

Alcohol, Other Drugs, and Health: Current Evidence

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Interventions

Brief Intervention for Illicit Drug Use in Primary Health Care Settings: Does It Work?

Brief intervention (BI) can decrease alcohol consumption among some patients with nondependent unhealthy use. But does BI have efficacy for illicit drugs? The World Health Organization published the first randomized trial of drug BI among 731 primary-care patients identified with the >70-item Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). Patients with current cannabis, cocaine, other stimulant, or opioid use were recruited from sexually-transmitted-disease and walk-in clinics, a dental clinic, and community primary care sites in Australia, Brazil, the US, and India. Few patients had other drug use (e.g., hallucinogens), but most reported recent tobacco and alcohol use. Patients scoring in the moderate-risk range for drug use were randomly assigned to BI (up to 60 minutes; median, 8–20 minutes) or no BI (until after the study). Patients scoring in either the low- or high-risk range for drug use were excluded.

- Brief intervention was associated with a 3-point greater decrease (compared with delayed BI) in a substance use score with a maximum of 336 points.
- Cannabis and stimulant scores also decreased more for BI subjects (by about

2–3 points on scales with a maximum of 39 points); opioid scores did not.

- Substance use was not significantly impacted by BI in the US.

Comments: These results suggest that BI for drugs may have some benefit in general health settings, although the clinical significance is unclear. The use of the same interviewers for the BI and follow-up assessments at most sites could introduce a bias favoring BI, and since the source of most patients was not what is usually considered primary care (meaning longitudinal, continuous comprehensive care), whether or not it will have important clinical benefits remains unknown. Nor has the clinical meaning of small differences in substance use scores been established. Screening and BI for illicit drug use is clearly more complex than it is for alcohol.

Richard Saitz, MD, MPH

Reference: Humeniuk R, Dennington V, Ali R, et al. *The Effectiveness of a Brief Intervention for Illicit Drugs Linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in Primary Health Care Settings: A Technical Report of Phase III Findings of the WHO ASSIST Randomized Controlled Trial.* Geneva, Switzerland: WHO, 2008.

Buprenorphine with Drug Counseling Is Superior to Oral Naltrexone with Counseling or Counseling Alone for Heroin Dependence

Opiate dependence and injection drug use are major vectors for HIV transmission across the globe, but many nations prohibit effective opioid substitution treatment (OST). In this randomized, double-blind, placebo-controlled trial conducted in Malaysia, subjects were assigned to placebo (n=39), oral naltrexone (n=43), or sublingual buprenorphine (n=44) after

standardized 14-day residential detoxification and initiation of group drug counseling. The study was stopped early because, over 24 weeks of follow-up,

- treatment retention was significantly higher for buprenorphine compared with naltrexone (hazard ratio [HR],

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Buprenorphine for Heroin Dependence (continued from page 1)

- 1.55) or placebo (HR, 2.15).
- time to first heroin use was significantly higher for buprenorphine compared with naltrexone (HR, 1.87) or placebo (HR, 2.02).
- time to heroin relapse (defined as 3 consecutive opiate-positive or missing urine tests) was significantly higher for buprenorphine compared with naltrexone (HR, 1.56) or placebo (HR, 2.17).
- no differences were detected between oral naltrexone and placebo.
- HIV risk behaviors did not differ between any of the groups.

Comments: Studies from around the world have demonstrated that OST with coun-

seling is superior to counseling alone. The superiority of OST over the oral form of the opiate antagonist naltrexone is similarly well-established. Nonetheless, significant barriers remain to the expansion of OST both within the US and internationally. Implementation and policy initiatives are needed to change “hearts and minds” about these evidence-based treatments for opiate dependence.

Peter D. Friedmann, MD, MPH

Reference: Schottenfeld RS, Chawarski MC, Mazlan M. Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9631):2192–2200.

