Alcohol, Other Drugs, and Health: Current Evidence

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Interventions and Assessments

Topiramate Reduces Drinking in Adults With Alcohol Dependence

Topiramate may decrease alcohol consumption among people with alcohol dependence by reducing the release of dopamine. To determine topiramate's efficacy for reducing drinking, researchers randomized 371 patients with alcohol dependence from 17 sites across the U.S. to receive topiramate (up to 300 mg per day) or placebo for 14 weeks. Only subjects without comorbid conditions (e.g., other substance use, depression) who wanted to quit or reduce drinking were eligible to enroll. All subjects received weekly, manual-guided adherence enhancement counseling.

- In analyses that considered all dropouts as having relapsed to baseline measures, topiramate recipients had greater reductions in the percentage of drinking days (from a mean of 82% to 44% compared with 82% to 52% for placebo recipients) and in liver enzymes. They also had greater increases in abstinent days (from a mean of 10% to 38% compared with 9% to 29% for placebo recipients).
- In analyses that considered dropouts as missing rather than as relapses, the differences between the topiramate and placebo groups were even greater.
- With both analytic approaches, topiramate recipients achieved ≥28 days of both continuous abstinence and continuous nonheavy drinking faster than placebo recipients did.

Comments: Topiramate is a promising treatment for alcohol dependence. Both analytic approaches suggest that broadening the use of topiramate to treat alcohol dependence among adults who want to reduce their drinking is warranted. However, because this randomized controlled trial had strict eligibility criteria to ensure that safety and efficacy could be measured, the generalizability of these findings to patients with comorbid illnesses, such as other substance disorders or psychiatric disease, may be limited.

Julia H. Arnsten, MD, MPH

Reference: Johnson BA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA.* 2007;298 (14):1641–1651.

Methadone Maintenance Plus Syringe Exchange Reduces HIV and HCV Incidence

Sharing syringe and other injection equipment places injection drug users (IDUs) at risk for bloodborne infections like HIV and HCV. Participation in syringe exchange programs plus receipt of methadone maintenance may reduce the likelihood of these infections, although few studies have examined this possibility. Therefore, researchers in Amsterdam assessed the effects of the combination of these strategies among 714 injection drug users at risk for HIV or HCV.

- Over 20 years of follow-up, neither methadone maintenance alone nor needle exchange alone was significantly associated with HIV or HCV seroincidence.
- However, daily methadone maintenance of ≥60 mg plus no drug injection or injection only with exchanged

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Methadone Maintenance (continued on from page 1)

needles (all in the past 6 months) significantly reduced both HIV and HCV seroincidence (adjusted incidence rate ratios 0.43 and 0.36, respectively, when compared with no methadone maintenance and drug injection without exchanging needles).

Comments: This study provides prospective evidence that a long-term, comprehensive public strategy to reduce bloodborne infections among IDUs must include both syringe exchange and opioid agonist therapy at effective dose levels. Although most relevant to policy in countries with recent outbreaks of HIV and HCV among IDUs, these findings are also applicable to communities in the United States that lack adequate access to opioid treatment programs and/or syringe exchange.

Peter D. Friedmann, MD, MPH

Reference: Van Den Berg C, et al. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction.* 2007;102 (9):1454–1462.

Extended-Release Naltrexone Works Particularly Well for Abstinent Patients With Dependence

Many patients with alcohol dependence do not receive the full benefits of treatment because they do not adhere to it. In part to address issues with adherence, extended-release naltrexone, which is released over a month after one injection, was developed.

In the pivotal randomized, placebo-controlled trial that showed the efficacy of naltrexone combined with psychosocial therapy, subjects with ≥7 days of abstinence benefited the most from the drug. However, achieving 7 days of abstinence before treatment is difficult. Therefore, researchers assessed naltrexone's efficacy, in that same clinical trial, among the subgroup of 82 subjects with ≥4 days of abstinence.

