hopkins University School of Hygiene and Public Health.

Tonic and phasic processes in the acute effects of alcohol.

Martin CS; Balaban CD; McBurney DH. *Experimental and Clinical Psychopharmacology* 14(2): 209-218, 2006. (30 refs.)

This article presents a novel method for measuring the acute effects of alcohol. One hundred twenty nonproblem drinkers aged 21-28 participated in 3 alcohol administration sessions that produced peak blood alcohol concentrations (BACs) near .09 g%. Subjective intoxication ratings were taken at multiple points across rising and falling BACs. Mathematical modeling techniques decomposed intoxication ratings into a tonic component sensitive to BAC level and a phasic component sensitive to BAC rate of change. This model provided a good fit to observed data. Tonic and phasic gain parameters showed high repeatability across sessions. The average phasic gain parameter was about 4 times larger than the average tonic gain parameter, indicating that subjective intoxication is usually more affected by BAC change than by BAC level. The associations of drinking practices with tonic and phasic gain parameters varied by gender and family history of alcoholism. Tonic-phasic modeling allows individual and group differences in the acute effects of alcohol to be studied as time-dynamic processes. Copyright 2006, American Psychological Assoc.

Serum cotinine level as predictor of lung cancer risk.

Boffetta P; Clark S; Shen M; Gislefoss R; Peto R; Andersen A. *Cancer Epidemiology, Biomarkers & Prevention* 15(6): 1184-1188, 2006. (37 refs.)

Background: No prospective studies are available on serum cotinine level as a marker of lung cancer risk.

Methods: We analyzed serum cotinine level among 1,741 individuals enrolled since the 1970s in a prospective study of Norwegian volunteers who developed lung cancer during the follow-up and 1,741 matched controls free from lung cancer. Serum cotinine was measured with a competitive immunoassay. Regression dilution was corrected for based on repeated measures on samples from 747 subjects. Results: Mean serum cotinine level was higher in cases than in controls. Compared with subjects with a cotinine level of ≤ 5 ng/mL, the odds ratio of lung cancer was increasing linearly, reaching 55.1 (95% confidence interval, 35.7-85.0) among individuals with a serum cotinine level of > 378 ng/mL. There was no clear suggestion of a plateau in risk at high exposure levels. Odds ratios were very similar in men and women. We found no association between serum cotinine level (range, 0.1-9.9 ng/mL) and lung cancer risk among self-reported nonsmokers and long-term quitters (79 cases and 350 controls). Discussion: The association between tobacco smoking and lung cancer risk might be stronger than is estimated from questionnaire-based studies. Serum cotinine level is a predictor of risk of lung cancer among smokers. The reported plateau in risk at high doses is likely due mainly to artifacts. There is no difference between men and women in the carcinogenicity of tobacco smoking. Copyright 2006, American Association for Cancer Research.

Recreational ecstasy use and the neurotoxic potential of MDMA: Current status of the controversy and methodological issues. (review).

Lyvers M. *Drug and Alcohol Review* 25(3): 269-276, 2006. (84 refs.)

The controversy over possible MDMA-induced serotonergic neurotoxicity in human recreational ecstasy users is examined critically in light of recent research findings. Although the designs of such studies have improved considerably since the 1990s, the evidence to date remains equivocal for a number of reasons, including (1) inconsistent findings on the existence and reversibility of persistent ecstasy-related serotonergic and cognitive deficits; (2) lack of clear association between changes in brain imaging measures and functional deficits attributed to MDMA-induced neurotoxicity; (3) the contribution of concomitant cannabis or other drug use to both brain imaging abnormalities and cognitive deficits; (4) methodological shortcomings such as failure to adequately match samples of ecstasy users and controls; (5) the questionable relevance of animal models of MDMA-induced neurotoxicity to typical human patterns of ecstasy use; and (6) the potential

role of inherent pre-drug deficits in serotonergic systems, impulse control and executive cognitive function that may predispose to excessive use of drugs including ecstasy. Given the retrospective nature of nearly all studies of ecstasy users to date, the controversy over whether MDMA has ever caused neurotoxicity or cognitive deficit in human ecstasy users is likely to continue for some time without resolution. Copyright 2006, Taylor & Francis.