Topiramate, Physical Health, and Psychosocial Function in Adults with Alcohol Dependence

Topiramate combined with weekly adherence enhancement counseling can decrease alcohol use in selected alcohol dependent individuals. To assess whether topiramate also improves physical health and psychosocial function, researchers analyzed data from a multisite, double-blind trial of 364 alcohol dependent individuals randomized to topiramate (up to 300 mg/day) or placebo. Sixty-three percent (112 of 179 patients) receiving topiramate completed the trial with 19% (34 patients) withdrawing due to side effects. Seventy-eight percent (144 of 185 patients) receiving placebo completed the trial with 3% (6 patients) withdrawing due to side effects.

- Compared with placebo, individuals who received topiramate had significantly greater decreases in liver enzymes, cholesterol, body mass index, blood pressure, obsessional thoughts about alcohol, and harmful consequences of drinking. These findings were similar whether the analyses excluded or used multiple imputation for noncompleters.
- Compared with placebo, individuals who received topiramate were significantly more likely to reach the

90th percentile (high function) on a measure of general activities, leisure-time activities, and household duties,* although the absolute number of individuals who reached this level was not clear.

Comments: These findings suggest topiramate can improve some measures of physical health and psychosocial function in individuals with alcohol dependence. Some of the physical health improvements may be due to decreased alcohol use but may also be due to the weight loss associated with topiramate. Although the results are encouraging, the effectiveness of topiramate in practice settings is uncertain because the study eligibility criteria were very selective, and nearly 40% of the topiramate group did not finish the trial despite weekly adherence enhancement counseling.

Kevin L. Kraemer, MD, MSc

*The Quality of Life Enjoyment and Satisfaction Questionnaire.

Reference: Johnson BA, Rosenthal N, Capece J, et al. Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med*. 2008;168(11):1188–1199.

Drug-related HIV Risk Behaviors Decrease during Treatment with Buprenorphine/Naloxone in Primary Care

Methadone maintenance treatment reduces HIV risk behaviors and transmission among opioid dependent patients; however, the impact of primary-care based buprenorphine/naloxone (B/N) maintenance treatment on HIV risk behaviors has not been examined. Researchers studied changes in HIV risk behaviors among 155 opioid dependent subjects receiving primary-care-based B/N maintenance treatment who were enrolled in a randomized controlled trial of 2 levels of psychosocial counseling. Neither counseling arm received HIV-specific risk reduction counseling.

- Past 3-month injection drug use decreased from 37% at baseline to 12% at 12 weeks and 7% at 24 weeks.
- Past 3-month needle sharing decreased from 8% at baseline to 4% at 12 weeks and 1% at 24 weeks.
- Past 3-month sex with a steady partner while under the influence of drugs or alcohol was the only sex-related HIV risk behavior that decreased (from 64% at baseline, to 13% at 12 weeks and 15% at 24 weeks).

- Other sex-related HIV risk behaviors, including using a condom less than 50% of the time with a steady partner and suggesting using a condom, did not change significantly during follow-up.
- No changes in HIV risk behaviors were detected by counseling group assignment.

Comments: This secondary analysis of a randomized controlled trial demonstrates that drug-related HIV risk behaviors decrease during B/N maintenance in primary care. Additional risk-reduction counseling interventions are needed to increase condom use and decrease non-drug-related sexual risk behaviors among B/N maintenance patients.

Alexander Y. Walley, MD, MSc

Reference: Sullivan LE, Moore BA, Chawarski MC, et al. Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. *J Subst Abuse Treat.* 2008;35(1):87–92.

Levetiracetam (Keppra) Shows Promise in Treating Alcohol Dependence

Anticonvulsants have shown promise as pharmacologic agents in the treatment of alcohol dependence, although none are yet approved by the Food and Drug Administration for this indication. Preliminary evidence suggests that levetiracetam (Keppra), used in treating partial onset seizures, diminished symptoms of alcohol withdrawal. In an open-label study of 20 alcohol dependent persons, investigators assessed the impact of a 10-week course of levetiracetam (1000 mg twice daily) on alcohol consumption.