In that subgroup, 380 mg of naltrexone in 28 subjects versus placebo in 28 subjects

- increased the time to first drink (median days, 41 versus 12);
- increased continuous abstinence over 6 months (32% versus 11%);
- increased time to first heavy drinking (>180 versus 20 days);
- decreased days with any drinking (median days per month, 0.7 versus 7.2);
- decreased days with heavy drinking (median days per month, 0.2 versus 2.9).

Smaller benefits, which were not always statistically significant, were found among the 28 subjects treated with 190 mg of naltrexone.

Comments: Requiring abstinence before starting treatment for alcohol dependence can be a barrier to care. But at least in this industry-sponsored secondary analysis of a small subgroup of subjects, those who achieved 4 days of abstinence before entering treatment responded well to extended-release naltrexone. Unfortunately, this and other medications with proven efficacy (e.g., acamprosate, oral naltrexone, and disulfiram) remain underutilized in the treatment of alcohol dependence.

Richard Saitz, MD, MPH

Reference: O'Malley SS, et al. Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent before treatment. *J Clin Psychopharm.* 2007;27(5):507–512.

Prevalence of Adolescent Substance Use Identified by Screening in Primary Care

Screening for alcohol and drug use among adolescents is advocated by the American Medical Association and others. However, the prevalence of adolescent substance use problems and disorders identified with an accepted screening instrument is not known.

Using the validated CRAFFT* instrument, researchers screened 2133 12- to 18-year olds (representing a 93% participation rate) from a network of various New England primary care practices. Researchers determined the prevalence of positive screening results (2 or more positive responses, which is highly correlated with having a substance-related diagnosis and needing treatment) in the overall sample, by visit type (e.g., well-child care, sick visit), and by practice site (urban hospital-based clinics, health maintenance organizations, rural family-medicine practices, and school-based health centers).

- Overall, 44% of subjects reported any lifetime use of alcohol or other drugs.
- Fifteen percent screened positive on the CRAFFT, with the highest prevalence of positive screens in school-based clinics (30%) and rural family practices (24%).
- The prevalence of positive screens was lower at well-child visits (11%) than at sick visits (23%).
- Statistical modeling estimated that 22% of the adolescents had nonproblematic use, 11% had problematic use (>1 substance-related problem during the past year but no diagnosis of abuse or dependence), 7% had abuse, and 3% had dependence.

Comments: The prevalence of substance use problems among adolescents, as determined with a validated tool in primary care settings, is high. Therefore, identifying and implementing efficacious approaches to address these problems is essential.

Jeffrey H. Samet, MD, MA, MPH

**Car Relax Alone Forget Friends Trouble* (the main words in 5 separate questions about alcohol and drug use)

Reference: Knight JR, et al. Prevalence of positive substance abuse screen results among adolescent primary care patients. *Arch Pediatr Adolesc Med.* 2007;161 (11):1035–1041.

Melatonin, Benzodiazepines, and Sleep Quality Among Patients Receiving Methadone

Both benzodiazepine abuse and sleep disorders are common worldwide among patients receiving methadone maintenance. This double-blind trial evaluated the effectiveness of melatonin in reducing sleep problems among 80 patients who were receiving methadone maintenance and abusing benzodiazepines. These patients were recruited into a benzodiazepine withdrawal program where they each received melatonin (5 mg per day) for 6 weeks, nothing for 1 week (washout week), and placebo for 6 weeks.

- Overall, subjects reported higher subjective sleep quality, regardless of treatment arm, at 6 weeks.
- About one-third of subjects had stopped using benzodiazepines (as identified by urine toxicology) by 6 weeks. Sleep quality among these subjects was not affected by melatonin but was significantly better than sleep quality among subjects who continued benzodiazepines.
- Of subjects who continued using benzodiazepines at 6 weeks, sleep quality significantly improved with melatonin versus placebo.
- Over approximately 21 months, 63 patients stopped using benzodiazepines, although all but 4 relapsed. Time to benzodiazepine relapse was significantly longer among subjects who received melatonin (125 days) versus placebo (42 days) in the first 6 weeks.

