

Library Watch

substance use
medical aspects

www.projectcork.org

Winter 2010

Internationally recognized guidelines for 'sensible' alcohol consumption: Is exceeding them actually detrimental to health and social circumstances?

Evidence from a population-based cohort study.

Batty GD; Lewars H; Emslie C; Gale CR; Hunt K. *Journal of Public Health* 31(3): 360-365, 2009. (33 refs.)

The health and social impact of drinking in excess of internationally recognized weekly (> 21 units in men; > 14 units in women) and daily (> 4 units in men; > 3 units in women) recommendations for 'sensible' alcohol intake are largely unknown. A prospective cohort study of 1551 men and women aged around 55 years in 1988 when typical alcohol consumption was recalled using a 7-day grid. An average of 3.4 years later (1990/92), study participants were re-surveyed (n = 1259; 84.7% of the target population) when they responded to nurse-administered enquiries regarding minor psychiatric morbidity, self-perceived health, hypertension, accidents, overweight/obesity and financial difficulties. Study members were followed up for mortality experience over 18 years. In fully adjusted analyses, surpassing guidelines for sensible alcohol intake was associated with an increased risk of hypertension [daily guidelines only: P-value(trend): 0.012], financial problems [weekly guidelines: P-value(difference): 0.046] and, to a lesser degree, accidents [weekly guidelines: P-value(difference): 0.065]. There was no association between either indicator of alcohol intake and mortality risk. In the present study, there was some evidence for a detrimental effect on health and social circumstances of exceeding current internationally recognized weekly and daily guidelines for alcohol intake. Copyright 2009, Oxford University Press.

New insights into the epidemiology and etiology of Fournier's gangrene: A review of 33 patients.

Czymek R; Hildebrand P; Kleemann M; Roblick U; Hoffmann M; Jungbluth T et al. *Infection* 37(4): 306-312, 2009. (36 refs.)

Background: Fournier's gangrene is a necrotizing fasciitis involving the perineal and genital regions. Even today, this often polymicrobial infection still carries a high mortality rate and continues to be a major challenge to the medical community. The

purpose of this study was to report our experience with this condition and to compare it with those reported in published studies. We also introduce our approach to treatment. Methods: We analyzed data from 33 patients with Fournier's gangrene who were managed in our hospital from 1996 to 2007, focusing on patient gender, age, etiology, predisposing conditions, comorbidities, bacteriology, sepsis, blood results, mortality, and spread of gangrene. Results: 18 (54.5%) of the 33 patients had been referred to our department by smaller district hospitals. The patient cohort consisted of 23 men and ten women with a median age of 59 years (range 40-79 years). The median time between the onset of symptoms and progression to gangrene was 6 days (range 2-28 days). An underlying cause was identified in 27 patients (81.8%). The commonest etiological events were perianal and perirectal abscesses (n = 13; 39.4%). Predisposing factors included diabetes mellitus in 12 cases (36.4%), chronic alcoholism in ten cases (30.3%), immunosuppression in six cases (18.2%), and prolonged immobilization in five cases (15.2%). 17 patients (51.5%) had a body mass index (BMI) of 25 or higher, and 13 patients (39.4%) had a BMI of 30 or higher. Positive cultures were obtained in 30 cases (90.9%). In 26 cases (78.8%), multiple microorganisms were recovered, including nine cases (27.3%) with both aerobes and anaerobes. Sepsis was present in 26 patients (78.8%). The mortality rate was 18.2%. Conclusion: Fournier's gangrene remains a major challenge with a high mortality. Our results suggest that women are more commonly affected than has generally been assumed. Contrary to published reports, we found that anorectal sources appear to account for more cases of Fournier's gangrene than urological sources. Copyright 2009, Urban & Vogel.

Management of injecting drug users admitted to hospital. (review).

Haber PS; Demirkol A; Lange K; Murnion B. *Lancet* 374(9697): 1284-1293, 2009. (118 refs.)

General hospital clinicians frequently deal with injecting drug users because substance use has diverse medical and psychiatric complications. Non-specialist clinicians often initiate management when specialist consultation is not available or accepted by the patient.

Here, we summarise evidence for the management of hospitalised injecting drug users. The first challenge is to engage a drug user into medical care. A non-judgmental approach towards patients and acceptance of their lifestyle choices facilitates engagement. Pragmatic clinical goals can be negotiated and achieved. We also describe common conditions of injecting drug users. Accurate diagnosis and appropriate management focus on common issues such as intoxication, withdrawal, pain management, drug seeking, psychological comorbidity, behavioural difficulties, and pregnancy. Effective management can reduce the medical and social effect of these conditions and is not difficult. Copyright 2009, Elsevier Science.

