

## **Antiretrovirals. Part III: Antiretrovirals and drugs of abuse.**

Wynn GH; Cozza KL; Zapor MJ; Wortmann GW; Armstrong SC. *Psychosomatics* 46(1): 79-87, 2005. (72 refs.)

The third in a series reviewing the HIV/AIDS antiretroviral drugs, this report summarizes the interactions between antiretrovirals and common drugs of abuse. In an overview format for primary care physicians and psychiatrists, the metabolism and drug interactions in the context of antiretroviral therapy are presented for the following drugs of abuse: alcohol, benzodiazepines, cocaine, GHB (liquid X), ketamine (special K), LSD (acid), MDMA (Ecstasy), opiates, PCP (angel dust), and THC (marijuana). Copyright 2005, American Psychiatric Association.

## **Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy. (review).**

Parrott AC. *Journal of Psychopharmacology* 19(1): 71-83, 2005. (120 refs.)

This review of chronic tolerance to MDMA (3,4-methylenedioxymetamphetamine) covers the empirical data on dosage escalation, reduced subjective efficacy and bingeing in recreational Ecstasy users. Novice users generally take a single Ecstasy tablet, regular users typically take 2-3 tablets, whereas the most experienced users may take 10-25 tablets in a single session. Reduced subjective efficacy following repeated usage is typically described, with many users subjectively reporting the development of tolerance. Intensive self-administration or bingeing is often noted by experienced users. This can comprise 'stacking' on several tablets together, and 'boosting' on successive doses over an extended period. Some experienced users snort Ecstasy powder nasally, whereas a small minority inject MDMA. Chronic tolerance and bingeing are statistically linked to higher rates of drug-related psychobiological problems. In terms of underlying mechanisms, neuroadaptive processes are certainly involved, but there is a paucity of evidence on hepatic and behavioural mechanisms. Further studies specifically designed to investigate chronic tolerance, involving two intermittent dose regimens, are required. Most animal research has involved

intensive MDMA dosing regimens designed to engender serotonergic neurotoxicity, and this may comprise another underlying mechanism. If distal serotonin axon terminal loss was also developing in recreational users, it may help to explain why reducing subjective efficacy, dosage escalation and increasing psychobiological problems often develop in parallel. In conclusion, there is extensive evidence for chronic pharmacodynamic tolerance to recreational Ecstasy/MDMA, but the underlying mechanisms are currently unclear. Several traditional processes are probably involved, but one of the possible causes is a novel mechanism largely unique to the ring substituted amphetamine derivatives, namely serotonergic neurotoxicity. Copyright 2005, Sage Publications Ltd.

## **A dose-response relationship between maternal smoking during late pregnancy and adult intelligence in male offspring.**

Mortensen EL; Michaelsen KF; Sanders SA; Reinisch JM. *Paediatric and Perinatal Epidemiology* 19(1): 4-11, 2005. (42 refs.)

An association between maternal smoking during pregnancy and cognitive and behavioural development has been observed in several studies, but potential effects of maternal smoking on offspring adult intelligence have not been investigated. The objective of the present study was to investigate a potential association between maternal smoking during pregnancy and offspring intelligence in young adulthood. Adult intelligence was assessed at the mean age of 18.7 years by a military draft board intelligence test (Borge Priens Prove) for 3044 singleton males from the Copenhagen Perinatal Cohort with information regarding maternal smoking during the third trimester coded into five categories (about 50% of the mothers were smokers). The following potential confounders were included as covariates in multivariable analyses: parental social status and education, single mother status, mother's height and age, number of pregnancies, and gestational age. In separate analyses, birthweight and length were also included as covariates. Maternal cigarette smoking during the third trimester, adjusted for the seven covariates, showed a negative association with offspring adult intelligence ( $P = 0.0001$ ). The mean

difference between the no-smoking and the heaviest smoking category amounted to 0.41 standard deviation, corresponding to an IQ difference of 6.2 points [95% confidence interval 0.14, 0.68]. The association remained significant when further adjusted for birthweight and length ( $P = 0.007$ ). Both unadjusted and adjusted means suggested a dose-response relationship between maternal smoking during pregnancy and offspring adult intelligence. When subjects with missing data were excluded, essentially the same results were obtained in the reduced sample ( $n = 1829$ ). These results suggest that smoking during pregnancy may have long-term negative consequences on offspring adult intelligence. Copyright 2005, Blackwell Publishing Ltd.