Comments: This small trial has several findings relevant to the vexing problems of sleep disturbance and benzodiazepine abuse among patients receiving methadone. Most of the improvement in sleep quality was attributable to stopping benzodiazepines, a finding clinicians may choose to highlight when discussing benzodiazepine use with their sleep-disturbed patients who receive methadone. Although melatonin did not improve benzodiazepine discontinuation overall, it improved sleep quality among patients who could not stop benzodiazepines and lengthened the time to relapse among those who did stop. If replicated, these findings will support melatonin's possible use for sleep problems among patients who receive methadone maintenance and use anxiolytics, and as an adjunct to decrease relapse to benzodiazepines.

Peter D. Friedmann, MD, MPH

Reference: Peles E, et al. Melatonin for perceived sleep disturbances associated with benzodiazepine withdrawal among patients in methadone maintenance treatment: a double-blind randomized clinical trial. *Addiction.* 2007;102 (12):1947–1953.

Inpatient Medical Care Plus Substance Use Treatment Improves Health Services Utilization

During hospitalization for substance use-related medical conditions (e.g., abscess, endocarditis), the underlying substance use is rarely addressed. Further, post-discharge referral for substance use treatment often goes uncompleted. Consequently, frequent re-admission and deterioration in health status are common.

In an attempt to break this cycle, researchers evaluated the impact of a special 12-bed unit on an inpatient day hospital (DH) that addressed patients' medical and substance use treatment needs. Patients were assigned to DH (n=63) or usual care (n=327) based on the availability of beds.

- Forty-nine percent of patients assigned to DH completed the 2-week program.
- In the 6 months following discharge, these DH completers were less likely than patients who received usual care to have ≥3 emergency department visits (adjusted odds ratio [AOR], 0.3) and were more likely to have ≥1 ambulatory care visit (AOR, 4.1). Hospital admissions did not differ significantly between the groups.
- Patients who were assigned to but did not complete the DH program demonstrated no post-discharge improvements in health service utilization.

Comments: Completing a program that integrated substance use care with hospital-based medical treatment for substance use-related conditions was associated with post-discharge improvements in health services utilization. Study limitations included nonrandom assignment of subjects and restriction of utilization data to nearby health facilities. Other models that bridge inpatient care for substance use-related conditions with effective outpatient treatment should be developed and evaluated. These models should be cost-effective and tailored to patients most likely to benefit from such services.

Marc N. Gourevitch, MD, MPH

Reference: O'Toole TP, et al. The effect of integrated medical-substance abuse treatment during an acute illness on subsequent health services utilization. *Med Care.* 2007;45 (11):1110–1115.

Do Patient Characteristics Moderate Naltrexone's Effects on Drinking?

Moderators of naltrexone's effects on drinking are not well understood. To address this, researchers randomized 180 heavy drinkers* who were not seeking alcohol treatment to receive 3 weeks of daily naltrexone (50 mg) or placebo. Subjects kept a real-time electronic diary about their drinking at specific times during the day.

Sixty-three percent of subjects had alcohol dependence. Overall, naltrexone was associated with a significantly lower mean percentage of drinking days (57% for the naltrexone group versus 65% for the placebo group). However, naltrexone was not associated with other drinking outcomes (drinks per day, drinks per drinking day, heavy drinking days) or subjective outcomes (e.g., drinking urge, stimulation, sedation).

In analyses that assessed possible moderators, naltrexone was associated with the following:

- reduced stimulation from drinking among women
- lower urge to drink among subjects with earlier age of alcoholism onset
- longer time between drinks among subjects with a family history of alcohol problems
- lower mean percent of heavy drinking days among subjects with the D4 dopamine receptor polymorphism DRD4-L

Comments: The effect of naltrexone on drinking in this study was small and limited to mean percentage of drinking days. The study identified several moderators of naltrexone's effects on drinking and several subjective measures, but each moderator interacted with naltrexone on only one, often intermediary, outcome. Although the nontreatment-seeking population and data collection with real-time electronic diaries are strengths of this study, further work is needed to identify which patients will have the best response to naltrexone.

Kevin L. Kraemer, MD, MSc

*Drank on ≥4 days per week and heavily (>6 drinks for men, >4 for women) on ≥2 days per week over the prior month

Reference: Tidey JW, et al. Moderators of naltrexone's effects on drinking, urge, and alcohol effects in non-treatment-seeking heavy drinkers in the natural environment. *Alcohol Clin Exp Res.* 2008;32(1):1–9.

