

## **Do alcohol-dependent individuals with DRD2 A1 allele have an increased risk of relapse? A pilot study.**

Dahlgren A; Wargelius HL; Berglund KJ; Fahlke C; Blennow K; Zetterberg H et al. *Alcohol and Alcoholism* 46(5): 509-513, 2011. (39 refs.)

**Aims:** The TaqIA polymorphism of the dopamine D2 receptor (DRD2) gene has been extensively studied in relation to alcoholism, and the TaqI A1 allele appears to be over-represented in alcohol-dependent individuals. In a recent study, this allele has also been associated with a highly increased mortality rate in alcohol-dependent individuals. In the present study, we investigated whether the TaqI A1 allele of the DRD2 gene region was associated with a higher relapse rate in alcohol-dependent individuals. **Methods:** Adult women (n = 10) and men (n = 40) with a diagnosis of alcohol-dependence were recruited from two Swedish 12-step treatment units for alcoholism. Subjects were genotyped for the TaqIA polymorphism. On average, 1.5 years after the end of the treatment program, subjects were re-interviewed by using the alcohol-related items from the Addiction Severity Index follow-up version. **Results:** Thirty-three (66%) subjects self-reported relapse and 17 (34%) abstinence during the follow-up period. Thirty-six percent (18/50) were carriers of the A1 allele of the DRD2 gene region, and 64% (32/50) were non-carriers. Among the carriers of the A1 allele, 89% (16/18) reported relapse in contrast to 53% (17/32) in the non-carriers (P = 0.01; odds ratio = 7.1). **Conclusion:** The present study is, to our knowledge, the first report of an association between the TaqI A1 allele and a substantially increased relapse rate. It should be emphasized that the number of subjects is relatively small, and this investigation should therefore be considered as a pilot study. Copyright 2011, Oxford University Press.

## **Cathinone derivatives: A review of their chemistry, pharmacology and toxicology. (review).**

Kelly JP. *Drug Testing and Analysis* 3(7-8, special issue): 439-453, 2011. (164 refs.)

The purpose of this review is to evaluate what is currently known about the pharmacology of cathinone

derivatives. Cathinone is the principal active constituent of khat responsible for the stimulant effects that have led khat to be known as a 'natural amphetamine'. Synthetic derivatives have been abused for their amphetamine-like stimulant effects, most notably methylone, methcathinone (ephedrone), and 4-methylmethcathinone (mephedrone). To date, cathinone and methcathinone have been studied most, demonstrating amphetamine-like effects in a range of in vitro and in vivo investigations, albeit less potently than amphetamines. In humans, cathinone derivatives are usually administered orally, and in some cases by insufflation. Methcathinone has a longer history of abuse, being produced from readily available starting materials, and administered by injection. Mephedrone has become the best publicised cathinone derivative, amid considerable media and public concern about its legal status, its ready availability, and reports of serious toxicity and deaths following its use. As a consequence, there has been a clampdown on cathinone derivatives, dramatically changing their legal status in a number of countries. However, little objective evidence-based comparative experiments have been conducted to date between these compounds and their related amphetamines in order to make clear risk judgements. Such assessments have largely been predictive in nature, based on their structural similarity to amphetamines. It can be assumed that, despite their illegal status, cathinone-related compounds will continue to be prevalent drugs of abuse for the foreseeable future. Copyright 2011, Wiley-Blackwell.

## **Severe toxicity following synthetic cannabinoid ingestion.**

Lapoint J; James LP; Moran CL; Nelson LS; Hoffman RS; Moran JH. *Clinical Toxicology* 49(8): 760-764, 2011. (35 refs.)

**Objective.** To report a case of seizures and supraventricular tachycardia (SVT) following confirmed synthetic cannabinoid ingestion. **Background.** Despite widespread use of legal synthetic cannabinoids, reports of serious toxicity following confirmed use of synthetic cannabinoids are rare. We report severe toxicity including seizures following intentional ingestion of the synthetic cannabinoid