#### **Childhood IQ, smoking, and cognitive change from age 11 to 64 years.**

Whalley LJ; Fox HC; Deary IJ; Starr JM. *Addictive Behaviors* 30(1): 77-88, 2005. (27 refs.)

We investigated whether smoking is a risk factor for relative cognitive decline from age 11 to 64 years. The potentially confounding effects of childhood IQ, occupational status, level of education, presence of heart disease, hypertension, and lung function were examined. Subjects were nondemented and living independently. They were all born in 1936, had been participants in the same Scottish national IQ survey in 1947, and were reexamined at age about 64 years in 2000-2002. Current smokers and nonsmokers had significantly different mental test scores at age 64. This difference remained after adjustment for childhood IQ. Multiple linear regression identified childhood IQ, level of education, occupational code, lung function, and smoking history as significant independent predictors of mental function at age 64. In this sample, smoking makes a small (<1% variance) independent negative contribution to cognitive aging. Copyright 2005, Elsevier Science Ltd.

#### **Cognitive performance and liver function among recently abstinent alcohol abusers [rapid communication].**

O'Mahony JF. *Addictive Behaviors* 30(2): 369-373, 2005. (33 refs.)

It has frequently been suggested that some of the enduring subtle cognitive impairments seen in sober alcohol-dependent persons may be a result of subclinical liver dysfunction. Cognitive performance and liver function among 85 recently abstinent alcohol-dependent persons were assessed by means of a neuropsychological examination and the GGT test of liver function. Unlike some previous studies, no relationships were found between the two areas of

functioning. It is argued that lack of statistical power did not account for the failure to find an association between the two domains. The proposition that residual cognitive impairment in abstinent alcoholic persons is (partly) mediated by earlier liver dysfunction rests on slight empirical foundations and remains speculative. Copyright 2005, Elsevier Science

#### **Cognitive predisposition to substance abuse in adult attention deficit hyperactivity disorder [rapid communication].**

Sharps MJ; Price-Sharps JL; Day SS; Villegas AB; Nunes MA. *Addictive Behaviors* 30(2): 355-359, 2005. (10 refs.)

Attention deficit hyperactivity disorder (ADHD) is associated with elevated levels of substance abuse (SA), but the cognitive linkages involved have been little explored. The present study used the Brown Attention Deficit Disorder Scales, the Six-Way Paragraphs, and the Substance Abuse Subtle Screening Inventory (SASSI) to investigate these relationships. It was shown that the ability to sustain attention is necessary to formulate an understanding of the most important aspects of any given piece of information, and that the diminished ability to sustain attention associated with tendencies toward ADHD impairs this type of cognition. These cognitive tendencies in turn were associated with elevated levels of SA. The results show the importance of understanding the cognitive processes involved in SA and ADHD. Copyright 2005, Elsevier Science Ltd.

#### **Effects of transdermal nicotine on prose memory and attention in smokers and nonsmokers.**

Poltavski DV; Petros T. *Physiology & Behavior* 83(5): 833-843, 2005. (39 refs.)

Previous research investigating cognitive effects of nicotine has produced mixed findings partly due to the use of abstaining smokers and cigarettes as a delivery system. The present study examined effects of nicotine delivered via a transdermal patch on prose memory and sustained attention in male smokers ( $n=25$ ) and nonsmokers ( $n=22$ ), who were randomly assigned to either a placebo or a nicotine condition. All groups were matched on their verbal ability and gross personality characteristics (state/trait anxiety levels, extroversion-introversion, and impulsivity level). In the nicotine condition, smokers were treated with a 21-mg transdermal patch, while nonsmokers received a 7-mg nicotine patch. Six hours following patch application, their performance was assessed on a computerized prose memory task and the Rapid Visual Information Processing task (RVIP) in a counterbalanced order and double-blind fashion. The

results demonstrated that smokers in the placebo group recalled a significantly greater number of propositions than their counterparts in the nicotine group. Nonsmokers in the nicotine condition also remembered significantly more of the prose material than smokers in the same condition and showed a trend towards better recall of propositions of medium importance in the nicotine condition in comparison to the nonsmokers in the placebo group. No between-group differences were found on the RVIP task. A significant effect of time was found for systolic blood pressure and heart rate. The results cannot be interpreted using the arousal theory of nicotine effects on attention and are explained on the basis of a dose-dependent nicotinic action possibly recruiting cholinergic cortical projections. Copyright 2005, Elsevier Science, Ltd.