Health Outcomes

Prescription Opioid Use and Diversion

Prescription opioid analgesics are the most commonly abused prescription medication. Further, these drugs are more frequently abused than heroin. Researchers in this study interviewed 586 drug users in New York City to determine patterns of prescription opioid use, misuse, and sales (diversion).

- Seventy-two percent of subjects used methadone, and 65% sold it.
- Methadone was used and sold by more individuals than was OxyContin, Vicodin, or Percocet.
- Fifty-eight percent of prescription drug users obtained prescription opioids for pain, withdrawal, or euphoria (which they used and/or sold) from doctors; 42% obtained them from dealers.
- Of subjects who reported using Oxycontin they obtained from physicians, 83% reported having used the drug primarily for pain; 50% used it primarily to prevent opioid withdrawal symptoms, and 38% used it primarily for euphoria.
- Prescription drug users were less likely to obtain prescription opioids for euphoria than for pain. When they obtained prescription opioids for euphoria, they usually did so from dealers.

Comments: This study helps to illuminate an emergent, and fairly American, drug abuse pattern—abuse and dependence on prescription opioids. Many individuals used these medications to avoid opioid withdrawal or to treat pain, an informative finding. Also, patients were less likely to use these physician-obtained medications for euphoria than for other indications, which is notable and most likely reflects a high level of opioid tolerance. Finally, many of these patients were interacting with physicians, suggesting that physicians should show caution when prescribing opioids and should consider offering office-based treatment (e.g., buprenorphine) or referral to specialty treatment (e.g., methadone) when indicated.

David A. Fiellin, MD

Reference: Davis WR, et al. Prescription opioid use, misuse, and diversion among street drug users in New York City. *Drug Alcohol Depend*. 2008;92(1–3):267–276.

Impact of Substance Use on Adherence to HIV Medications

High levels of adherence to highly active antiretroviral therapy (HAART) are associated with improved outcomes for patients with HIV. Through interviews with 659 patients with HIV, researchers in this study assessed whether illicit substance use and receiving substance use treatment influence adherence to HAART.

Forty-two percent of the patients had used illicit drugs in the past 6 months (current use); 30% had used illicit drugs but not in the past 6 months (former use), and 28% had never used illicit drugs.

Adherence was

- significantly less common among subjects with current use (60%) than among subjects with former (68%) or no (77%) use;
- similar between subjects with former use who had received recent substance use treatment and subjects with no use;
- lower in subjects with former use who had *not* received recent substance use treatment than in subjects with no use (adjusted odds ratio, 0.6; P=0.05);
- lower in subjects with current use than in subjects with no use, regardless of receipt of substance use treatment.

Comments: This study demonstrates the potential adverse impact of illicit drug use on adherence to HIV medications. It also indicates the importance of ongoing substance use treatment for people with past substance use. The study is limited because it did not evaluate biologic outcomes (e.g., CD4 cell count or HIV viral load) or the impact of alcohol separately from the impact of illicit substance use in multivariate analyses. Nonetheless, these findings support the importance of engaging patients with HIV and substance use (current or former) in substance use treatment.

David A. Fiellin, MD

Reference: Hicks PL, et al. The impact of illicit drug use and substance abuse treatment on adherence to HAART. *AIDS Care*. 2007;19(9):1134–1140.

Combining Healthy Behaviors, Including Moderate Drinking, Reduces MI in Women

Certain behaviors can reduce the risk of myocardial infarction (MI) in women. However, little data are available on the magnitude of the risk reduction from a combination of these behaviors.

Researchers in Sweden assessed the benefit of following a healthy diet plus drinking about ≥0.5 alcoholic drinks per day, not smoking, having a waist-hip ratio <0.85, and being physically active among 24,444 postmenopausal women without cancer, cardiovascular disease, or diabetes at baseline. A healthy diet included a high intake of vegetables, fruit, whole grains, fish, and legumes; being physically active involved at least 40 minutes of daily walking or bicycling and 1 hour of weekly exercise.

