

Ajulemic acid: A novel cannabinoid produces analgesia without a "high".

Burstein SH; Karst M; Schneider U; Zurier RB. *Life Sciences* 75(12): 1513-1522, 2004. (28 refs.)

A long-standing goal in cannabinoid research has been the discovery of potent synthetic analogs of the natural substances that might be developed as clinically useful drugs. This requires, among other things, that they be free of the psychotropic effects that characterize the recreational use of cannabis. An important driving force for this goal is the long history of the use of cannabis as a medicinal agent especially in the treatment of pain and inflammation. While few compounds appear to have these properties, ajulemic acid (AJA), also known as CT-3 and IP-751, is a potential candidate that could achieve this goal. Its chemical structure was derived from that of the major metabolite of Delta(9)-THC, the principal psychotropic constituent of cannabis. In preclinical studies it displayed many of the properties of non-steroidal anti-inflammatory drugs (NSAIDs); however, it seems to be free of undesirable side effects. The initial short-term trials in healthy human subjects, as well as in patients with chronic neuropathic pain, demonstrated a complete absence of psychotropic actions. Moreover, it proved to be more effective than placebo in reducing this type of pain as measured by the visual analog scale. Unlike the narcotic analgesics, signs of dependency were not observed after withdrawal of the drug at the end of the one-week treatment period. Data on its mechanism of action are not yet complete; however, the activation of PPAR-gamma, and regulation of eicosanoid and cytokine production, appear to be important for its potential therapeutic effects. Copyright 2004, Elsevier Science Ltd.

Alcohol consumption: An overview of benefits and risks. (review).

Standridge JB; Zylstra RG; Adams SM. *Southern Medical Journal* 97(7): 664-672, 2004. (73 refs.)

Published health benefits of regular light-to-moderate alcohol consumption include lower myocardial infarction rates, reduced heart failure rates, reduced risk of ischemic stroke, lower risk for dementia, decreased risk of diabetes and reduced risk of osteoporosis. Numerous complimentary biochemical changes have been identified that explain the beneficial effects of moderate alcohol consumption. Heavy alcohol consumption, however, can negatively affect neurologic,

cardiac, gastrointestinal, hematologic, immune, psychiatric and musculoskeletal organ systems. Binge drinking is a significant problem even among moderate drinkers and is associated with particularly high social and economic costs. A cautious approach should be emphasized for those individuals who drink even small amounts of alcohol. Physicians can apply the research evidence describing the known risks and benefits of alcohol consumption when counseling their patients regarding alcohol consumption. Copyright 2004, Southern Medical Association.

An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis.

Brady CM; DasGupta R; Dalton C; Wiseman OJ; Berkley KJ; Fowler CJ. *Multiple Sclerosis* 10(4): 425-433, 2004. (31 refs.)

The majority of patients with multiple sclerosis (MS) develop troublesome lower urinary tract symptoms (LUTS). Anecdotal reports suggest that cannabis may alleviate LUTS, and cannabinoid receptors in the bladder and nervous system are potential pharmacological targets. In an open trial we evaluated the safety, tolerability, dose range, and efficacy of two whole-plant extracts of Cannabis sativa in patients with advanced MS and refractory LUTS. Patients took extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension. Assessments included urinary frequency and volume charts, incontinence pad weights, cystometry and visual analogue scales for secondary troublesome symptoms. Twenty-one patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment ($P < 0.05$, Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly ($P < 0.05$, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks. There were few troublesome side effects, suggesting that cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS. Copyright 2004, Arnold, Hodder Headline PLC.

Caffeine ingestion increases the insulin response to an oral-glucose-tolerance test in obese men before and after weight loss.

Petrie HJ; Chown SE; Belfie LM; Duncan AM; McLaren DH; Conquer JA et al. *American Journal of Clinical Nutrition* 80(1): 22-28, 2004. (53 refs.)