Alcohol and illicit drug use as precipitants of atrial fibrillation in young adults: A case series and literature review.

Krishnamoorthy S; Lip GYH; Lane DA. *American Journal of Medicine* 122(9): 851-U83, 2009. (37 refs.)
BACKGROUND: Atrial fibrillation in young patients (≤ 45 years) is uncommon. There is the perception that the precipitant in such cases is alcohol, but we also have noted cases related to illicit drug abuse. There are no clear guidelines on the treatment of atrial fibrillation in patients presenting with "lone atrial fibrillation" precipitated by alcohol or illicit drugs.
METHODS: We retrospectively analyzed young (defined as ≤ 45 years) patients with "lone" atrial fibrillation who were admitted to the hospital with electrocardiographically confirmed diagnosis of atrial fibrillation or atrial flutter, precipitated by either alcohol or illicit drugs, over a 6-year period.
RESULTS: Eighty-eight patients aged ≤ 45 years were admitted with atrial fibrillation or atrial flutter. In 22 patients, (mean [SD] age 33.6 [8.4] years; 20 male), alcohol ($n = 19$) and/or illicit drugs ($n = 3$) were found to be the precipitant. One patient required electrical cardioversion, with the remaining patients cardioverting back to sinus rhythm either pharmacologically or spontaneously. Twelve (54.5%) were investigated for atrial fibrillation burden by 24-hour Holter monitoring and the majority also underwent a transthoracic echocardiogram (81.8%). At discharge, 14 (63.6%) patients were treated with anti-arrhythmic drugs and 10 received either antiplatelets or anticoagulants. Most (85%) patients were followed-up for at least 12 months, during which time 6 had further paroxysms; all of whom continued to abuse either alcohol or illicit drugs.
CONCLUSIONS: Alcohol and illicit drugs are arrhythmogenic and are associated with atrial fibrillation. Apart from abstinence, the optimal management of such patients and the long-term effects of these substances on the heart and atrial

fibrillation recurrences are still unclear. Copyright 2009, Elsevier Science.

Crack eye.

Miller AD; Sherman SC. *Journal of Emergency Medicine* 37(1): 75-76, 2009. (2 refs.)

This is a case report of a 34-year-old woman with a history of crack cocaine use who presented after 2 weeks of increasing pain and blurred vision of the right eye. "Crack eye syndrome" was first described in 1989. The term is used to describe corneal injury associated with crack cocaine use. There are several reasons smoking crack cocaine predisposes to corneal injury. First, crack cocaine smoke has a direct toxic effect on the corneal epithelium. This effect is exaggerated by the anesthetic properties of cocaine that lead to a decreased corneal blink reflex. Additionally, devitalization of the corneal nerves decreases the corneal epithelial integrity, leading to neurotrophic keratopathy. Repeated exposure to the alkaloid smoke may cause chronic chemical burns. Finally, in some patients, the smoke acts as a direct irritant, causing excessive eye rubbing that results in infectious complications. Culture isolates frequently grow *Staphylococcus aureus* and streptococcal species, although fungal infections are occasionally present. This patient stated that when she smokes crack, she frequently rubs her eyes. She both used intranasal heroin and smoked cocaine on a regular basis. Examination revealed a hypopyon in the anterior chamber of the right eye and a large corneal ulceration. Copyright 2009, Elsevier Science.

Hypoxic brain injury following heroin overdose.

O'Brien P; Todd J. *Brain Impairment* 10(2): 169-179, 2009. (38 refs.)

Hypoxic brain injury is an under recognised consequence of heroin overdose. This article documents the disability experienced by 10 people with hypoxic brain injuries following heroin overdose who presented in the 2-year period July 1997 to June 1999 at the Royal Talbot Rehabilitation Centre, a brain injury rehabilitation facility in Melbourne, Australia. Medical histories of these clients were reviewed and follow-up interviews were conducted between 2 and 4 years post-injury. Measures included the Functional Independence Measure (FIM) and the Community Integration Questionnaire (CIQ). The results showed that there were significant and enduring consequences for most of the 10 participants. At follow-up two participants had died from subsequent overdose, three required support to live in the community and one lived in an aged care facility. Only one participant was able to return to work. Cognitive problems were

present in most of the group and problem solving and social interaction difficulties were the most commonly recorded problems. Three cases are described in detail to highlight some of the significant issues identified in this sample. Implications for the rehabilitation of people with brain injury following heroin overdose are discussed. Copyright 2009, Australian Academy Press.

