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MAY - JUNE 2008

Interventions and Assessments

Opioid Maintenance Therapy Saves Lives

Opioid-dependent patients are 13 times more likely to die than their age- and sex-matched peers in the general population. To examine predictors of long-term mortality, Australian researchers conducted a 10-year follow-up study of 405 heroin-dependent patients who had participated in a randomized trial comparing methadone and buprenorphine.

- Overall mortality was 8.8 deaths per 1000 person-years of follow-up (0.66 during opioid maintenance treatment and 14.3 while out of treatment).
- Each additional opioid maintenance treatment episode lasting more than 7 days decreased mortality by 28%.
- Subjects who were using more heroin at baseline had a 12% lower mortality rate overall, likely because they spent more time in opioid maintenance treatment.

Comments: Often overlooked in the controversy over opioid maintenance therapy is the reality that opioid dependence has a high fatality rate. The current study highlights that opioid maintenance treatment saves lives. The selection of the treatment episode as greater than 7 days strongly suggests that opioid maintenance, not detoxification, reduces mortality. The time is right to promulgate opioid maintenance therapy with either buprenorphine or methadone as the standard-of-care, first-line treatment for opioid dependence.

Peter D. Friedmann, MD, MPH

Reference: Gibson A, Degenhardt L, Mattick RP, et al. Exposure to opioid maintenance treatment reduces long-term mortality. *Addiction*. 2008;103(3):462-468.

Computerized Alcohol Screening and Brief Intervention May Reduce Hazardous Drinking

Web-based strategies have the potential to improve delivery of alcohol screening and brief intervention. In a controlled study, researchers randomized 429 university students who screened positive for hazardous or harmful drinking* to either a single web-based brief intervention, a web-based brief intervention with follow-up interventions at 1 and 6 months, or a control group receiving an educational pamphlet only. Interventions included alcohol assessments and personalized feedback. Participants completed web-based outcome assessments at 6 and 12 months.

- Compared with controls, participants in the single intervention group re-

ported significantly lower frequency of drinking at 6 months (rate ratio [RR], 0.79), lower total alcohol consumption at 6 and 12 months (RR, 0.77 at both times), and fewer academic consequences at 6 and 12 months (RR, 0.76 and 0.80, respectively).

- Participants in the multidose group had similar results as the single-dose group but also reported fewer drinks on drinking days at 6 months (RR, 0.85), lower frequency of heavy drinking episodes at 6 months (RR 0.65), and fewer adverse consequences of heavy drinking at 12 months (RR, 0.81).

Comments: These findings suggest computerized web-based interventions have
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*Subjects scored 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT).

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Computerized Screening and Intervention (continued from page 1)

potential to increase the use of alcohol screening and brief intervention in outpatient settings without sacrificing the efficacy of face-to-face interventions. Because the study's computerized interventions occurred in a university health clinic before a clinical visit, it is possible the intervention prompted participants to have further alcohol discussions with their clinicians. This

technology will require further testing in other settings and populations.
Kevin L. Kraemer, MD, MSc

Reference: Kypri K, Langley JD, Saunders JB, et al. Randomized controlled trial of web-based alcohol screening and brief intervention in primary care. *Arch Intern Med.* 2008;168(5):530-536.

Treatment for Alcohol Withdrawal Is Poor Despite Proven Therapies

Evidence-based practice guidelines are clear that patients at risk for alcohol withdrawal should be monitored and treated with benzodiazepines if the risk is high enough or symptoms are substantial. In a retrospective record review, researchers studied the implementation of such an approach—symptom-triggered therapy—at 2 large general hospitals on 124 inpatients from over 40 different specialty services. The protocol required that patients be able to communicate.

- More than half of patients (52%) were treated inappropriately.
- Thirty-five had no recent heavy alcohol use and therefore were not at risk for withdrawal, 9 could not communicate well, and 20 had neither recent heavy drinking nor were able to communicate.
- Eleven patients had adverse outcomes (i.e., seizure, delirium,

death), 7 of whom had received inappropriate treatment.