JWH-018 and detail confirmation by laboratory analysis. Case Report. A healthy 48 year old man had a generalized seizure within thirty minutes of ingesting an ethanol mixture containing a white powder he purchased from the Internet in an attempt to get high. Seizures recurred and abated with lorazepam. Initial vital signs were: pulse, 106/min; BP, 140/88 mmHg; respirations, 22/min; temperature, 37.7 degrees C. A noncontrast computed tomography of the brain and EEG were negative, and serum chemistry values were normal. The blood ethanol concentration was 3.8 mg/dL and the CPK 2,649 U/L. Urine drug screening by EMIT was negative for common drugs of abuse, including tetrahydrocannabinol. On hospital day 1, he developed medically refractory SVT. The patient had no further complications and was discharged in his normal state of health 10 days after admission. The original powder was confirmed by gas chromatography mass spectrometry to be JWH-018, and a primary JWH-018 metabolite was detected in the patient's urine (200 nM) using liquid chromatography tandem mass spectrometry. Discussion. Synthetic cannabinoids are legal in many parts of the world and easily obtained over the Internet. Data on human toxicity are limited and real-time confirmatory testing is unavailable to clinicians. The potential for toxicity exists for users mistakenly associating the dose and side effect profiles of synthetic cannabinoids to those of marijuana. Conclusion. Ingestion of JWH-018 can produce seizures and tachyarrhythmias. Clinicians, lawmakers, and the general public need to be aware of the potential for toxicity associated with synthetic cannabinoid use. Copyright 2011, Informa Healthcare.

### **The emergence and analysis of synthetic cannabinoids.**

Hudson S; Ramsey J. *Drug Testing and Analysis* 3(7-8, special issue): 466-478, 2011. (35 refs.) In late 2008, several synthetic cannabinoids were detected in herbal smoking mixtures. Typical of these products were 'Spice Gold', 'Spice Silver' and 'Yucatan Fire', but many other products have since appeared. The analytes detected, such as JWH-018 and CP47,497 are experimental compounds, some of which were never designed for human use. Both scientific and anecdotal evidence suggest that these compounds are more potent than traditional cannabis and are being widely used. As a result, authorities around the world are now beginning to control them by either naming individual compounds or using generic legislation. This, however, is easier said than done as the synthetic cannabinoids detected are constantly changing in attempts by manufacturers to evade legislation. This paper includes background

information in the style of a brief monograph, as an aid to rapidly understanding the pharmacological aspects of these compounds in the forensic context, and then presents a comprehensive set of data, obtained from analysis of purchased products by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Copyright 2011, Wiley-Blackwell.

### **The subjective effects of alcohol-tobacco co-use: An ecological momentary assessment investigation.**

Piasecki TM; Jahng S; Wood PK; Robertson BM; Epler AJ; Cronk NJ et al. *Journal of Abnormal Psychology* 120(3): 557-571, 2011. (67 refs.) Alcohol and tobacco use covary at multiple levels of analysis, and co-use of the 2 substances may have profound health consequences. To characterize the motivationally relevant processes contributing to co-use, the current study used ecological momentary assessment (EMA) to examine the subjective consequences of naturally occurring simultaneous use of alcohol and tobacco. Current smokers who reported frequently drinking alcohol (N = 259) used electronic diaries to monitor their daily experiences for 21 days. Participants responded to prompted assessments and also initiated recordings when they smoked a cigarette or completed the first drink in a drinking episode. Momentary reports of smoking and alcohol consumption were associated with one another, and these effects remained after adjustment for occasion- and person-level covariates. When participants consumed alcohol, they reported increased pleasure and decreased punishment from the last cigarette. Smoking was associated with small increases in pleasure from the last drink. Ratings of buzzed and dizzy were synergistically affected by co-use of alcohol and tobacco. Co-use was also followed by higher levels of craving for both alcohol and tobacco. Results point to the importance of reward and incentive processes in ongoing drug use and suggest that alcohol intensifies real-time reports of the motivational consequences of smoking more strongly than smoking affects corresponding appraisals of alcohol effects. Copyright 2011, American Psychological Association.

### **Mental health issues in fetal alcohol spectrum disorder. (review).**

Pei J; Denys K; Hughes J; Rasmussen C. *Journal of Mental Health* 20(5): 473-483, 2011. (48 refs.) Background. High numbers of individuals with Fetal Alcohol Spectrum Disorders (FASD) have been described as having mental health problems. Aims. This article summarizes research about mental health

problems in FASD and considers related developmental and environmental issues. Method. A computer-based literature search was conducted in the databases Medline, PsycINFO, Google Scholar, Academic Search Complete, and Education Resources Information Centre for articles addressing the prevalence and types of mental health issues in individuals affected by FASD. Results. High rates of mental disorders within the FASD and prenatal alcohol exposure (PAE) population were found to be consistently reported for both internalizing and externalizing disorders. Moreover, problems that emerge in childhood may reflect a convergence of genetic, environmental, and neurophysiological factors that persist into adulthood. Conclusions. Researchers are beginning to document the impacts of PAE on later mental health development. Further longitudinal study is needed to determine whether there is an increasing severity of mental health deficits and consequences with age, and whether any such changes reflect increasingly deteriorating environmental factors or brain-based factors. Additionally, research is needed to design interventions to better address the unique mental health needs of this population. Copyright 2011, Informa Healthcare.