- During 6.2 years of follow-up, 308 cases of primary MI occurred.
- In adjusted analyses, each of the assessed health behaviors was inversely and independently associated with the risk of MI, although results for physical activity were not significant.
- The risk of MI was significantly lower among women with a healthy diet* plus the following:
    - alcohol consumption (relative risk [RR] 0.5)
    - alcohol consumption and not smoking (RR, 0.2)
    - alcohol consumption, not smoking, and physical activity (RR, 0.1)
    - alcohol consumption, not smoking, physical activity, and a waist-to-hip ratio <0.85 (RR, 0.08)
- Most MIs were attributable to the lack of these healthy behaviors.

Comments: In a recent study by Mukamal et al (http://www.bu.edu/aodhealth/issues/issue_jan07/ellison_mukamal.htm), men with healthy lifestyles who drank alcohol had a greater reduction in MI risk than did men with healthy lifestyles who did not drink. The present study shows a similar finding among women: it supports the notion that combining a Mediterranean-type diet and other healthy lifestyle factors, including low alcohol intake, may substantially reduce the risk of myocardial infarction in women.

R. Curtis Ellison, MD

*Compared with women without any healthy lifestyle behaviors

Reference: Akesson A, et al. Combined effect of low-risk dietary and lifestyle behaviors in primary prevention of myocardial infarction in women. *Arch Intern Med.* 2007;167(19):2122–2127.

Characteristics of Adolescents Who Use Cannabis But Not Tobacco

Cannabis is associated with tobacco use and has been described as a "gateway" drug. But, whether adolescents who use cannabis only differ from those who use both cannabis and tobacco is unclear. To explore these possible differences, researchers assessed social and academic performance among a nationally representative sample of 5263 Swiss adolescents who either used cannabis only, cannabis and tobacco, or neither.

Subjects who used cannabis only, compared with subjects who *used both* cannabis and tobacco, were

- more likely to practice sports (adjusted odds ratio [AOR], 2.4), be on an academic track (AOR, 2.6), and get good grades (AOR, 1.6);
- less likely in the past month to use cannabis ≥10 times [AOR, 0.3] and get drunk ≥3 times [AOR, 0.6]).

Subjects who used cannabis only, compared with subjects *who never used* cannabis or tobacco, were

- more likely to practice sports (AOR, 1.4), be on an academic track (AOR, 1.4), and report good peer relationships (AOR, 1.6) as well as be truant (AOR, 2.3), get drunk ≥3 times in the last month (AOR, 4.5), and use other illegal drugs in last month (AOR, 2.3);
- less likely to report a good relationship with their parents (AOR, 0.6).

Comments: Unexpectedly, this cross-sectional study found that adolescents who smoked cannabis only were more likely than adolescents who never used cannabis or tobacco to be engaged in sports, in an academic track, and to report good peer relationships. At the same time, cannabis only users were more likely to be truant, to get drunk, and to use other drugs. Prospective longitudinal analyses are needed to determine whether cannabis use is a cause or effect of these outcomes and how the interaction between tobacco and cannabis smoking influences adolescent development.

Alexander Y. Walley, MD, MSc

Reference: Suris JC, et al. Some go without a cigarette: characteristics of cannabis users who have never smoked tobacco. *Arch Pediatr Adolesc Med.* 2007;161(11):1042–1047.

Racial Differences in Treatment Received and in Treatment Completed

Racial and ethnic minorities may be less likely than others to complete treatment for alcohol dependence. In this study, researchers assessed whether racial/ethnic differences in type of treatment received (outpatient or residential) could explain differences in treatment completion rates. They analyzed the discharge data of 10,591 patients (4141 African Americans, 3120 Hispanics, and 3330 whites) treated in the publicly funded programs of a large, urban county in California.