Comparative treatment and mortality correlates and adverse event profile of implant naltrexone and sublingual buprenorphine.

Reece AS. *Journal of Substance Abuse Treatment* 37(3): 256-265, 2009. (71 refs.)

There is increasing interest in the use of implantable naltrexone as a new treatment for opiate dependence. This center has been one of the leaders in this form of treatment in Australia and has recently completed a registry-controlled review of our mortality data. As part of the study of the safety profile of this therapy, we were interested to review both the treatment correlates of previously presented mortality data and of adverse events. A total of 255 naltrexone implant therapy (NIT) and 2,518 buprenorphine (BLIP) patients were followed for 1,322.22 and 8,030.02 patient-years, respectively. NIT patients had significantly longer days in treatment per episode (mean standard deviation, 238.32 +/- 110.11 vs. 46.96 +/- 109.79), total treatment duration (371.21 +/- 284.64 vs. 162.50 +/- 245.76), and mean treatment times but fewer treatment episodes than BUP (all $p < .0001$). Serious local tissue reaction or infection each occurred in 1% of 200 NIT episodes. These data show that NIT economizes treatment resources without compromising safety concerns. Copyright 2009, Elsevier Science.

Unintentional and intentional injuries due to opiate abuse.

Stenbacka M. *Heroin Addiction and Related Clinical Problems* 10(4): 29-32, 2008

Alcohol and drug abuse runs a generally higher risk of fatal and non-fatal injury risk. But the overall injury pattern in relation to opiate abuse is not well known. Aim. The aim of the study is to analyse intentional and unintentional injuries -in the forms of accidents and suicides, as reported in the case histories of opiate abusers compared to the general population in Stockholm. Method: The analyses are based on a cohort of 1700 drug abusers identified in 1967 and followed until 2003 and 2005 with respect to causes of death, and inpatient care stays. Results: The results show that 817 (48%) subjects took opiate as their primary drug and nearly one third of these had died due to an intentional or an unintentional injury. Nearly

60 percent of the opiate abusers had been treated, at least once, in hospital for an injury. On average, the total cohort had been treated in hospital for an injury 1.6 times (range, 0-40 times), while the opiate abusers who had been treated in hospital for a drug-related diagnosis at least once had, on average, also been treated for an injury diagnosis 2.8 times (0-20 times) during the follow-up period. Conclusion: Societal support and injury prevention need to be improved in this vulnerable group. Copyright 2008, European Opiate Addiction Treatment Association.

Ethanol-drug absorption interaction: Potential for a significant effect on the plasma pharmacokinetics of ethanol vulnerable formulations.

Lennernas H. *Molecular Pharmaceutics* 6(5): 1429-1440, 2009. (84 refs.)

Generally, gastric emptying of a drug to the small intestine is controlled by gastric motor activity and is the main factor affecting the onset of absorption. Accordingly, the emptying rate from the stomach is mainly affected by the digestive state, the properties of the pharmaceutical formulation and the effect of drugs, posture and circadian rhythm. Variability in the gastric emptying of drugs is reflected in variability in the absorption rate and the shape of the plasma pharmacokinetic profile. When ethanol interacts with an oral controlled release product, such that the mechanism controlling drug release is impaired, the delivery of the dissolved dose into the small intestine and the consequent absorption may result in dangerously high plasma concentrations. For example, the maximal plasma concentration of hydromorphone has individually been shown to be increased as much as 16 times through in vivo testing as a result of this specific pharmacokinetic ethanol-drug formulation interaction. Thus, a pharmacokinetic ethanol-drug interaction is a very serious safety concern when substantially the entire dose from a controlled release product is rapidly emptied into the small intestine (dose dumping), having been largely dissolved in a strong alcoholic beverage in the stomach during a sufficient lag-time in gastric emptying. Based on the literature, a two hour time frame for screening the in vitro dissolution profile of a controlled release product in ethanol concentrations of up to 40% is strongly supported and may be considered as the absolute minimum standard. It is also evident that the dilution, absorption and metabolism of ethanol in the stomach are processes with a minor effect on the local ethanol concentration and that ethanol exposure will be highly dependent on the volume and ethanol concentration of the fluid ingested, together with the rate of intake and gastric emptying. When and in which patients a

clinically significant dose dumping will happen is almost impossible to predict and will depend on drinking behavior and the highly variable gastrointestinal factors of importance for dissolution, transit and absorption. Therefore, controlled release products which show a vulnerability to ethanol during two hours in vitro should be required to demonstrate clinical safety by going through in vivo testing with an alcoholic beverage of up to 40% ethanol and of a sufficient volume (probably 120 mL or more), consumed in a relatively short period of time. Alternatively, such preparations should be reformulated in accordance with quality-by-design principles. Copyright 2009, American Chemical Society.