Background: Caffeine ingestion decreases the insulin sensitivity index (ISI) for an oral-glucose-tolerance test (OGTT) and decreases insulin-induced glucose disposal in lean male subjects during a hyperinsulinemic clamp. Objective: We examined the effects of caffeine ingestion on insulin and glucose homeostasis in obese men before and after a nutrition and exercise intervention. Design: Nine sedentary, obese [body mass index (in kg/m²): 34.0 +/- 1.0] men who had refrained from exercise and caffeine ingestion for 48 h underwent 2 oral-glucose-tolerance tests (OGTTs). The subjects randomly received caffeine (5 mg/kg) or placebo 1 h before each OGTT. After a 12-wk nutrition and exercise intervention, during which time the subjects avoided dietary caffeine, the OGTTs were repeated. Results: The intervention resulted in decreases (P less than or equal to 0.05) in body weight (8.5 +/- 1.5 kg), percentage body fat (2.8 +/- 0.7%), and fasting glucose, insulin, and proinsulin concentrations and increases in the ISI for the placebo OGTT (P less than or equal to 0.05). Caffeine caused a greater (P less than or equal to 0.05) OGTT insulin response and a lower (P less than or equal to 0.05) ISI both before and after weight loss. The proinsulin-insulin ratio indicated that neither weight loss nor caffeine affected the nature of the beta cell secretion of insulin. Conclusions: A nutrition and exercise intervention improved, whereas caffeine ingestion impaired, insulin-glucose homeostasis in obese men. The results are consistent with previous findings that caffeine ingestion contributes to insulin resistance. Copyright 2004, The American Society for Clinical Nutrition, Inc.

Cannabis improves night vision: a case study of dark adaptometry and scotopic sensitivity in kif smokers of the Rif mountains of northern Morocco.

Russo EB; Merzouki A; Mesa JM; Frey KA; Bach P. *Journal of Ethnopharmacology* 93(1): 99-104, 2004. (31 refs.)

Previous reports have documented an improvement in night vision among Jamaican fishermen after ingestion of a crude tincture of herbal cannabis, while two members of this group noted that Moroccan fishermen and mountain dwellers observe an analogous improvement after smoking kif, sifted Cannabis sativa mixed with tobacco (Nicotiana rustica). Field-testing of night vision has become possible with a portable device, the LKC Technologies Scotopic Sensitivity Tester-1

(SST-1). This study examines the results of double-blinded graduated THC administration 0-20 mg (as Marinol(R)) versus placebo in one subject on measures of dark adaptometry and scotopic sensitivity. Analogous field studies were performed in Morocco with the SST-1 in three subjects before and after smoking kif. In both test situations, improvements in night vision measures were noted after THC or cannabis. It is believed that this effect is dose-dependent and cannabinoid-mediated at the retinal level. Further testing may assess possible clinical application of these results in retinitis pigmentosa or other conditions. Copyright 2004, Elsevier Science Ireland.

Carbohydrate-deficient transferrin (CDT) as a biomarker in persons suspected of alcohol abuse.

Golka K; Sondermann R; Reich SE; Wiese A. *Toxicology Letters* 151(1): 235-241, 2004. (11 refs.)

The coherence of carbohydrate-deficient transferrin (CDT) as a biomarker of alcohol abuse was investigated with 15 conventional laboratory parameters, with the self-reported medical history and with clinical findings, all previously reported to be associated with chronic alcohol intake. In total, 100 male persons who were at least suspected of abusing alcohol were assessed. Medical history, clinical picture and physical examination were taken, and laboratory parameters regarding blood count, liver enzymes, serum lipids, iron balance, Ig A and uric acid were determined. These data were correlated with the CDT values, the daily ethanol intakes reported, and several findings from medical history and clinical examination. The mean CDT level (mean +/- S.D.) of the entire group was 29.4 +/- 19.7 U/l. Eighty-one patients admitted a daily ethanol intake of 60 g or more. The ratio ASPALT (de Ritis ratio) appeared as the best conventional parameter correlated with both CDT and ethanol intake. Mean corpuscular volume (MCV), serum iron, AST and red blood cell count also correlated significantly with CDT. CDT, AST and ferritin correlated significantly with the reported daily ethanol intake. It is concluded that CDT provides a reliable estimate of long-term alcohol intake. Copyright 2004, Elsevier Science Ireland.

Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: A review. (review).

McDonough M; Kennedy N; Glasper A; Bearn J. *Drug and Alcohol Dependence* 75(1): 3-9, 2004. (25 refs.)