Comments: People who have not been drinking heavily recently cannot have and should not be treated for alcohol withdrawal. People who cannot communicate can and sometimes should receive withdrawal treatment but not using a symptom scale that requires verbal communication. Known effective treatments exist for alcohol withdrawal, and they are quite straightforward. If this report is in any way representative of other hospitals in the US, we have a large challenge to appropriately implementing care for this common condition.

Richard Saitz, MD, MPH

Reference: Hecksel KA, Bostwick JM, Jaeger TM, et al. Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. *Mayo Clin Proc.* 2008;83(3):274-279.

Adherence to Practice Guidelines Improves Outcomes of Opiate Agonist Treatment

Although treating heroin dependence with high-dose methadone and psychosocial services is well-supported by clinical trial data and practice guidelines, many opioid treatment programs (OTP) do not follow all evidence-based practices. To determine whether adhering to guidelines improves patient outcomes, researchers analyzed data from 232 patients recruited from OTPs in the US Veterans Administration

health system that were selected based on whether they were guideline-concordant or guideline-discordant. OTPs in both the guideline-concordant and guideline-discordant groups were geographically similar, as were baseline measures of heroin use, employment, illegal activities, and mental health among patients. The sample also had a high level of psychiatric impairment.

Adherence to Guidelines in Opiate Agonist Treatment (continued from page 2)

- In the guideline-concordant OTPs, 79% of patients received doses of methadone in the recommended high-dose range compared with 47% of patients in the guideline-discordant OTPs.
- Guideline-concordant OTPs had more full-time equivalent staff than guideline-discordant clinics despite similar numbers of patients.
- At 6-month follow-up, patients in guideline-concordant OTPs had greater reductions in heroin use, greater improvements in global mental health, and a higher percentage of opioid-free urine tests.

Comments: These results demonstrate that adherence to practice guidelines (which emphasize clinical practices found

efficacious in controlled trials—e.g., high-dose methadone and psychosocial services) improves opioid treatment outcomes in everyday practice with severely impaired patients. Greater effort should be made to increase adherence to clinical practice guidelines for OST through policy changes.

Julia H. Arnsten, MD, MPH

Reference: Humphreys K, Trafton JA, Oliva EM. Does following research-derived practice guidelines improve opiate-dependent patients' outcomes under everyday practice conditions? Results of the Multisite Opiate Substitution Treatment study. *J Subst Abuse Treat.* 2008; 34(2):173-179.

American Heart Association Releases Guidelines on Treatment of Cocaine-Associated Chest Pain

There are approximately 500,000 cocaine-associated emergency department visits annually, and it is estimated that 40% involve chest pain. Cocaine increases heart rate and blood pressure, constricts the coronary arteries, induces a prothrombic state, and accelerates atherosclerosis. The American Heart Association conducted a systematic review of the literature to assist in the care of patients with cocaine-associated chest pain (CACP). Primary findings and recommendations are as follows:

- Myocardial infarction (MI) occurs in 0.7% to 6% of patients who present with CACP.
- Patients with CACP, unstable angina, or MI should be treated similarly to those with possible acute coronary syndrome, including the provision of aspirin. In addition, intravenous benzodiazepines should be provided.
- Persistent hypertension should be managed with sodium nitroprusside, nitroglycerin, or intravenous phentolamine.
- Patients at low risk (no electrocardiogram [ECG] changes and no elevation in cardiac troponins) can be

safely observed in a chest pain observation unit for 6 to 12 hours.

- Patients at high-risk (ECG changes and elevated troponins) should be admitted to a telemetry bed. In these patients, β -blockers should be avoided acutely, and antithrombic and antiplatelet therapy should be administered per standard guidelines.
- In all patients, substance abuse counseling should be part of discharge planning.

Comments: The literature is limited due to the low number of randomized clinical trials or well-performed observational studies. Nonetheless, this review provides a useful compilation of the available literature on this topic.

David A. Fiellin, MD

Reference: McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation.* 2008;117(14):1897-1907.