Human immunodeficiency virus (HIV) infection of human macrophages is increased by dopamine: A bridge between HIV-associated neurologic disorders and drug abuse.

Gaskill PJ; Calderon TM; Luers AJ; Eugenin EA; Javitch JA; Berman JW. *American Journal of Pathology* 175(3): 1148-1159, 2009. (75 refs.)

The prevalence of human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND) that result from HIV infection of the central nervous system is increasing. Macrophages, the primary target for HIV within the central nervous system, play a central role in HIV-induced neuropathogenesis. Drug abuse exacerbates HAND, but the mechanism(s) by which this increased neuropathology results in more severe forms of HAND in HIV-infected drug abusers is unclear. The addictive and reinforcing effects of many drugs of abuse, such as cocaine and methamphetamine, are mediated by increased extracellular dopamine in the brain. We propose a novel mechanism by which drugs of abuse intensify HIV neuropathogenesis through direct effects of the neurotransmitter dopamine on HIV infection of macrophages. We found that macrophages express dopamine receptors I and 2, and dopamine activates macrophages by increasing ERK 1 phosphorylation. Our results demonstrate for the first time that dopamine increases HIV replication in human macrophages and that the mechanism by which dopamine mediates this change is by increasing the total number of HIV-infected macrophages. This increase in HIV replication is mediated by activation of dopamine receptor 2. These findings suggest a common mechanism by which drugs of abuse enhance HIV replication in macrophages and indicate that the drug abuse-heightened levels of central nervous system dopamine could increase viral replication, thereby accelerating the development of HAND. Copyright 2009, American Society of Investigative Pathology.

Low vitamin D status of patients in methadone maintenance treatment.

Kim TW; Alford DP; Holick MF; Malabanan AO; Samet JH. *Journal of Addiction Medicine* 3(3): 134-138, 2009. (40 refs.)

Aim: To examine the prevalence and risk factors of low vitamin D status (vitamin D deficiency or insufficiency) among patients in a methadone maintenance treatment (MMT) program. Design: Cross-sectional study of subjects recruited from an MMT program in a higher latitude (Boston, MA). Measurements: Standardized survey and medical record review were used to assess patient characteristics. Serum was tested to determine vitamin D deficiency (25-hydroxyvitamin D <20 ng/mL) and insufficiency (25-hydroxyvitamin D between 20 and 30 ng/mL). Multivariable analyses were used to assess risk factors associated with vitamin D deficiency. Findings: Low vitamin D status was found in 52% of the subjects (48 of 93), deficiency in 36%, and insufficiency in an additional 16%. Older age (OR = 3.47; 95% CI 1.31-9.22) and black or Hispanic race/ethnicity (OR 3.34; 95% CI 1.30-8.58) were significantly associated with higher risk of vitamin D deficiency. Conclusion: Low vitamin D status was present in a majority of patients recruited from an MMT program. This raises the question as to whether this is a generalizable phenomenon and whether these patients are at higher risk of complications of low vitamin D status including bone pain, periodontal disease, osteomalacia, and cardiovascular disease. Copyright 2009, Lippincott, Williams & Wilkins.

The biological responses to resveratrol and other polyphenols from alcoholic beverages.

Brown L; Kroon PA; Das DK; Das S; Tosaki A; Chan V et al. *Alcoholism: Clinical and Experimental Research* 33(9): 1513-1523, 2009. (119 refs.)