Aim: To examine the clinical course of gamma-hydroxybutyrate (GHB) withdrawal and generate management guidelines. Design: Review and analysis of all published reports of GHB or GHB precursor withdrawal identified from electronic searches. Findings:

In total, 38 cases of GHB (n=28) or GHB precursor (n=10) withdrawal were identified, 36 of which were from the US. A rapidly deteriorating course into delirium (53% of cases) was typical for heavily dependent users. Symptoms were broadly similar to alcohol withdrawal but often occurred earlier in usage with delirium being associated with severe dependence as determined by more frequent ingestion. High dose benzodiazepines were effective in pharmacological management of GHB withdrawal. In benzodiazepine refractory cases withdrawal responded to other sedative agents, mainly pentobarbital or chloral hydrate. No withdrawal seizures but one death was recorded. Conclusions: GHB withdrawal is potentially life threatening and requires vigorous clinical management, preferably as an inpatient for severe cases. A management algorithm is proposed. Copyright 2004, Elsevier Science Ireland Ltd.

Club drugs: MDMA, gamma-hydroxybutyrate (GHB), rohypnol, and ketamine.

Gahlinger PM. *American Family Physician* 69(11): 2619-2626, 2004. (59 refs.)

Club drugs are substances commonly used at nightclubs, music festivals, raves, and dance parties to enhance social intimacy and sensory stimulation. The most widely used club drugs are 3,4-methylenedioxymethamphetamine (MDMA), also known as ecstasy; gamma-hydroxybutyrate (GHB); flunitrazepam (Rohypnol); and ketamine (Ketalar). These drugs are popular because of their low cost and convenient distribution as small pills, powders, or liquids. Club drugs usually are taken orally and may be taken in combination with each other, with alcohol, or with other drugs. Club drugs often are adulterated or misrepresented. Any club drug overdose should therefore be suspected as polydrug use with the actual substance and dose unknown. Persons who have adverse reactions to these club drugs are likely to consult a family physician. Toxicologic screening generally is not available for club drugs. The primary management is supportive care, with symptomatic control of excess central nervous system stimulation or depression. There are no specific antidotes except for flunitrazepam, a benzodiazepine that responds to flumazenil. Special care must be taken for immediate control of hyperthermia, hypertension, rhabdomyolysis, and serotonin syndrome. Severe drug reactions can occur even with a small dose and may require critical care. Club drug overdose usually resolves with full recovery within seven hours. Education of the patient and family is essential. Copyright 2004, American Academy of Family Physicians.

Concomitant abuse of anabolic androgenic steroids and human chorionic gonadotrophin impairs spermatogenesis in power athletes.

Karila T; Hovatta O; Seppala T. *International Journal of Sports Medicine* 25(4): 257-263, 2004. (24 refs.)

Abuse of anabolic androgenic steroids (AASs) may be an aetiological factor in male infertility among recreational power athletes. They try to avoid AAS-induced deterioration in spermatogenesis by combining doses of human chorionic gonadotrophin (HCG) and/or antiestrogens with their AAS abuse. Eighteen healthy male power athletes using massive doses of AASs were recruited for the study. Semen samples were collected during AAS abuse and 1.5 and 6 months after cessation of the abuse. They were also asked about their reproductive activity six years after the study. At the end of the AAS cycle, the sperm count was $33.49 \times 10^6/\text{ml}$ (mean \pm SD), and only one subject had azoospermia. At 1.5 months after cessation of the AAS cycles, the mean sperm concentration was $30.42 \times 10^6/\text{ml}$, and after six months $77 \pm 70 \times 10^6/\text{ml}$. There were significant differences between the sample drawn six months after cessation of AAS abuse and both samples drawn during and 1.5 months after the abuse (p less than or equal to 0.05, repeated measures of ANOVA). There was a significant positive correlation between HCG dose during the cycle and the relative amount of morphologically abnormal spermatozoa ($r = 0.60$, $p < 0.01$). The concomitant abuse of HCG and supra-physiological AAS dose cause transient impairment on semen quality in males, although spermatogenesis is maintained with this regimen despite prolonged abuse of massive doses of AAS. Copyright 2004, Georg Thieme Verlag KG.

Methamphetamine abstinence syndrome: Preliminary findings.

Newton TF; Kalechstein AD; Duran S; Vansluis N; Ling W. *American Journal on Addictions* 13(3): 248-255, 2004. (28 refs.)

Retrospective reports suggest that chronic use of methamphetamine is associated with a prolonged abstinence syndrome; however, there are no prospective studies confirming this. Nineteen non-treatment-seeking methamphetamine-dependent volunteers participated in a study of mood during initial abstinence. Moderate levels of depression were reported during the first several days of abstinence, minimal levels reported thereafter. The most prominent symptoms were anhedonia, irritability, and poor concentration. The abstinence syndrome associated with methamphetamine dependence varied considerably in intensity and duration but generally was mild and resolved quickly for most

individuals. Copyright 2004, American Academy of Psychiatrists in Alcoholism and Addictions.