- The rate for completing outpatient treatment was lowest among African Americans (18%), followed by whites (27%) and Hispanics (30%). The rate of completing residential treatment was also lowest among African Americans (31%), followed by Hispanics (43%) and whites (46%).
- In analyses adjusted for potential confounders, African Americans (odds ratio [OR], 1.9) and Hispanics (OR, 2.1) were more likely than whites to enter outpatient (versus residential) treatment.
- Further analyses indicated that if minority patients in outpatient care had the same probability of receiving residential treatment as did white patients with otherwise similar characteristics, the disparity in completion rates would improve for African Americans and resolve for Hispanics.

Comments: This study showed that completion rates for outpatient and residential alcohol treatment were low among all racial/ethnic groups but lowest among African Americans. Even if African Americans had an equal probability as whites of entering residential treatment, they would still be less likely to complete treatment. This study is unable to determine whether racial and ethnic minorities should be steered to residential alcohol treatment. But, it does underscore the need to improve the retention and completion rates of patients with alcohol dependence, especially African Americans, enrolled in publicly funded alcohol treatment programs.

Kevin L. Kraemer, MD, MSc

Reference: Bluthenthal RN, et al. Are racial disparities in alcohol treatment completion associated with racial differences in treatment modality entry? Comparison of outpatient treatment and residential treatment in Los Angeles County, 1998 to 2000. *Alcohol Clin Exp Res*. 2007;31 (11):1920–1926.

Moderate Drinking May Improve Fasting Glucose in People with Diabetes

Data on the association between moderate drinking and glycemic control are conflicting. To clarify this association, researchers in Israel conducted a randomized trial of 109 subjects with type 2 diabetes who had not consumed >1 drink in the past week. Subjects, aged 41 to 74 years, were given either about 1 glass of wine or nonalcoholic beer (control) daily with dinner. Each subject received dietary counseling, was instructed to consume a specific amount of calories, completed food diaries and questionnaires, and underwent blood testing.

Results for the 91 patients who completed the 3-month trial include the following:

- Fasting blood glucose decreased in the alcohol group (from 140 to 118 mg/dl) but not in the control group.
- In the alcohol group, decreases were greatest among patients with higher levels of hemoglobin A1c at baseline.
- Postprandial glucose levels did not significantly differ between the groups.
- No notable adverse effects were reported.

Comments: In this study, patients with diabetes who had abstained for a week but started consuming about a glass of wine per day had a rather marked improvement in their fasting blood glucose levels. Those with more severe disease (i.e., higher baseline levels of hemoglobin A1c) showed the largest effect from alcohol, a finding supported from many observational studies. Since subjects were followed for only 3 months, long-term effects cannot be estimated from this study.

R. Curtis Ellison, MD

Reference: Shai I, et al. Glycemic effects of moderate alcohol intake among patients with type 2 diabetes: a multi-center, randomized clinical intervention trial. *Diabetes Care.* 2007;30(12):3011–3016.

Issues of *Substance Abuse* Dedicated to Screening and BI

Two recent issues of *Substance Abuse*—the journal published by The Association for Medical Education and Research in Substance Abuse—focused on alcohol and drug screening and brief intervention (BI). Topics explored include the following:

- The history of screening and brief intervention
- Screening and BI as a public health approach to managing substance abuse
- Methodological issues in screening and BI research
- Communication during BIs
- Quality issues in alcohol screening
- Cost-effectiveness and cost-benefit of screening and BI
- Training to improve emergency doctors' skills in screening and BI
- BI and multiple risk factors in primary care
- Adolescents' preferences for substance abuse screening in primary care practice
- Alternatives to person-delivered intervention approaches in college students
- Measuring performance of BI in the VA

Comments: These special issues are timely given the large federal efforts to actively disseminate screening and brief intervention throughout the U.S. The research suggests that although screening and brief intervention is now a mature clinical practice, many questions ranging from efficacy to implementation in different settings remain.

Richard Saitz, MD, MPH
Rosanne T. Guerriero, MPH

References: Substance Abuse. 2007;28 (3). Alcohol/Drug Screening and Brief Intervention: Advances in Evidence-Based Practice. Part I.; *Substance Abuse.* 2007;28(4). Alcohol/Drug Screening and Brief Intervention: Advances in Evidence-Based Practice. Part II.

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Many others periodically reviewed
(see www..aodhealth.org)

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