- Mean daily drinks consumed diminished from >5 per day at baseline to <2 per day during weeks 5–10 ($p=.0005$). Significant improvements were also observed in alcohol craving scores and the alcohol composite score (but not other composite scores) of the ASI-Lite.*
- Alcohol withdrawal scores were low at baseline (mean CIWA-Ar** score, 2.8) and remained low during the course of the study.
- Side effects were reported in 4 participants and included irritability and sedation.

Comments: In this study, participants' alcohol consumption diminished significantly while taking levetiracetam, but, since individual level data were not presented, the proportion of patients achieving abstinence is not known. Because open-label studies cannot distinguish the impact of the medication from that of participants' motivation to drink less, the study is not definitive. However, because anticonvulsants can reduce withdrawal symptoms and have clear potential for treating alcohol dependence, as recently demonstrated with topiramate, the authors rightly suggest that levetiracetam should next be studied for this indication in a blinded controlled trial.

Marc N. Gourevitch, MD, MPH

*Addiction Severity Index, Lite version; **Clinical Institute Withdrawal Assessment for Alcohol, Revised version.

Reference: Sarid-Segal O, Piechniczek-Buczek J, Knapp C, et al. The effects of levetiracetam on alcohol consumption in alcohol-dependent subjects: an open label study. *Am J Drug Alcohol Abuse.* 2008;34(4):441–447.

Effectiveness of a Smoking Cessation Intervention in Substance Abuse Treatment Programs

Patients in treatment for substance use disorders have a high prevalence of smoking. Treating nicotine dependence in substance abuse treatment (SAT) settings, however, is uncommon. Researchers conducted a randomized trial to evaluate the effectiveness of a smoking cessation intervention in SAT programs. The intervention consisted of nicotine replacement therapy plus 9 weekly cognitive-

behavioral group counseling sessions and was compared with treatment-as-usual (TAU). Participants included 225 smokers (≥ 10 cigarettes per day) from 5 methadone maintenance programs and 2 drug- and alcohol-dependence treatment programs. Counseling attendance was highest in the first 3 weeks (40–60%).

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Smoking Cessation Programs in Substance Abuse Treatment (continued from page 3)

- In addition to significantly better smoking abstinence rates during treatment (see table, below) participants in the intervention arm had significantly greater reductions in cigarettes smoked per day, exhaled carbon monoxide levels, cigarette craving, and nicotine withdrawal.

Smoking Abstinence Rates (%)		
	Intervention arm	TAU arm
Weeks 2–7 (treatment period)	10–11	<1
Week 13 follow-up	5.5	0
Week 26 follow-up	5.7	5.2

- There was no difference between groups on rates of SAT retention, abstinence from primary substance of abuse, or craving for primary substance of abuse.

Comments: Combining nicotine replacement therapy and counseling is modestly effective in reducing smoking, with more significant impacts on number of cigarettes smoked and craving for cigarettes. These results indicate that SAT programs may offer a unique means of integrating nicotine dependence treatment with treatment for substance abuse.

Julia H. Arnsten, MD, MPH

Reference: Reid MS, Fallon B, Sonne S, et al. Smoking cessation treatment in community-based substance abuse rehabilitation programs. *J Subst Abuse Treat.* 2008;35(1):68–77.

HEALTH OUTCOMES

Universal Screening, Assessment, and Treatment of Substance Use at Prenatal Visits Improves Obstetric Outcomes

Substance use during pregnancy remains a serious problem. This naturalistic study from Kaiser Permanente examined whether Early Start, a coordinated program of prenatal substance abuse screening, treatment, and patient/provider education, including a licensed substance-use treatment specialist onsite in the obstetric clinic, improved perinatal outcomes. Investigators compared obstetric outcomes among 2073 women treated by Early Start; 1203 women who screened positive for alcohol or drug use and were assessed by Early Start, but did not receive treatment; 156 women who screened positive but were never assessed or treated; and 46,553 women who screened negative for substance use.