Availability of Smoking Cessation Services for Patients in Substance Abuse Treatment Programs

Patients in treatment for drug use disorders have a high prevalence of smoking, but treating nicotine dependence in outpatient substance abuse treatment (OSAT) facilities is uncommon. To evaluate the availability of smoking cessation services in US OSAT programs and to identify factors associated with offering such services, researchers analyzed interviews with 550 pairs of OSAT administrative directors and clinical supervisors completed between 2004 and 2005 from a nationally representative sample of programs.

- 41% of all programs offered either counseling or pharmacotherapy to help patients quit smoking, and 16.5% of all programs offered pharmacotherapy.

- Among programs offering pharmacotherapy, approximately one-third offered bupropion or other antidepressants, one-third offered nicotine replacement therapy, and one-third offered both.
- Factors independently associated with the availability of smoking cessation counseling or pharmacotherapy included hospital affiliation, breadth of services (more medical staff was associated with greater availability of smoking cessation medications), smoking assessment, and physical health as an important treatment goal.
- The availability of addiction treatment medications other than methadone was associated with a twofold

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Availability of Smoking Cessation Treatment (continued from page 3)

increase in the availability of both smoking cessation counseling and pharmacotherapy services.

- Overall, 98% of OSAT programs were smoke-free.

Comments: Smoking is highly prevalent among patients in substance abuse treatment, but smoking cessation treatment in OSAT settings remains limited. To better integrate treatment for tobacco dependence with substance abuse treatment, new policies are needed at state and federal

levels. Such policies, already implemented in some states, should include staff training and support of smoke-free OSAT programs.

Julia H. Arnsten, MD, MPH

Reference: Friedmann PD, Jiang L, Richter KP. Cigarette smoking cessation services in outpatient substance abuse treatment programs in the United States. *J Subst Abuse Treat.* 2008;34(2):165-172.

Health Outcomes

Adopting Moderate Alcohol Consumption in Middle Age Reduces Cardiovascular Risk

Despite the known cardiovascular (CV) benefits of moderate alcohol consumption, initiation of alcohol use in middle age to obtain those benefits is not recommended. To assess whether adopting moderate alcohol use in middle age would lower CV risk, King et al. examined a cohort of men and women aged 45-64 years who were participating in a 10-year observational study.

Among the 7697 participants who were nondrinkers at baseline and had no existing CV disease at 6-year follow-up, 6075 were available for assessment at the end of the study. A fatal or non-fatal CV event between years 6 and 10 was assessed as the primary outcome. Moderate alcohol use was classified as 1-7 drinks per week for women or 1-14 drinks per week for men. Authors calculated the reduction of CV events and mortality after 4 years controlling for known CV risk factors in the 6075 available participants.

- Overall, a 38% reduction (6.9% versus 10.7%) in CV events was found among new moderate drinkers com-

pared with nondrinkers (OR 0.62; 95% CI, 0.40-0.95).

- New drinkers experienced no change in overall mortality.
- New drinkers had significantly lower LDL (123.5 mg/dl versus 127.8 mg/dl) and higher HDL (54.7 mg/dl versus 51.7 mg/dl) cholesterol than nondrinkers.

Comments: Despite the relatively brief follow-up, the CV benefit noted was impressive and adds to similar cohort data involving men. Given the cohort study design and the risks of alcohol-related injury or malignancy, these data are insufficient to change current recommendations. Nonetheless, they do enhance the case for a randomized controlled trial to resolve whether to recommend moderate alcohol consumption to those without past alcohol problems to yield cardioprotective benefits.

Jeffrey H. Samet, MD, MA, MPH

Reference: King DE, Mainous AG 3rd, Geesey ME. Adopting moderate alcohol consumption in middle age: subsequent cardiovascular events. *Am J Med.* 2008;121(3):201-206.

Are Myocardial Infarction Survivors Who Smoke Marijuana at Higher Risk of Death?

Although a previous study demonstrated an increased risk of myocardial infarction (MI) within 1 hour of smoking marijuana compared with periods of nonuse, the net impact of marijuana use on mortality has not been established. Researchers studied 1913 adults hospitalized for MI between 1989 to 1994 to determine whether marijuana smoking within 1 year of MI was associated with increased risk of mortality.

