

### **Effects of concurrent use of alcohol and cocaine. (review).**

Pennings EJM; Leccese AP; de Wolff FA. *Addiction* 97(7): 773-783, 2002. (81 refs.)

The combination of alcohol and cocaine is popular among drug users, perhaps because of more intense feelings of 'high' beyond that perceived with either drug alone, less intense feelings of alcohol-induced inebriation and tempering of discomfort when coming down from a cocaine 'high'. A review is presented of the medical literature on psychological and somatic effects and consequences of combined use of alcohol and cocaine in man. The search was carried out with Medline, the Science Citation Index/Web of Science and Toxline. Exclusion and inclusion criteria for this search are identified. There is generally no evidence that the combination of the two drugs does more than enhance additively the already strong tendency of each drug to induce a variety of physical and psychological disorders. A few exceptions must be noted. Cocaine consistently antagonizes the learning deficits, psychomotor performance deficits and driving deficits induced by alcohol. The combination of alcohol and cocaine tends to have greater-than-additive effects on heart rate, concomitant with up to 30% increased blood cocaine levels. Both prospective and retrospective data further reveal that co-use leads to the formation of cocaethylene, which may potentiate the cardiotoxic effects of cocaine or alcohol alone. More importantly, retrospective data suggest that the combination can potentiate the tendency towards violent thoughts and threats, which may lead to an increase of violent behaviours. Copyright 2002, Society for the Study of Addiction to Alcohol and Other Drugs.

### **A review of three commonly prescribed skeletal muscle relaxants. (review).**

Harden RN; Argoff C. *Journal of Back and Musculoskeletal Rehabilitation* 15(2-3): 63-66, 2000. (24 refs.)

Skeletal muscle relaxants (SMR) are commonly used drugs prescribed for the treatment of muscle spasm and discomfort. Although many have been in use for decades, physicians may be unaware of the accumulating evidence of their risks, benefits, safety and side effects. This review examines the efficacy, side effects, and safety of three commonly prescribed SMRs: metaxalone, cyclobenzaprine,

and carisoprodol. All three appear to have equal efficacy, but their side effects vary considerably. Metaxalone has the fewest reports of side effects, and no reports of major safety issues. Cyclobenzaprine, closely related to the tricyclic antidepressants, causes the expected lethargy and anticholinergic side effects, and may have some toxicity in overdose and in combination with other substances. Carisoprodol raises the greatest concern. Reports in the literature suggest a significant potential for physical and psychological dependence perhaps suggesting a potential for misuse. It also has, perhaps, the greatest toxicity. A secondary goal of this review is to stimulate more discourse about these commonly used, but poorly understood compounds. Copyright 2000, IOS Press.

### **Acute psychological and neurophysiological effects of MDMA in humans.**

Vollenweider FX; Liechti ME; Gamma A; Greer G; Geyer M. *Journal of Psychoactive Drugs* 34(2): 171-184, 2002. (124 refs.)

Since the mid 1990s, MDMA has been increasingly used as a recreational drug called "Ecstasy" by young people in Europe and the United States. However, despite the widespread recreational use of Ecstasy, systematic data on the psychological and neurobiological effects of MDMA have been scant. To further our understanding of the mechanism of action of MDMA, the authors conducted several studies in healthy human volunteers in an effort to characterize the psychological, cognitive and behavioral effects of MDMA in healthy human volunteers. Prospective placebo-controlled within-subject study designs and standardized psychometric ratings and neuropsychological tests were used to assess the acute, short-term and prolonged effects of the drug. To elucidate the role of various neurotransmitter and receptor systems involved in the action of MDMA in humans, the blocking effects of specific receptor antagonists on MDMA-induced psychological alterations and measures of sensory information processing were studied. To identify the functional neuroanatomy involved in the action of MDMA, Positron Emission Tomography (PET) was used. The present contribution summarizes the acute effect of MDMA on psychological and cognitive measures, information processing, and regional brain activity in healthy human volunteers. Copyright 2002, Haight-Ashbury Publications.