- Adjusting for maternal age, ethnicity, and number of prenatal visits, women who screened positive but were not treated had more preterm deliveries (odds ratio [OR], 2.1), placental abruption (OR, 6.8), and intrau-

terine fetal demise (OR, 16.2) compared with women treated by Early Start.

Comments: This study suggests that screening and treatment of substance-involved pregnant women during prenatal visits improves obstetric outcomes. The authors correctly note that the study design cannot eliminate the possibility that greater motivation, not the intervention, improved outcomes in the treatment group. That said, this study adds to a growing literature demonstrating that substance-involved patients are more likely to receive needed services in medical settings with routine screening, trained staff, and on-site access to a substance-use treatment specialist.

Peter D. Friedmann, MD, MPH

Reference: Goler NC, Armstrong MA, Taillac CJ, et al. Substance abuse treatment linked with prenatal visits improves perinatal outcomes: a new standard. *J Perinatol.* 2008;28(9):597–603.

Adolescent Cannabis Use Has a Dose-Response Association with Adverse Social Outcomes in Adulthood

Whether adolescent cannabis use causes adverse social outcomes or whether it is merely a marker of other causes is not clear from existing research. Investigators in New Zealand studied a birth cohort of 1003 subjects born in 1977 to determine the association between cannabis use from ages 14 to 21 and education, income, employment, relationship quality, and life satisfaction at age 25. Potential confounding factors, including socioeconomic status, family

functioning, exposure to child abuse, childhood and adolescent adjustment, early adolescent academic achievement, and comorbid mental health and substance use disorders were prospectively measured and adjusted for in the final analyses. Subjects were divided into 6 groups based on self-reported cannabis use ranging from no use to use on greater than 400 occasions.

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Cannabis Use and Adverse Outcomes in Adulthood (continued from page 4)

- Subjects demonstrated statistically significant linear trends for decreased university degree attainment, decreased income, increased welfare dependence, increased unemployment, decreased relationship satisfaction, and decreased life satisfaction with increased cannabis use in adolescence.
- This dose-response relationship was consistent for all outcomes in unadjusted and adjusted analyses regardless of whether cannabis categories were based on total times used, average annual frequency, or age periods (14–21 years or 14–18 years).

Comments: Although these findings may be subject to re-

porting bias and may not be immune to residual confounding, the results demonstrate a consistent dose-response association between adolescent cannabis use and subsequent adverse social outcomes, even when adjusted for pre-existing factors. Complete evidence for a causative biologic mechanism will require similarly strong studies in other populations at different ages as well as studies with more direct measures of cannabis use and its consequences than self-reports.

Alexander Y. Walley, MD, MSc

Reference: Fergusson DM, Boden JM. Cannabis and later life outcomes. *Addiction*. 2008;103(6):969–976.

Moderate Wine Drinking Is Associated with Decreased Prevalence of Nonalcoholic Fatty Liver Disease

Since heavy drinking is a major risk factor for cirrhosis, most physicians are reluctant to allow consumption of any alcohol among patients with liver disease, including nonalcoholic fatty liver disease (NAFLD). To determine whether a relationship exists between moderate alcohol consumption (≤ 10 g of alcohol per day) and NAFLD, researchers analyzed data from 7211 nondrinkers and moderate drinkers of wine (n=945), beer (n=2237), liquor (n=688), and mixed drinks (n=673) who participated in the 3rd National Health and Nutrition Examination Survey (NHANES III). Multivariable analysis was adjusted for age, gender, race, neighborhood, income, education, caffeine intake, and physical activity. Suspected NAFLD was based on unexplained serum alanine aminotransferase (ALT) elevation using both the NHANES III reference laboratory cut point (ALT>43) and the 95th percentile of healthy subjects cut point (ALT>30 for men and >19 for women).