- Of 1913 MI patients followed for a mean of 3.8 years, 317 died.
- Of 52 subjects who used marijuana in the year following MI, 7 died during follow-up.
- In comparisons to nonusers, the hazard ratios in sub-

jects using marijuana less than weekly and weekly or more were 2.5 and 4.2, respectively.

- Additional analyses controlling for concurrent use of cocaine, tobacco, and alcohol found similar effects.

Comments: Marijuana use before MI is associated with increased risk of mortality after MI. Determining whether marijuana use directly increases mortality or is a marker of another unmeasured cause awaits further study.

Alexander Y. Walley, MD, MSc

Reference: Mukamal KJ, Maclure M, Muller JE, et al. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *Am Heart J.* 2008; 155(3):465-470.

Alcohol Tolerance: Prevalence and Potential Implications in Young Drinkers

Some teenagers and young adults report tolerance (an increase in the amount required to achieve intoxication) without meeting criteria for alcohol dependence. To define the prevalence and correlates of tolerance in this age group, investigators analyzed data from a sample of 649 persons aged 18-22 years who drank alcohol and whose alcohol and other substance use was well-characterized.

Tolerance was defined as participants reporting that they needed to “drink a great deal more in order to get an effect” or “could no longer get high on the amount [they] used to drink.”

- Nine percent of participants reported tolerance but no current or past alcohol use disorder (AUD).*
- Persons with tolerance but not an AUD were more likely to have alcohol-related problems than those without tolerance.
- Though participants with tolerance but no AUD re-

ported illicit drug use more commonly than those without tolerance, tolerance was not associated with illicit drug use in multivariable analysis.

Comments: Nearly 1 in 10 young adults who drink alcohol report tolerance but do not meet criteria for alcohol abuse or dependence. Tolerance is associated with alcohol consequences in this age group, yet many current screening tools do not ask about tolerance. Research on the potential health benefits of identifying and intervening with young people who drink and have tolerance but not an alcohol use disorder is needed.

Marc N. Gourevitch, MD, MPH

*AUD includes alcohol abuse and dependence.

Reference: Schuckit MA, Smith TL, Hesselbrock V, et al. Clinical implications of tolerance to alcohol in nondependent young drinkers. *Am J Drug Alcohol Abuse*. 2008;34(2):133-149.

Effects of Buprenorphine after Accidental Ingestion by Children

Buprenorphine is a partial agonist at the mu-opioid receptor used to treat opioid dependence. There is a ceiling to the opioid effects that buprenorphine produces, leading to a greater safety profile than most opioids, although adverse effects could result from accidental ingestion in opioid naïve subjects. Researchers sought to identify and analyze all exposures to buprenorphine in children <6 years of age as reported in a national monitoring system over a 3-year period. Primary findings were as follows:

- Of the 86 events identified, 77% involved buprenorphine/naloxone tablets.
- The mean dose of buprenorphine ingested was 3 mg with a range of 0.03 to 24 mg. No child who ingested <4 mg experienced a severe effect, while all of the children who ingested >4 mg experienced some effect.
- In the 54 children who developed toxicity, clinical

effects included lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), irritability (5%), pallor (3%), and coma (2%). There were no fatalities.

Comments: This study provides useful information and guidance regarding the likely effects of buprenorphine after accidental ingestion by young children. The author's conclusions that “any child ingesting >2 mg and children <2 years of age ingesting more than a lick or taste should be referred to the emergency department” for a minimum of 6 hours of observation are prudent. Patients receiving buprenorphine products should be instructed about safe storage to avoid accidental exposures.

David A. Fiellin, MD

Reference: Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. *Pediatrics*. 2008;121(4);e782-e786.

Does Moderate Alcohol Use Help Healthy Elderly Men Live to Age 90 Years?