**Methadone: A review of drug-drug and pathophysiological interactions. (review).**

Kapur BM; Hutson JR; Chibber T; Luk A; Selby P. *Critical Reviews In Clinical Laboratory Sciences* 48(4): 171-195, 2011. (236 refs.)

Numerous established and potential drug interactions with methadone are clinically important in people treated with methadone either for addiction or for chronic pain. Methadone users often have comorbidities and are prescribed drugs that may interact with methadone. Methadone is extensively metabolized by cytochrome P450 (CYP) 3A4 and to a lesser extent by CYP 1A2, 2D6, 2D8, 2C9/2C8, 2C19, and 2B6. Eighty-six percent of methadone is protein bound, predominately to alpha(1)-acid glycoprotein (AGP). Polymorphisms in or interactions with CYPs that metabolize methadone, changes in protein binding, and other pathophysiological conditions affect the pharmacokinetic properties of methadone. It is critical for health care providers who treat patients on methadone to have adequate information on the interactions of methadone with other drugs of abuse and other medications. We set out to describe drug-drug interactions as well as physiological and pathophysiological factors that may impact the pharmacokinetics of methadone. Using MEDLINE, we conducted a systematic search for papers and related abstracts published between 1966 and June 2010.

Keywords that included methadone, drug-drug interactions, CYP P450 and AGP identified a total of 7709 papers. Other databases, including the Cochrane Database of Systematic Reviews and Scopus, were also searched; an additional 929 papers were found. Final selection of 286 publications was based on the relevance of each paper to the topic. Over 50 such interactions were found. Interactions of methadone with other drugs can lead to increased or decreased methadone drug levels in patients and result in potential overdose or withdrawal, respectively. The former can contribute to methadone's fatality. Prescribers of methadone and pharmacists should enquire about any new medications (including natural products and over-the-counter medications) periodically, and especially when an otherwise stable patient suddenly experiences drug craving, withdrawal or intoxication. Copyright 2011, Informa Healthcare.

**Unique brain areas associated with abstinence control are damaged in multiply detoxified alcoholics.**

Duka T; Trick L; Nikolaou K; Gray MA; Kempton MJ; Williams H et al. *Biological Psychiatry* 70(6): 545-552, 2011. (47 refs.)

Background: The ability to abstain from drinking, despite incentives to imbibe, is essential to recovery from alcoholism. Methods: We used an incentive conflict task to investigate ability to abstain from responding during presentations of incentive cues. Both alcoholic (n = 23) and healthy subjects (n = 22) were required to withhold responding during the simultaneous presentation of two visual stimuli in which the individual presentation allowed responding for monetary reward. Brain structures activated during performance of the task were studied using functional magnetic resonance imaging in healthy volunteers (n = 8), and changes in gray matter volume were studied in a separate group of patients (n = 29) compared with control subjects (n = 31) in regions of interest identified on functional magnetic resonance imaging. Results: Abstinent alcoholic patients were severely impaired on the incentive conflict task. The impairment was greater in patients with experience of several versus a single detoxification. Healthy volunteers, during the same incentive conflict task, showed distinct patterns of brain activation (including gyrus rectus, ventromedial prefrontal cortex, and superior frontal gyrus). Reduction of gray matter volume in ventromedial prefrontal cortex and superior frontal gyrus of patients was more extensive in those with multiple detoxifications. Conclusions: Performance deficits in alcoholics are associated with withdrawal-induced impairments in prefrontal

subfields, which are exacerbated following repeated episodes of detoxification. Detoxification thus compromises functional and structural integrity of prefrontal cortex and may thus impair the ability to control future drinking. Performance in the incentive conflict task is a sensitive biomarker for such deficits. Copyright 2011, Elsevier Science.