### **Alcohol consumption and mortality: Modelling risks for men and women at different ages.**

White IR; Altmann DR; Nanchahal K. *British Medical Journal* 325(7357): 191-194, 2002. (39 refs.)

**Objective:** To estimate the relation between alcohol consumption and risk of death, the level of alcohol consumption at which risk is least, and how these vary with age and sex. **Design:** Analysis using published systematic reviews and population data. **Setting:** England and Wales in 1997. **Main outcome measures:** Death from any of the following causes: cancer of lip, oral cavity, pharynx, oesophagus, colon, rectum, liver, larynx, and breast, essential hypertension, coronary heart disease, stroke, cirrhosis, non-cirrhotic chronic liver disease, chronic pancreatitis, and injuries. **Results:** A direct dose-response relation exists between alcohol consumption and risk of death in women aged 16-54 and in men aged 16-34. At older ages the relation is U shaped. The level at which the risk is lowest increases with age, reaching 3 units a week in women aged over 65 and 8 units a week in men aged over 65. The level at which the risk is increased by 51% above this minimum is 8 units a week in women aged 16-24 and 5 units a week in men aged 16-24, increasing to 20 and 34 units a week in women and men aged over 65, respectively. **Conclusions:** Substantially increased risks of all cause mortality can occur even in people drinking lower than recommended limits, and especially among younger people. Copyright 2002, British Medical Association.

### **Biphasic alcohol response differs in heavy versus light drinkers.**

King AC; Houle T; de Wit H; Holdstock L; Schuster A. *Alcoholism: Clinical and Experimental Research* 26(6): 827-835, 2002. (60 refs.)

**Background:** Most studies of risk factors for alcohol-related problems have focused on biological family history as a primary risk factor. However, other factors, such as early-age heavy drinking, are also risk factors for sustained or progressive heavy consumption. Little is currently known about the mechanisms underlying binge or heavy drinking. **Methods:** This study examined the acute subjective and objective effects of ethanol in heavy drinkers versus light drinkers. Thirty-four subjects participated in this within-subjects study consisting of three early-evening testing sessions in which subjects consumed a beverage containing either 0.8 or 0.4 g/kg ethanol or placebo. **Results:** Compared with lighter drinkers, heavy drinkers were more sensitive to the positive stimulant-like effects of ethanol ( $p < 0.05$ ), especially during the increasing limb of the blood alcohol curve. Heavy drinkers also showed less sedation and cortisol response after alcohol than the light drinkers ( $p < 0.05$ ). **Conclusions:** The results indicate that young adult binge drinkers show a biphasic alcohol response,

with heightened sensitivity to stimulant-like alcohol effects and greater tolerance to sedative alcohol effects compared with their light-drinking counterparts. Copyright 2002, Research Society on Alcoholism. Used with permission.

### **Breast cancer survival in African American women: Is alcohol consumption a prognostic indicator?**

McDonald PAG; Williams R; Dawkins F; Adams-Campbell LL. *Cancer Causes and Control* 13(6): 543-549, 2002. (48 refs.)

**Objective:** Compromised breast cancer survival in African American women is well established. Factors associated with poorer survival in this group are not fully elucidated. This analysis examined the influence of alcohol consumption on breast cancer survival in African American women accrued to a hospital-based study. **Methods:** One hundred twenty-five postmenopausal women (mean age = 64.2 +/- 12.2 years) diagnosed with invasive breast carcinoma between August 1989 and December 1994, and accrued to a hospital-based study of the disease, were followed for survival through December 1998. Cox proportional hazards regression models, adjusted for cigarette smoking, summary stage of disease, and treatment explored the association between alcohol use and breast cancer survival. **Results:** Premorbid alcohol consumption of at least one drink per week was associated with 2.7-fold increase in risk of death (95% CI 1.3- 5.8). **Conclusions:** This study suggests compromised breast cancer survival among postmenopausal women who reported drinking at least one alcoholic beverage per week, a preliminary finding that warrants further investigation. Copyright 2002, Rapid Communications of Oxford, Ltd.