Although excessive consumption of ethanol causes multi-organ damage, moderate consumption, particularly of red wine, is protective against all-cause mortality. These protective effects could be due to one or many components of the complex mixture of bioactive compounds present in red wine including flavonols, monomeric and polymeric flavan-3-ols, highly colored anthocyanins as well as phenolic acids and the stilbene polyphenol, resveratrol. The therapeutic potential of resveratrol, firstly in cancer chemoprevention and then later for cardioprotection, has stimulated many studies on the possible mechanisms of action. Further indications for resveratrol have been developed, including the prevention of age-related disorders such as neurodegenerative diseases, inflammation, diabetes,

and cardiovascular disease. These improvements are remarkably similar yet there is an important dichotomy: low doses improve cell survival as in cardio- and neuro-protection yet high doses increase cell death as in cancer treatment. Fewer studies have examined the responses to other components of red wine, but the results have, in general, been similar to resveratrol. If the nonalcoholic constituents of red wine are to become therapeutic agents, their ability to get to the sites of action needs to be understood. This mini-review summarizes recent studies on the possible mechanisms of action, potential therapeutic uses, and bioavailability of the nonalcoholic constituents of alcoholic beverages, in particular resveratrol and other polyphenols. Copyright 2009, Research Society on Alcoholism.

The genetic basis of individual differences in reward processing and the link to addictive behavior and social cognition. (review).

Yacubian J; Buchel C. *Neuroscience* 164(1, Special Issue): 55-71, 2009. (182 refs.)

Dopaminergic neurotransmission is widely recognized to be critical to the neurobiology of reward, motivation and addiction. Interestingly, social interactions and related behavior also activate the same neuronal system. Consequently, genetic variations of dopamine neurotransmission are thought influence reward processing that in turn may affect distinctive social behavior and susceptibility to addiction. This review focuses on advances made to date in an effort to link genetic individual variations and reward processing as a possible basis for addictive behaviors. Copyright 2009, IMBRO.

The neurobiology of addiction: Where we have been and where we are going.

Koob GF; Simon EJ. *Journal of Drug Issues* 39(3): 759-776, 2009. (30 refs.)

A number of dramatic breakthroughs in the neurobiology of addiction have occurred in the past 40 years. Two domains will be highlighted: the neurocircuitry of addiction and the molecular biology of addiction targets. The neurobiological substrates for the reinforcing effects of drugs of abuse have been largely identified both at the initial site of action and in the circuitry involved. In human imaging studies, decreases in dopaminergic function have been identified as a key element of addiction, lending support for research on the role of dopamine in addiction. Three novel areas currently are emerging: the role of deficits in frontal cortex functioning, changes in the brain neurocircuitry that convey long-term vulnerability to relapse, and the role of nondopaminergic systems in the neuroadaptations

associated with the development of drug dependence. There have been major advances in our understanding of the molecular biology of addiction; the greatest contribution has been in the understanding of the molecular mechanisms of opioid action. This paper reviews the major developments in our understanding of the molecular biology of the endogenous opioid system and the use of genomics to advance our knowledge of the function and regulation of opioid receptors and endorphins. Copyright 2009, Journal of Drug Issues, Inc.

Debunking the claim that abstinence is usually healthier for smokers than switching to a low-risk alternative, and other observations about anti-tobacco-harm-reduction arguments.

Phillips CV. *Harm Reduction Journal* 6(1): article 29, 2009. (17 refs.)

Nicotine is so desirable to many people that when they are given only the options of consuming nicotine by smoking, with its high health costs, and not consuming nicotine at all, many opt for the former. Few smokers realize that there is a third choice: non-combustion nicotine sources, such as smokeless tobacco, electronic cigarettes, or pharmaceutical nicotine, which eliminate almost all the risk while still allowing consumption of nicotine. Widespread dissemination of misleading health claims is used to prevent smokers from learning about this lifesaving option, and to discourage opinion leaders from telling smokers the truth. One common misleading claim is a risk-risk comparison that has not before been quantified: A smoker who would have eventually quit nicotine entirely, but learns the truth about low-risk alternatives, might switch to an alternative instead of quitting entirely, and thus might suffer a net increase in health risk. While this has mathematical face validity, a simple calculation of the tradeoff -- switching to lifelong low-risk nicotine use versus continuing to smoke until quitting -- shows that such net health costs are extremely unlikely and of trivial maximum magnitude. In particular, for the average smoker, smoking for just one more month before quitting causes greater health risk than switching to a low-risk nicotine source and never quitting it. Thus, discouraging a smoker, even one who would have quit entirely, from switching to a low-risk alternative is almost certainly more likely to kill him than it is to save him. Similarly, a strategy of waiting for better anti-smoking tools to be developed, rather than encouraging immediate tobacco harm reduction using current options, kills more smokers every month than it could possibly ever save. Copyright 2009, BioMed Central.