### **Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk.**

Chen WY; Rosner B; Hankinson SE; Colditz GA; Willett WC. *Journal of the American Medical Association* 306(17): 1884-1890, 2011. (44 refs.)

Context: Multiple studies have linked alcohol consumption to breast cancer risk, but the risk of lower levels of consumption has not been well quantified. In addition, the role of drinking patterns (ie, frequency of drinking and "binge" drinking) and consumption at different times of adult life are not well understood. Objective: To evaluate the association of breast cancer with alcohol consumption during adult life, including quantity, frequency, and age at consumption. Design, Setting, and Participants: Prospective observational study of 105 986 women enrolled in the Nurses' Health Study followed up from 1980 until 2008 with an early adult alcohol assessment and 8 updated alcohol assessments. Main Outcome Measures Relative risks of developing invasive breast cancer. Results During 2.4 million person-years of follow-up, 7690 cases of invasive breast cancer were diagnosed. Increasing alcohol consumption was associated with increased breast cancer risk that was statistically significant at levels as low as 5.0 to 9.9 g per day, equivalent to 3 to 6 drinks per week (relative risk, 1.15; 95% CI, 1.06-1.24; 333 cases/100 000 person-years). Binge drinking, but not frequency of drinking, was associated with breast cancer risk after controlling for cumulative alcohol intake. Alcohol intake both earlier and later in adult life was independently associated with risk. Conclusions: Low levels of alcohol consumption were associated with a small increase in breast cancer risk, with the most consistent measure being cumulative alcohol intake throughout adult life. Alcohol intake both earlier and later in adult life was independently associated with risk. Copyright 2011, American Medical Association.

### **Alcohol consumption in relation to aberrant DNA methylation in breast tumors.**

Tao MH; Marian C; Shields PG; Nie J; McCann SE; L. *Alcohol* 45(7): 689-699, 2011. (47 refs.)

The mechanism for the observed association of alcohol consumption breast cancer risk is not known; understanding that mechanism could improve

understanding of breast carcinogenesis and optimize prevention strategies. Alcohol may impact breast malignancies or tumor progression by altering DNA methylation. We examined promoter methylation of three genes, the E-cadherin, p16, and retinoic acid-binding receptor-beta 2 (RAR-beta(2)) genes in archived breast tumor tissues from participants in a population-based case-control study. Real time methylation-specific PCR was performed on 803 paraffin-embedded samples, and lifetime alcohol consumption was queried. Unordered polytomous and unconditional logistic regression were used to derive adjusted odds ratios (ORs) and 95% confidence intervals (CIs). RAR-beta(2) methylation was not associated with drinking. Among premenopausal women, alcohol consumption was also not associated with promoter methylation for E-cadherin and p16 genes. In case-case comparisons of postmenopausal breast cancer, compared with lifetime never drinkers, promoter methylation likelihood was increased for higher alcohol intake for E-cadherin (OR = 2.39; 95% CI, 1.15-4.96), in particular for those with estrogen receptor-negative tumors (OR = 4.13; 95% CI, 1.16-14.72), and decreased for p16 (OR = 0.52; 95% CI, 0.29-0.92). There were indications that the association with p16 was stronger for drinking at younger ages. Methylation was also associated with drinking intensity independent of total consumption for both genes. We found alcohol consumption was associated with DNA methylation in postmenopausal breast tumors, suggesting that the association of alcohol and breast cancer may be related, at least in part, to altered methylation, and may differ by drinking pattern. Copyright 2011, Elsevier Science.

### **Alcohol intake in prairie voles is influenced by the drinking level of a peer.**

Anacker AMJ; Loftis JM; Ryabinin AE. *Alcoholism: Clinical and Experimental Research* 35(10): 1884-1890, 2011. (33 refs.)

Background: Peer interactions can have important effects on alcohol-drinking levels, in some cases increasing use, and in other cases preventing it. In a previous study, we have established the prairie vole as a model animal for the effects of social relationships on alcohol intake and have observed a correlation of alcohol intake between individual voles housed together as pairs. Here, we investigated this correlated drinking behavior, hypothesizing that 1 animal alters its alcohol intake to match the drinking of its partner. Methods: Adult prairie voles were tested for baseline drinking levels with continuous access to 10% alcohol and water for 4 days. In Experiment 1, high alcohol drinkers (> 9 g/kg/d) were paired with low alcohol