### **Benefits of smoking cessation for longevity.**

Taylor DH Jr; Hasselblad V; Henley SJ; Thun MJ; Sloan FA. *American Journal of Public Health* 92(6): 990-996, 2002. (26 refs.)

**Objectives:** This study determined the life extension obtained from stopping smoking at various ages. **Methods:** We estimated the relation between smoking and mortality among 877243 respondents to the Cancer Prevention Study II. These estimates were applied to the 1990 US census population to examine the longevity benefits of smoking cessation. **Results:** Life expectancy among smokers who quit at age 35 exceeded that of continuing smokers by 6.9 to 8.5 years for men and 6.1 to 7.7 years for women. Smokers who quit at younger ages realized greater life extensions. However, even those who quit much later in life gained some benefits: among smokers who quit at age 65 years, men gained 1.4 to 2.0 years of life, and women gained 2.7 to 3.7 years. **Conclusions:** Stopping smoking as early as possible is important, but cessation at any age provides

meaningful life extensions. Copyright 2002, American Public Health Association. Used with permission.

**Decision-making and addiction (part I): Impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences.**

Bechara A; Damasio H. *Neuropsychologia* 40(10): 1675-1689, 2002. (51 refs.)

Some substance dependent individuals (SDI) suffer from a decision-making impairment akin to that seen in neurological patients with lesions of the ventromedial (VM) prefrontal cortex. The somatic-marker hypothesis posits that decision-making is a process that depends on emotion and that deficits in emotional signaling will lead to poor decision-making. In this study, we tested the hypothesis that SDI who perform disadvantageously on a decision-making instrument, the gambling task (GT), have a deficit in the somatic signals that help guide their decision in the advantageous direction. Since deficits in decision-making/somatic markers can also result from dysfunctional amygdala, we asked indirectly (i.e. via tests sensitive to VM or amygdala dysfunction) whether such a deficit in SDI is restricted to VM dysfunction or includes the amygdala. Using the GT, and skin conductance response (SCR) as an index of somatic state activation, we studied groups of SDI (n = 46), normal controls (n = 49), and VM patients (n = 10). A subgroup of SDI showed defective performance on the GT coupled with impaired anticipatory SCR, but normal SCR to punishment, and normal acquisition of conditioned SCR to an aversive loud sound. This supports the hypothesis that the poor decision-making in some SDI is associated with defective somatic state activation that is linked to a dysfunctional VM cortex. Thus, the dysfunctional VM cortex underlying the "myopia" for the future in some SDI may be one of the principle mechanisms underlying the transition from casual substance taking to compulsive and uncontrollable behavior Copyright 2002, Pergamon Press.

**Decision-making and addiction (part II): Myopia for the future or hypersensitivity to reward?**

Bechara A; Dolan S; Hinds A. *Neuropsychologia* 40(10): 1690-1705, 2002. (57 refs.)

On a decision-making instrument known as the "gambling task" (GT), a subgroup of substance dependent individuals (SDI) opted for choices that yield high immediate gains in spite of higher future losses. This resembles the behavior of patients with ventromedial (VM) prefrontal cortex lesions. In this

study, we addressed the possibility that hypersensitivity to reward may account for the "myopia" for the future in this subgroup of SDI. We used a variant version of the GT, in which the good decks yielded high immediate punishment but higher delayed reward. The bad decks yielded low immediate punishment and lower delayed reward. We measured the skin conductance response (SCR) of Subjects after receiving reward (reward SCR) and during their pondering from which deck to choose (anticipatory SCR). A subgroup of SDI who was not impaired on the original GT performed normally on the variant GT. The subgroup of SDI who was impaired on the original GT showed two levels of performance on the variant GT. One subgroup (36% of the sample) performed poorly on the variant GT, and showed similar behavioral and physiological impairments to VM patients. The other subgroup of SDI (64% of the sample) performed normally on the variant task, but had abnormally large physiological responses to reward. i.e. large SCR after receiving reward (reward SCR) and large SCR in anticipation of Outcomes that yield large reward. Thus, the combined cognitive and physiological approach of assessing decision-making characterizes three sub-populations of SDI. One sub-population is without impairments that can be detected by any measure of the GT paradigm. Another sub-population is similar to VM patients in that they are insensitive to the future, both positive and negative. A third sub-population is hypersensitive to reward, so that the presence or the prospect of receiving, reward dominates their behavior. Copyright 2002, Pergamon Press.