- Using the reference-laboratory cut point, suspected NAFLD was observed in 3.2% of nondrinkers and 0.4%

of participants who reported moderate wine consumption (adjusted odds ratio [OR], 0.15).

- Using the healthy-subject cut point, suspected NAFLD was observed in 14.3% of nondrinkers and 8.6% of participants who reported moderate wine consumption (OR, 0.51).
- No significant effects were seen for moderate consumers of beer or spirits.

Comments: These results indicate that moderate wine consumption may have a protective effect against NAFLD. Although the authors adjusted for many factors that relate to beverage preference in the US, other lifestyle habits of wine drinkers could explain these results.

R. Curtis Ellison, MD

Reference: Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. *Hepatology*. 2008;47(6):1947–1954.

College-Student Drinking Patterns during the First 4 Years

Risky drinking is common among college students and is associated with negative consequences. To identify drinking trajectories in this group, researchers in Sweden examined AUDIT* scores in a cohort of 359 students each year over their first 4 college years. Trajectories of students with risky drinking at college admission (AUDIT scores ≥ 11 for men and ≥ 7 for women) and a random sample of those with lower risk scores were analyzed. The prevalence of risky drinking at baseline was 27%.

- Over the 4-year assessment period, 16% of the students consistently reported risky drinking, and 13% increased consumption from lower risk to risky drinking.

- Among students with risky drinking at admission, the majority (59%) continued risky drinking over the study period.
- Less than half (41%) reported a decrease in drinking.
- Among those with lower risk drinking at baseline, most continued lower risk drinking (83%). Fourteen percent had an increase in drinking over their college years, and 3% had an increase around the end of their college years.
- Gender differences influenced trajectories. Men were more likely to report consistent risky drinking, while women were more likely to report a decrease.

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*Alcohol Use Disorders Identification Test.

College Student Drinking Patterns (continued from page 5)

Comments: Periodic reassessment and interventions regarding drinking and consequences over the course of the college years are needed, not only because students with risky drinking do not appear to get better on their own, but because drinking may increase during this period of critical change for young adults.

Nicolas Bertholet, MD, MSc

Reference: Johnsson KO, Leifman A, Berglund M. College students' drinking patterns: trajectories of AUDIT scores during the first four years at university. *Eur Addict Res.* 2008;14(1):11–18.

Crack Cocaine's Effect on HIV Disease Progression in Women: What Are the Major Outcomes?

Despite the central role of substance use in the acquired immunodeficiency syndrome (AIDS) epidemic, the role of individual substances on human immunodeficiency virus (HIV) disease progression has been a complicated puzzle. Cook and colleagues studied the impact of crack cocaine use among 1686 HIV-seropositive women in the Women's Interagency Cohort Study between 1996 and 2004, the era of highly active antiretroviral therapy (HAART). Outcomes examined included death, AIDS-defining illness, CD4 count, and HIV viral load.

To identify the impact of crack cocaine specifically, researchers controlled for known potential confounders in multivariable analyses, including age, race/ethnicity, education, income, baseline HIV viral load and CD4 cell count, year of HIV diagnosis, study site, HAART adherence, and problem drinking. Analyses were based on patterns of use: 1203 women (71.4%) were nonusers of crack cocaine, 429 (25.4%) were intermittent users, and 54 (3.2%) were persistent users.

- Persistent use was significantly associated with increased death, AIDS-defining illness, and HIV viral load and with a decrease in CD4 count compared with nonusers.
- Intermittent users had an increase in AIDS-defining illnesses compared with nonusers and had intermediate CD4 counts and HIV viral loads.

Comments: This study provides the most definitive evidence to date that crack cocaine use adversely impacts HIV disease progression clinically and immunologically in women. Although the authors are careful to note minor methodological deficiencies, from a pragmatic perspective, the HIV clinical progression puzzle as it relates to crack cocaine use in women has been notably elucidated.