**Gamma hydroxybutyric acid (GHB) withdrawal does not occur at therapeutic dosage.**

Addolorato G; Caputo F; Leggio L; Vignoli T; Abenavoli L; Lorenzini F et al. *Drug and Alcohol Dependence* 77(2): 209-211, 2005. (4 refs.)

This letter was prompted by a recent review by McDonough et al, which misquoted the daily dose of GHB. As these authors point out, the data cited about the GHB daily dose currently used for treatment of alcoholism is not correct. In fact, in our study the therapeutic administration of GHB was 50 mg/kg of body weight fractioned in three daily doses. In a subject with a medium weight of 70 kg, the dose of GHB is equivalent to 3500 mg/day (3.5 g/day) and not to 35 g/day as the authors affirm. Therefore, the medium therapeutic dose of GHB is about five times lower than the minimum daily dose of GHB associated with withdrawal. In conclusion, withdrawal and physical dependence do not appear when GHB, used at therapeutic dosage, is discontinued. Moreover, craving and abuse of GHB during treatment for alcohol addiction is a limited phenomenon that should not preclude its medical use. Copyright 2005, Elsevier Science..

**Interactions between cannabinoid and opioid receptor systems in the mediation of ethanol effects.**

Manzanares J; Ortiz S; Oliva JM; Perez-Rial S; Palomo T. *Alcohol and Alcoholism* 40(1): 25-34, 2005. (78 refs.)

Over the past few years, advances in the investigation of the neurochemical circuits involved in the development and treatment of alcohol dependence have identified peptides and receptors as potential key targets in the treatment of problems related to alcohol consumption. The endogenous opioid system is

modified by alcohol intake in areas of the brain related to reward systems, and differential basal levels of opioid gene expression are found in rodents with a high preference for ethanol. This suggests a greater vulnerability to alcohol consumption in relation to differences in genetic background. Further evidence of the involvement of opioid peptides in alcohol dependence is the ability of the opioid antagonist naltrexone to reduce alcohol intake in animal models of dependence and in alcohol-dependent patients. Abundant evidence indicates that the activation of cannabinoid receptors stimulates the release of opioid peptides, therefore the cannabinoid receptor antagonists may presumably alter opioid peptide release, thus facilitating the reduction of ethanol consumption. However, little is known about the effects of ethanol on the endogenous cannabinoid system, the vulnerability of cannabinoid receptors to alcohol intake or their neurochemical implications in reducing consumption of alcohol. In this paper, we review the role of opioid and cannabinoid receptor systems, their vulnerability to alcohol intake and the development of dependence, and the targeting of these systems in the treatment of alcoholism. Copyright 2004, Oxford University Press.

**Fetal exposure to prescription drugs and adult sexual orientation.**

Ellis L; Hellberg J. *Personality and Individual Differences* 38(1): 225-236, 2005. (20 refs.)

This study was undertaken to determine if prenatal exposure to therapeutic drugs contributes to variations in sexual orientation. Especially suspect were drugs that could affect the delicate balance of sex hormone levels that appear to guide the sexual differentiation of the fetal brain. The recollections of 5102 mothers concerning their use of therapeutic drugs during pregnancy were linked to reports of the sexual orientation of their offspring (as provided by either the offspring themselves or by their mothers). About 14% of the mothers recalled having taken at least one of 19 prescription drugs (or classes of drugs) during their pregnancy. Regarding male offspring, little evidence was found that prenatal exposure to any of these medications was associated with variations in sexual orientation. However, even after controlling for age, education, and self-rated recall ability of the mothers, exposure to two types of drugs was significantly related to sexual orientation among female offspring. One type consisted of amphetamine-based diet pills and the other was comprised of synthetic thyroid medications. A month-by-month analysis revealed that during the first trimester consumption of all

prescription drugs was unusually high for mothers of female homosexual offspring. Prescription medications that affect the mother's and/or the female fetuses' developing immune system may alter the feminization/demasculinization of the brain in ways that cause variations in the offspring's adult sexual orientation. Copyright 2005, Elsevier Science.