**Club drugs: methylenedioxyamphetamine, flunitrazepam, ketamine hydrochloride, and gamma-hydroxybutyrate.**

Smith KM; Larive LL; Romanelli F. *American Journal of Health-System Pharmacy* 59(11): 1067-1076, 2002. (97 refs.)

The abuse of methylene-dioxyamphetamine (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 phenylcyclidine, ketamine interacts with the N-methyl-D-aspartate channel. Analgesic effects occur at lower doses and amnestic 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, flunk trazepam, ketamine hydrochloride, and GHB, particularly by young people in social settings such as clubs, should put health care professionals on guard to recognize and manage serious reactions. Copyright 2002, American Society of Health-System Pharmacists.

### **Development of hypertension over 6 years in a birth cohort of young middle-aged men: The Cardiovascular Risk Factor Study in southern Sweden (CRISS).**

Henriksson KM; Lindblad U; Gullberg B; Agren BA; Nilsson-Ehle P; Rastam L. *Journal of Internal Medicine* 252(1): 21-26, 2002. (20 refs.)

**Objectives.** To explore the development of hypertension (HT) in a cohort of young middle-aged men. **Design.** Prospective birth-cohort study of men surveyed over 6 years. **Setting.** Helsingborg County Hospital, Sweden, 1990-97. **Subjects.** A total of 628 men born in 1953-54, all surveyed at 37, 40 and 43 years of age. **Main outcome measures.** Systolic blood pressure (SBP), diastolic blood pressure (DBP), S-cholesterol, body mass index (BMI), alcohol consumption, ethnicity. HT was defined as SBP greater than or equal to 140 mmHg and/or DBP greater than or equal to 90 mmHg, or ongoing treatment. Using SBP < 130 mmHg and DBP < 85 mmHg as reference, the odds of conversion to HT in men with high normal blood pressure (BP) (SBP 130-139 mmHg and DBP 85-89 mmHg) was investigated. **Results.** At age 37, 243 men (39%) had reference BP, 167 (26%) had high normal BP and 218 (35%) were hypertensive. Corresponding numbers at age 40 were 265 (42%), 166 (27%) and 197 (31%); and at age 43, 180 (29%), 142 (22%) and 306 (49%), respectively. High normal BP at baseline was associated with the development of HT both at age 40 (odds ratio (OR)=2.45 confid-

ence interval (CI): 1.42-4.22) and at age 43 (OR=2.46, CI: 1.59-3.80), independent of other cardiovascular disease risk factors and ethnicity. The progression to HT was predicted also by S-cholesterol, alcohol consumption, BMI and weight gain. **Conclusions.** Over a short-term period, a substantial proportion of young middle-aged men with high normal BP develop HT with overweight and alcohol consumption as important determinants. These findings have implications for the prevention, screening and medical care of HT in this target population. Copyright 2002, Blackwell Scientific Publications, Ltd.

### **Eclipse: Does it live up to its health claims?**

Slade J; Connolly GN; Lymperis D. *Tobacco Control* 11(Supplement): II64-II70, 2002. (20 refs.)