Jeffrey H. Samet, MD, MA, MPH

Reference: Cook JA, Burke-Miller JK, Cohen MH, et al. Crack cocaine, disease progression, and mortality in a multicenter cohort of HIV-1 positive women. *AIDS.* 2008;22(11):1355–1363.

Does Moderate Alcohol Use Protect against Low Bone Density and Osteoporotic Fractures?

Heavy alcohol use can increase the risk for osteoporosis and osteoporotic fractures. To assess the association of moderate alcohol use with bone density, osteoporotic fracture, and bone changes over time, researchers conducted a systematic review and meta-analysis of the literature published before May 2007. Thirty-three studies met content and quality criteria for inclusion in at least 1 of the analyses.

- In 4 studies assessing the relationship between alcohol consumption and bone density, femoral neck bone density increased 0.045 g/cm² for each drink per day over the range of 0–3 drinks per day.
- In studies assessing the relationship between alcohol consumption and hip fracture risk, compared with abstainers, risk for hip fracture decreased for individuals consuming >0–0.5 drinks per day (5 studies; pooled relative risk [RR], 0.84*), >0.5–1 drinks per day (11 studies; RR, 0.80) and >1–2 drinks per day (10 studies; RR, 0.91*). Risk of hip fracture increased

for individuals consuming >2 drinks per day (6 studies; RR, 1.39).

- Several studies indicated that, compared with abstainers, moderate alcohol use was generally associated with decreased bone loss over time.

*Not significant.

Comments: These data suggest moderate alcohol use is associated with increased bone density at the hip and decreased risk for osteoporotic hip fractures. Although the researchers note that the exact range of alcohol use to improve bone outcomes cannot be determined from the existing data, the beneficial alcohol use levels reported in this study are, in general, consistent with current low-risk drinking recommendations.

Kevin L. Kraemer, MD, MSc

Reference: Berg KM, Kunins HV, Jackson JL, et al. Association between alcohol consumption and both osteoporotic fracture and bone density. *Am J Med.* 2008;121(5):406–418.

Differing Health Effects Related to Quantity and Frequency of Drinking

There is increasing appreciation of the importance of drinking patterns as they relate to health effects. In this analysis, researchers assessed the relationship between quantity and frequency of alcohol consumption and mortality by linking data from the 1988 National Health Interview Survey with the National Death Index through 2002. The cohort included 20,765 current drinkers age ≥ 18 years. At 14-year follow up, 2547 had died.

- Men who consumed ≥ 5 drinks (compared with 1 drink) on drinking days had a relative risk (RR) of mortality of 1.30 for cardiovascular disease (nonsignificant), 1.53 for cancer, and 1.42 for other causes. Women who consumed ≥ 5 drinks on drinking days had an RR of mortality from other causes of 2.88.
- Men with the highest consumption frequency (compared with the lowest) had an RR of 0.79 for cardiovascular disease, 1.23 for cancer, and 1.30 for other causes (nonsignificant). Relative risk for cancer in women with the highest

consumption frequency (≥ 3 days per week) was 1.65.

- Increasing frequency of drinking had no significant effect on total mortality risk for either men or women.

Comments: The numbers of deaths in some of the higher alcohol-intake categories were rather small, especially for women, leading to less precise estimates of effect. But the findings are interesting and noteworthy; for example, for men, quantity and frequency effects trended in opposite directions for cardiovascular disease. In addition, frequency of drinking was associated with risk for cancer death, but I am not aware of studies other than this one that showed an increase in cancer risk from more frequent drinking when adjusted for total intake.

R. Curtis Ellison, MD

Reference: Breslow RA, Graubard BI. Prospective study of alcohol consumption in the United States: Quantity, frequency, and cause-specific mortality. *Alcohol Clin Exp Res.* 2008; 32(3):513–521.

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