Although moderate alcohol use is associated with lower total mortality, it is not known whether alcohol use helps individuals survive to very old age and to function well in old age. To identify modifiable factors associated with survival to age 90 years, researchers prospectively followed 2357 men (mean age 72 years at baseline) for up to 25 years and assessed the association of self-reported baseline and follow-up characteristics with survival to age 90 years and late-life physical function.

- Forty-one percent of participants survived to age 90 years or beyond.
- Regular exercise and the absence of smoking, diabetes, hypertension, and obesity at baseline were associated with survival to age 90 years in age-adjusted and multivariable models.
- Alcohol use was not associated with survival to age 90 years in the models.

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Moderate Alcohol Use and Longevity (continued from page 5)

- Late-life physical function was higher in baseline daily drinkers and in those who drank 1-6 drinks per week compared with those who drank <1 drink per week, but these differences were not statistically significant.

Comments: In this study, moderate alcohol use did not help “younger” elderly men reach age 90 years or to have better physical function in late life. The study did not assess the trajectory of alcohol use before or after the baseline

measurement. It is possible the potential survival benefit from moderate alcohol use is derived from alcohol use earlier in life and in those with cardiovascular risk factors.

Kevin L. Kraemer, MD, MSc

Reference: Yates LB, Djoussé L, Kurth T, et al. Exceptional longevity in men: modifiable factors associated with survival and function to age 90 years. *Arch Intern Med.* 2008; 168(3):284-290.

Wine, but Not Other Alcoholic Beverages, Associated with Less Dementia

Few studies have examined whether moderate amounts of different alcoholic beverages, such as beer, wine, and spirits, have similar protective effects for the risk of dementia. Swedish researchers conducted a prospective study to address the question in a random sample of 1462 Swedish women aged 38-60 years at baseline and followed over 34 years. Of this sample, 162 women developed a diagnosis of dementia. Alcohol intake and other lifestyle habits were recorded at baseline and on 3 subsequent occasions. Results were as follows:

- Wine was protective for dementia in a statistical analysis that included alcohol drinking at baseline and during follow-up, with the strongest association among women whose only alcohol consumption was wine.
- The association was stronger among smokers than among nonsmokers.
- Consumption of spirits at baseline was associated with a slightly increased risk of dementia.
- Beer consumption did not have an effect on dementia

risk; however, its association with longevity was comparable to that of wine.

Comments: In this study, women who consumed only wine had a large decrease in risk of dementia that was not seen with beer or spirits. The analysis was well-done. Researchers studied a population-based sample, they included not only baseline data on alcohol intake but repeated updates over 34 years, and there were enough never-drinkers (20-25%) to provide an appropriate comparison group. Although these findings from analyses that adjusted for education and social class suggest that only wine decreases the risk of dementia, the possibility remains that other lifestyle factors may have influenced the results.

R. Curtis Ellison, MD

Reference: Mehlig K, Skoog I, Guo X, et al. Alcoholic beverages and incidence of dementia: 34-year follow-up of the prospective population study of women in Göteborg. *Am J Epidemiol.* 2008;167(6):684-691.

Effects of Exercise and Alcohol Intake on Cardiovascular Risk and Total Mortality

In an effort to determine the combined influence of leisure-time physical activity and alcohol intake on the risk of fatal ischemic heart disease (IHD), researchers conducted a prospective cohort study of 11,914 Danish men and women aged 20 or older at baseline and followed them for approximately 20 years. None of the subjects had a preexisting diagnosis of heart disease. Of the 5901 total deaths occurring over the study period, 1242 were attributed to IHD. Analyses were adjusted for alcohol consumption, physical activity, tobacco use, body mass index, education, and marital status.

- For both genders, being physically active (low or moderate-to-high levels versus none) was associated with lower hazard ratios for both fatal IHD and all-cause mortality regardless of weekly alcohol consumption.

- Alcohol intake was inversely associated with fatal IHD and had a U-shaped association with all-cause mortality.

Comments: Results from this large prospective study show that physical activity and all levels of alcohol consumption have independent inverse associations with fatal IHD risk. For all-cause mortality, at least some physical activity resulted in a lower risk, but heavier drinking (defined as 15+ drinks per week in this study) did not.