**Objective:** To examine the plausibility of health claims for Eclipse, a novel smoking article being marketed by the RJ Reynolds Tobacco Company (RJR) as potentially reducing the risk of cancer and other diseases compared to conventional cigarettes. **Data sources:** A company product website (www.eclipse.rjrt.com) summarizing scientific studies of various versions of Eclipse, and the published review of these studies by an expert panel convened by RJR, an independent study comparing the smoke yields of major carcinogens from Eclipse and two low yield "ultralight" brands (Now and Carlton), and an analysis of the levels of these compounds in Eclipse and Premier (its predecessor) over time. **Analysis:** The overall doses and effects of toxins in the aerosol from Eclipse are smaller than those from most conventional cigarettes on a per mg basis. However, two tests that compared Eclipse on a per cigarette basis revealed that Eclipse was as or more toxic than an ultralight cigarette. **Studies show that consumers smoke Eclipse (like they do cigarettes) at puff volumes and puff frequencies for higher than those used for the Federal Trade Commission (FTC) test. RJR's test results, which are based on aerosols generated under FTC conditions, may not reflect actual human dosing, since the operating temperature of Eclipse is highly dependent on these puffing parameters. Even under FTC/International Organization for Standardization (ISO) standard measures, Eclipse smoke carcinogen yields were higher than Now, but similar to Carlton. The yields of carcinogens from Premier and different versions of Eclipse have increased over time. Furthermore, the human studies reviewed by the RJR expert panel do not offer compelling evidence of reduced harm, as they have not been conducted in smokers who have adopted Eclipse. Conclusion:** There is as yet unsatisfactory evidence that Eclipse is less harmful than conventional cigarettes. Eclipse appears to be at least as toxic as some commercially available cigarette brands. Consumers may be misled by RJR's health claims into believing that Eclipse is a safer alternative to conven-

tional cigarettes, underscoring the need for regulatory intervention. Copyright 2002, BMJ Publishing Group.

**Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users.**

Arnsten JH; Demas PA; Grant RW; Gourevitch MN; Farzodegan H; Howard AA et al. *Journal of General Internal Medicine* 17(5): 377-381, 2002. (20 refs.)

Despite a burgeoning literature on adherence to HIV therapies, few studies have examined the impact of ongoing drug use on adherence and viral suppression, and none of these have utilized electronic monitors to quantify adherence among drug users. We used 262 electronic monitors to measure adherence with all antiretrovirals in 85 HIV-infected current and former drug users, and found that active cocaine use, female gender, not receiving Social Security benefits, not being married, screening positive for depression, and the tendency to use alcohol or drugs to cope with stress were all significantly associated with poor adherence. The strongest predictor of poor adherence and, in turn, failure to maintain viral suppression, was active cocaine use. Overall adherence among active cocaine users was 27%, compared to 68% among subjects who reported no cocaine use during the 6-month study period. Consequently, 13% of active cocaine users maintained viral suppression, compared to 46% of nonusers. Interventions to Improve adherence should focus on reducing cocaine use, developing adaptive coping skills, and identifying and treating depression. Copyright 2002, Blackwell Science Ltd.

**Morphological and biochemical corneal changes induced by alcohol.**

Grutters G; Ritz-Timme S; Reichelt JA; Nolle B. *Ophthalmologie* 99(4): 266-269, 2002. (13 refs.)

In our cornea bank, it was noticed that corneas from donors with alcoholism seemed to be of lower quality than corneas from other donors. High blood ethanol concentrations can induce high alcohol concentrations in aqueous and vitreous humor. This could be demonstrated in the case of a lethal alcohol intoxication. We conducted in vitro experiments to clarify the question of alcohol-induced changes of corneas. The corneas were stored in a standardized culture medium including ethanol, formic acid, methanol, and acetaldehyde in concentrations to be expected in chronic alcoholism. During cultivation over 4 weeks, endothelial morphology and extent of aspartic acid racemization in stromal proteins were evaluated. The extent of aspartic acid racemization

served as a biochemical parameter of alcohol-induced protein changes of the corneas. In the in vitro experiments, a drop in the endothelial cell counts could be seen in corneas stored in culture medium with acetaldehyde. The extent of aspartic acid racemization increases in corneas stored in medium containing ethanol, which obviously is the result of alcohol-induced protein degradation. High concentrations of ethanol and its metabolics can be detected in vitreous and aqueous humor in chronic alcoholism. Clearly, these concentrations have a direct toxic effect on the corneal endothelium (acetaldehyde) and on the stromal proteins (ethanol). Copyright 2002, Springer-Verlag.