Poppy seed consumption and toxicological analysis of blood and urine samples.

Moeller MR; Hammer K; Engel O. *Forensic Science International* 143(2-3): 183-186, 2004. (12 refs.)

Poppy seeds contain morphine in different amounts. Reported concentrations are up to 294 mg morphine/kg poppy seeds. Since penalties based on Street Traffic Law (24a StVG) in Germany (administrative offence) require definitive proof of morphine in blood samples, and the "Grenzwertkommission" in consultation with the Ministry of Transportation recommended a threshold of free morphine of 10 ng/mL, the question arose whether the consumption of poppy seeds can lead to a blood concentrations equal or higher than 10 ng/mL of free morphine. Therefore, five volunteers ate poppy seed products (50 mg morphine/kg poppy seeds). In urine, all on-site tests were enzyme immunologically positive for opiates and were positive to morphine by GC/MS. All the blood samples were negative to morphine by EIA and to free morphine by GUMS. However, after hydrolysis, morphine was detected by GUMS in all cases. Accordingly, in Germany, penalties based on 24a StVG are not likely to cause road users any concerns should they have consumed poppy seeds. Driver Licensing Authorities, however, should be advised of this problem to avoid unjustified legal measures. Copyright 2004, Elsevier Scientific Publishers Ireland, Ltd.

Effects of grapefruit juice on the pharmacokinetics of the enantiomers of methadone.

Benmebarek M; Devaud C; Gex-Fabry M; Golay KP; Brogli C; Baumann P et al. *Clinical Pharmacology and Therapeutics* 76(1): 55-63, 2004. (43 refs.)

Background and Objectives. Cytochrome P450 (CYP) 3A4 is the main CYP isozyme involved in methadone metabolism. We investigated the influence of grapefruit juice, which contains inhibitors of intestinal CYP3A, on the steady-state pharmacokinetics of methadone. Methods. For 5 days, 8 patients undergoing methadone maintenance treatment received 200 mL water or grapefruit juice 30 minutes before and again together with their daily dose of methadone. Blood sampling for R-, S-, and R,S-methadone plasma determination was

performed over a 24-hour period. CYP3A activity was determined by measuring the plasma 1'-hydroxymidazolam/midazolam ratio. Results. A decrease in the midazolam ratio was measured in all patients after grapefruit juice (mean +/- SD before grapefruit juice, 9.3 +/- 5.9; mean +/- SD after grapefruit juice, 3.9 +/- 1.2; P < .05). Grapefruit juice led to a mean 17% increase in the area under the curve extrapolated to 24 hours for both enantiomers of methadone (range, 3% to 29% [P < .005]; range, -4% to 37% [P < .05]; and range, 1% to 32% [P < .01]; for R-, S-, and R,S-methadone, respectively). A similar increase in peak level and decrease in apparent clearance were measured with grapefruit juice, whereas time to peak level, terminal half-life, and apparent volume during the terminal phase of R-, S-, and R,S-methadone were not affected by grapefruit juice. No symptom of overmedication was either detected by the clinical staff or reported by the patients. Conclusions. Grapefruit juice administration is associated with a modest increase in methadone bioavailability, which is not expected to endanger patients. However, it cannot be excluded that a much stronger effect may occur in some patients, and thus grapefruit juice intake is not recommended during methadone maintenance treatment, in particular in patients initiating such a treatment. Copyright 2004, Mosby, Inc.

Does diet affect breast cancer risk? (review).

Holmes MD; Willett WC. *Breast Cancer Research* 6(4): 170-178, 2004. (103 refs.)

The role of specific dietary factors in breast cancer causation is not completely resolved. Results from prospective studies do not support the concept that fat intake in middle life has a major relation to breast cancer risk. However, weight gain in middle life contributes substantially to breast cancer risk. Alcohol is the best established dietary risk factor, probably by increasing endogenous estrogen levels. Hypotheses relating diet during youth to risk decades later will be difficult to test. Nevertheless, available evidence is strong that breast cancer risk can be reduced by avoiding weight gain during adult years, and by limiting alcohol consumption. Copyright 2004, Biomed Central Ltd.

..