R. Curtis Ellison, MD

Reference: Pedersen JØ, Heitmann BL, Schnohr P, et al. The combined influence of leisure-time physical activity and weekly alcohol intake on fatal ischaemic heart disease and all-cause mortality. *Eur Heart J.* 2008;29(2):204-212.

The Impact of Peer and Parental Modeling on Impaired Driving in Teenagers

Motor vehicle accidents are the leading cause of death for young people, and up to 40% involve substance-related impairment. To better understand the factors contributing to impaired driving in this age group, investigators administered anonymous questionnaires to 994 urban and 1600 rural 10th and 12th grade students on Vancouver Island, Canada. Of the sample, 1192 students had driving permits that required adult supervision and limitations on the number of nonrelatives in the car.

- Just over half of students reported riding in a car with an adult who had been drinking, and one-fifth to one-third reported driving with an adult who had smoked cannabis.
- One-fifth to one-third of students reported riding with a peer driver who had been drinking and about one-third had ridden with a cannabis-impaired peer driver.
- Of students with driving permits, up to one-fifth reported driving after drinking or after smoking cannabis. More favorable attitudes towards these substances were associated with increased driving after use.
- Riding with impaired peers but not adults was inde-

pendently associated with increased driving after substance use. Having ridden with both impaired peers and adults increased both driving after drinking and after cannabis.

Comments: The influence of peers and parents on adolescent behavior is well-described, but this study suggests that peer and adult modeling of risky driving has synergistic effects on adolescents' likelihood of impaired driving. Although this study cannot discern whether the adults drove after drinking "under the limit," children riding with them are unlikely to make such distinctions. In addition to counseling teens about the dangers of driving alone or with peers under the influence of drugs or alcohol, physicians are in a good position to counsel parents about driving after substance use and its risks to themselves and their children, regardless of amounts.

Peter D. Friedmann, MD, MPH

Reference: Leadbeater BJ, Foran K, Grove-White A. How much can you drink before driving? The influence of riding with impaired adults and peers on the driving behaviors of urban and rural youth. *Addiction*. 2008;103(4):629-637.

Special Report

Exhaustive Review of the Literature Reveals Even Moderate Alcohol Intake Increases Risk of Cancer

The Cancer Institute of New South Wales, Australia, has released a comprehensive analysis of current evidence for the association between alcohol consumption and risk of cancer. Limited to systematic reviews and meta-analyses of the highest methodological quality, the 194-page monograph, entitled *Alcohol as a Cause of Cancer*, revealed that even moderate alcohol consumption is associated with an often dramatic increase in the risk of several types of cancer. Key findings are as follows:

- Alcohol intake of approximately 2 drinks per day increases the risk of cancer of the oral cavity and pharynx by 75 percent, the risk of esophageal cancer by 50 percent, and the risk of laryngeal cancer by 40 percent.
- Moderate intake also significantly increases the risk of colorectal cancer, liver cancer, and stomach cancer.
- Intake of approximately 4 drinks per day increases the risk of any cancer by 22 percent, while 8 drinks per day increases the risk by 90 percent.
- The risk of breast cancer is 11 to 22 percent higher in women who drink alcohol than in women who do not.

Comments: The authors were unable to identify levels of consumption associated with no risk of cancer. Although the World Health Organization lists alcohol as a Group-I carcinogen, as noted in the introduction to this study, few people are aware that even moderate consumption can cause cancer. These findings may be limited by possible underreporting of alcohol use or misclassification of exposure (e.g., light or ex-drinkers classified as nondrinkers). Nonetheless, information about the association between alcohol and cancer needs to be more widely available so that the public can make informed choices about their behavior.

The full report is available for download at www.cancerinstitute.org.au/cancer_inst/publications/index.html.

Richard Saitz, MD, MPH
Donna Vaillancourt, Managing Editor

Reference: Lewis S, Campbell S, Proudfoot E, et al. *Alcohol as a Cause of Cancer*. Sydney, Cancer Institute NSW, May 2008.

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