**Nicotinic receptor expression following nicotine exposure via maternal milk.**

Narayanan U; Birru S; Vaglenova J; Breese CR. *Neuroreport* 13(7): 961-963, 2002. (18 refs.)

Studies have shown nicotine is excreted into maternal milk, so that suckling offspring would be a target of the drug during the pre-weaning period. Since nicotine exposure leads to an upregulation of neuronal nicotinic receptors, this study examines the hypothesis that nicotine delivered via maternal milk is capable of altering neuronal nicotinic receptor regulation in the drug-exposed rat pups. The present study showed that postnatal nicotine exposure via maternal milk was sufficient to induce an upregulation in brain nicotinic receptors similar to that seen in adults that smoke. Such exposure may result in altered neuronal development and synaptic activity and structure, potentially leading to long-term behavioral, learning, and memory deficits. Copyright 2002, Rapid Science Publishers.

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### **Sleep deprivation, disorganization and fragmentation during opiate withdrawal in newborns.**

O'Brien CM; Jeffery HE. *Journal of Paediatrics and Child Health* 38(1): 66-71, 2002. (22 refs.)

Objective: To determine specific sleep characteristics in neonatal opiate withdrawal, referred to as the Neonatal Abstinence Syndrome (NAS), by measuring sleep efficiency, deprivation, disorganization and fragmentation in three groups: (i) healthy term neonates; (ii) opiate-exposed neonates who were treated for opiate withdrawal; and (iii) a group of opiate-exposed neonates who did not require treatment. Methods: A cohort study recording sleep patterns of neonates at 2-10 days of age (after 36 or more weeks of gestation) was carried out. Twenty-one neonates were exposed to opiates during pregnancy and 15 neonates were healthy

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controls. Sleep characteristics were predefined, and treated newborns were divided into early and stabilized treatment groups. Polygraphic recordings of sleep, movement and breathing were made continuously after a daytime feed. Results: Sleep deprivation, disorganization and fragmentation were found in newborns with NAS and were associated with the severity of the withdrawal. Neonates treated for NAS displayed increased wakefulness during early treatment (deprivation), but were similar to controls once stabilized. Both treated and non-treated groups had reduced amounts of quiet sleep (deprivation). Treated newborns showed an increase in indeterminate sleep (disorganization) and arousals-to-wakefulness (fragmentation). Conclusion: This study determined the exact nature and degree of sleep disturbances in newborns during acute opiate withdrawal. The findings contribute to a further understanding of the physiology underlying neonatal opiate withdrawal and suggest that some changes in sleep are due to opiate withdrawal but others may reflect opiate dependency in utero. Copyright 2002, Australian College of Paediatrics.

### **The Delphic oracle: A multidisciplinary defense of the gaseous vent theory.**

Spiller HA; Hale JR; De Boer JZ. *Journal of Toxicology. Clinical Toxicology* 40(2): 189-196, 2002. (27 refs.)

Ancient historical references consistently describe an intoxicating gas, produced by a cavern in the ground, as the source of the power at the oracle of Delphi. These ancient writings are supported by a series of associated geological findings. Chemical analysis of the spring waters and travertine deposits at the site show these gases to be the light hydrocarbon gases methane, ethane, and ethylene. The effects of inhaling ethylene, a major anesthetic gas in the mid-20th century, are similar to those described in the ancient writings. We believe the probable cause of the trancelike state of the Priestess (the Pythia) at the oracle of Delphi during her mantic sessions was produced by inhaling ethylene gas or a mixture of ethylene and ethane from a naturally occurring vent of geological origin. Copyright 2002, Marcel Dekker