Toxicokinetics of drugs of abuse: Current knowledge of the isoenzymes involved in the human metabolism of tetrahydrocannabinol, cocaine, heroin, morphine, and codeine. (review).

Maurer HH; Sauer C; Theobald DS. *Therapeutic Drug Monitoring* 28(3): 447-453, 2006. (72 refs.)

This review summarizes the major metabolic pathways of the drugs of abuse, tetrahydrocannabinol, cocaine, heroin, morphine, and codeine, in humans including the involvement of isoenzymes. This knowledge may be important for predicting their possible interactions with other xenobiotics, understanding pharmacokinetic and pharmacogenetic variations, toxicological risk assessment, developing suitable toxicological analysis procedures, and finally for understanding certain pitfalls in drug testing. The detection times of these drugs and/or their metabolites in biological samples are summarized and the implications of the presented data on the possible interactions of drugs of abuse with other xenobiotics discussed. Copyright 2006, Lippincott, Williams & Wilkins.

Smokeless tobacco (snuff) use and periodontal bone loss.

Bergstrom J; Keilani H; Lundholm C; Radestad U. *Journal of Clinical Periodontology* 33(8): 549-554, 2006. (47 refs.)

Objective: The aim of the present cross-sectional study was to investigate a possible association between the use of Swedish moist snuff and periodontal bone loss. Materials and Methods: The study was carried out on 84 apparently healthy men in the age range 26-54 years, 25 current snuff users, 21 former snuff users, and 38 never-users. The periodontal bone height was evaluated from bitewing radiographs measuring the distance from the cement-enamel junction (CEJ) to the periodontal bone crest (PBC) at pre-molars and molars in each quadrant of the dentition. Results: The mean (95% confidence interval (95% CI)) CEJ-PBC distance was 1.00 (0.87-1.13), 1.12 (0.97-1.26), and 1.06 (0.95-1.16) mm for current users, former users, and never-users, respectively. The association between snuff use and bone height level controlling for age was

not statistically significant (ANOVA $F=0.3$, $p > 0.05$). There was, further, no statistically significant difference between light and heavy exposure users controlling for age (ANOVA $F=1.0$, $p > 0.05$). Conclusion: Our observations suggest that the use of Swedish moist snuff is not associated with periodontal bone loss. Copyright 2006, Blackwell Publishing.

The association between marijuana smoking and lung cancer: A systematic review. (review).

Mehra R; Moore BA; Crothers K; Tetrault J; Fiellin DA. *Archives of Internal Medicine* 166(13): 1359-1367, 2006. (46 refs.)

Background: The association between marijuana smoking and lung cancer is unclear, and a systematic appraisal of this relationship has yet to be performed. Our objective was to assess the impact of marijuana smoking on the development of premalignant lung changes and lung cancer. Methods: Studies assessing the impact of marijuana smoking on lung premalignant findings and lung cancer were selected from MEDLINE, PSYCHLIT, and EMBASE databases according to the following predefined criteria: English-language studies of persons 18 years or older identified from 1966 to the second week of October 2005 were included if they were research studies (ie, not letters, reviews, editorials, or limited case studies), involved persons who smoked marijuana, and examined premalignant or cancerous changes in the lung. Results: Nineteen studies met selection criteria. Studies that examined lung cancer risk factors or premalignant changes in the lung found an association of marijuana smoking with increased tar exposure, alveolar macrophage tumoricidal dysfunction, increased oxidative stress, and bronchial mucosal histopathologic abnormalities compared with tobacco smokers or nonsmoking controls. Observational studies failed to demonstrate significant associations between marijuana smoking and lung cancer after adjusting for tobacco use. The primary methodologic deficiencies noted include selection bias, small sample size, limited generalizability, overall young participant age precluding sufficient lag time for lung cancer outcome identification, and lack of adjustment for tobacco smoking. Conclusion: Given the prevalence of marijuana smoking and studies predominantly supporting biological plausibility of an association of marijuana smoking with lung cancer on the basis of molecular, cellular, and histopathologic findings, physicians should advise patients regarding potential adverse health outcomes until further rigorous studies are performed that permit definitive conclusions. Copyright 2006, American Medical Association.