**Mood and impulsivity of recreational Ecstasy users in the week following a "rave".**

Travers KR; Lyvers M. *Addiction Research & Theory* 13(1): 43-52, 2005. (38 refs.)

Two days following widely attended "rave" or dance party events, questionnaires assessing mood (Beck Depression Inventory, or BDI-II) and impulsivity (Impulsiveness, Venturesomeness and Empathy Scale, or IVE) were completed by 43 attendees who reported using Ecstasy at the events, and by 31 Ecstasy-naive controls who attended the same events. Participants who had taken Ecstasy at the events were significantly more depressed two days later than controls, according to analysis of their BDI-II scores. There was no group difference in impulsivity as measured by the IVE. Levels of self-reported Ecstasy use were not related to depression or impulsivity scores. Results are considered in terms of the hypothetical mood effect of short-term depletion of serotonin induced by MDMA, as well as several alternative non-pharmacological explanations. Copyright 2005, Taylor & Francis Ltd.

**No increased levels of the nicotine metabolite cotinine in smokers with schizophrenia. (review).**

Bozikas VP; Niopas I; Kafantari A; Kanaze FI; Gabrieli C; Melissidis P et al. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 29(1): 1-6, 2005. (47 refs.)

The prevalence of smoking cigarettes has repeatedly been found to be greater in schizophrenia as compared with other psychiatric patients and the general population. Patients with schizophrenia have been found to engage in heavy smoking and consumption of higher doses of nicotine, probably by deeper inhalation of cigarettes. The aim of the study was to assess nicotine exposure through smoking by measuring urinary cotinine, the major nicotine metabolite, in a group of smokers from Greece of smokers with schizophrenia and smokers from the general population. Participants were current smokers and belonged to one of two groups: 35 patients with schizophrenia and 48 healthy controls matched in age, education, and gender. The quantitative analysis of cotinine, the major metabolite of nicotine, in urine samples was performed by a modified high

performance liquid chromatography (HPLC). Patients with schizophrenia who smoke presented a significantly larger time interval between last cigarette smoked and urine sample collection, as well as a significantly higher average number of cigarettes consumed daily than normal smokers. Urinary cotinine levels of patients with schizophrenia who smoke did not significantly differ from that of normal smokers when adjusted for average number of cigarettes per day and time interval between last cigarette smoked and urine collection. These results suggest that patients with schizophrenia did not present higher nicotine exposure through smoking compared with smokers from the community. The pharmacokinetic or pharmacodynamic properties of nicotine, as well as patient medications of the patients may explain our findings. Copyright 2005, Elsevier Science Ltd.

**One hundred seventy two deaths involving the use of oxycodone in Palm Beach County.**

Wolf BC; Lavezzi WA; Sullivan LM; Flannagan LM. *Journal of Forensic Sciences* 50(1): 192-195, 2005. (18 refs.)

Oxycodone is a potent semi-synthetic narcotic prescribed for the management of pain. Previous investigators have reported that the abuse of oxycodone is most frequently seen in conjunction with the abuse of other drugs, although fatalities have been reported with oxycodone alone. We undertook a retrospective review of cases investigated by the Palm Beach County Medical Examiner's Office in which postmortem toxicologic studies indicated the presence of oxycodone. A total of 172 consecutive cases were studied, with 18 in which death was attributed to oxycodone toxicity, 117 to combined drug toxicity, 23 to trauma, 9 to natural causes and 5 to another drug or drugs. The postmortem blood concentrations of oxycodone overlapped among the groups. The mean blood concentration among the cases of toxicity was 0.69 mg/L, combined drug toxicity 0.72 mg/L and trauma 0.62 mg/L. Concentrations were lower in cases of deaths attributed to natural causes or to another drug or drugs (mean each 0.087 mg/L). Benzodiazepines, detected in 96 cases, were the most common co-intoxicants in the cases of combined drug toxicity, followed by cocaine, which was found in 41. The most frequently encountered benzodiazepine was alprazolam. This study confirms that deaths in which oxycodone is a factor are most commonly cases of combined drug toxicity. The incidence of alprazolam as a co-intoxicant has not been previously recognized. Copyright 2005, American Society of Testing Materials.