drinkers (< 5 g/kg/d) of the same sex on either side of a mesh divider for 4 days with continuous access to the same 2-bottle choice test. In Experiment 2, high drinkers were paired with high drinkers and low drinkers paired with low drinkers. In both experiments, animals were again separated following pairing, and drinking was retested in isolation. In Experiment 3, alcohol-naive animals were tested for saccharin consumption (0.05%) first in isolation and then in high saccharin drinkers paired with low saccharin drinkers, and then in another isolation period. Results: In Experiment 1, high drinkers paired with low drinkers significantly decreased their alcohol intake and preference from baseline drinking in isolation, and drinking levels remained significantly lower during isolation following pairing. Interestingly, there was variability between pairs in whether the high drinker decreased or the low drinker increased intake. In Experiment 2, high drinkers paired with high drinkers did not significantly change their intake level or preference, nor did low drinkers paired with low drinkers, and no changes occurred during the subsequent isolation. In Experiment 3, there was no change in saccharin intake or preference when high drinkers were paired with high drinkers or low paired with low, or in the subsequent isolation. Conclusions: Alcohol drinking of prairie voles can be altered under social conditions, such that 1 animal changes its alcohol intake to more closely match the intake of the other animal, helping to explain previous findings of correlated alcohol drinking. The effect does not extend to saccharin, a naturally rewarding sweet substance. This behavior can be used to model the peer pressure that can often affect alcohol intake in humans. Copyright 2011, Wiley-Blackwell.

#### **Increased blood pressure after abrupt cessation of daily cannabis use.**

Vandrey R; Umbricht A; Strain EC. *Journal of Addiction Medicine* 5(1): 16-20, 2011. (26 refs.)

Objective: Cannabis is the most widely used illicit drug. Acute cannabis administration increases blood pressure (BP) and heart rate and tolerance develops to these effects with heavy use. A valid and reliable withdrawal syndrome occurs in most daily users, but few studies have assessed the cardiovascular effects of withdrawal. The objective of this report is to describe unexpected changes in cardiovascular function during brief periods of supervised cannabis use and abstinence in daily cannabis users. Methods: A within-subjects ABAC crossover study in which inpatient volunteers smoked cannabis ad libitum (A), and abstained from cannabis (B/C). Vital signs were obtained 3 times daily during 11 inpatient days for 13

daily cannabis users (11 men, 8 African American). Results: BP increased significantly during periods of cannabis abstinence compared with periods of cannabis use. The magnitude of increase was substantial in a subset (N = 6) of participants, with mean increases of up to 22.8 mm Hg systolic and 12.3 mm Hg diastolic BP observed. A main effect of heart rate was not observed. Secondary analysis limited to morning assessments suggested that resting heart rate increased during abstinence, but the magnitude of this effect was not clinically significant. Conclusions: Abrupt cessation of heavy cannabis use may cause clinically significant increases in BP in a subset of users. BP should be monitored among those attempting to reduce or quit frequent cannabis use, particularly those with preexisting hypertension. The time course of this effect is currently unknown and requires further study. Copyright 2011, Lippincott, Williams & Wilkins.

#### **New findings on biological factors predicting addiction relapse vulnerability.**

Sinha R. *Current Psychiatry Reports* 13(5): 398-405, 2011. (94 refs.)

Relapse is a highly prevalent phenomenon in addiction. This paper examines the new research on identifying biological factors that contribute to addiction relapse risk. Prospective studies examining relapse risk are reviewed, and clinical, biological, and neural factors that predict relapse risk are identified. Clinical factors, patient-related factors, and subjective and behavioral measures such as depressive symptoms, stress, and drug craving all predict future relapse risk. Among biological measures, endocrine measures such as cortisol and cortisol/corticotropin (ACTH) ratio as a measure of adrenal sensitivity and serum brain-derived neurotrophic factor were also predictive of future relapse risk. Among neural measures, brain atrophy in the medial frontal regions and hyperreactivity of the anterior cingulate during withdrawal were identified as important in drug withdrawal and relapse risk. Caveats pertaining to specific drug abuse type and phase of addiction are discussed. Finally, significant implications of these findings for clinical practice are presented, with a specific focus on determining biological markers of relapse risk that may be used to identify those individuals who are most at risk of relapse in the clinic. Such markers may then be used to assess treatment response and develop specific treatments that will normalize these neural and biological sequelae so as to significantly improve relapse outcomes. Copyright 2011, Springer