

Alcohol, Other Drugs, and Health: Current Evidence

SEPTEMBER–OCTOBER 2017

TABLE OF CONTENTS

INTERVENTIONS & ASSESSMENTS

Buprenorphine Is Superior to Morphine for the Treatment of Neonatal Abstinence Syndrome, 1

High-dose Baclofen: No Effect on Maintenance of Abstinence, 1

HEALTH OUTCOMES

Heroin Is Increasingly the Initial Opioid Used by Individuals Who Develop Opioid Use Disorder, 2

“Moderate” Drinking Linked to Hippocampal Atrophy and Cognitive Dysfunction, 3

Opioid Agonist Treatment During Incarceration Saves Lives After Prison Release, 3

Exposure to Alcohol Content Posted by Peers on Social Media Increases Alcohol Initiation and Heavy Drinking, 4

People With Low Socio-Economic Status and Alcohol Consumption Have a Greater Risk of Poor Health Outcomes, 4

Does “Light” Drinking Increase the Risk of Cancer? 4

HIV & HCV

Harm Reduction Strategies and Opioid Agonist Treatment Decrease HCV Incidence, 5

Persistent Unhealthy Drinking Is Associated With More Advanced HIV Disease Severity, 5

PRESCRIPTION DRUGS & PAIN

Referral to and Engagement in Substance Use Disorder Treatment After Aberrant Urine Drug Test Varies by Substance Detected, 6

INTERVENTIONS & ASSESSMENTS

Buprenorphine Is Superior to Morphine for the Treatment of Neonatal Abstinence Syndrome

Neonatal abstinence syndrome (NAS) due to in utero exposure to opioids may result in autonomic instability, tremor, irritability, poor feeding, and loose stools. Two-thirds of infants born with this condition do not respond to conservative measures including minimizing stimulation, in-rooming, breastfeeding, and frequent calorically dense feeds and therefore may require tapering doses of opioid medication to manage symptoms. If medication is required, typically morphine is administered in 80% of cases of NAS due to opioids and is often associated with increased length of stay and resource utilization. The authors of this single site, double blind, double dummy trial randomly assigned 63 (of the planned 80) term infants (≥ 37 weeks gestation) to buprenorphine or morphine for the treatment of NAS with the primary endpoint of treatment duration. Infants born to mothers receiving buprenorphine or methadone during pregnancy were included.

- Using an intent-to-treat analysis, the median duration of NAS treatment was significantly shorter with buprenorphine than with morphine (15 days versus 28 days).
- Median length of hospital stay was shorter in the buprenorphine group (21 days versus 33 days). Adjunctive phenobarbital was administered in 5 of 33 infants (15%) in the buprenorphine group and in 7 of 30 infants (23%) in the morphine group. Overall, 13 adverse events occurred; 2 were considered serious. There were no differences between the 2 groups with regard to adverse events.

Comments: Despite the small sample size and the single site design, the results of this study suggest that buprenorphine is superior to morphine for the treatment of NAS due to opioid exposure, in terms of treatment duration and length of stay. The results of this study cannot be generalized to preterm infants and those exposed to benzodiazepines in utero as these were important exclusion criteria.

Jeanette M. Tetrault, MD

Reference: Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. *N Engl J Med.* 2017;376(24):2341–2348.

High-dose Baclofen: No Effect on Maintenance of Abstinence

Evidence of baclofen’s efficacy for the treatment of alcohol use disorder is inconsistent. This 2-arm, placebo-controlled, double-blind randomized trial evaluated the efficacy of high-dose baclofen on the maintenance of abstinence over a 20-week period in 39 French specialized centers. Participants (N=320) reported having been abstinent from alcohol for 3–14 days at baseline. The treatment was administered over 26 weeks (7-week titration period with increases in doses up to 180 mg/day, 17-week maintenance period, 2-week tapering-off period). The primary outcome was rate of abstinence during 20 consecutive weeks from day 29 to the end of the maintenance period.

(continued page 2)

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High-dose Baclofen: No Effect on Maintenance of Abstinence

(continued from page 1)

- 190 (59%) participants completed the trial.
- In analyses using multiple imputation techniques, there were no differences in the rates of abstinence between groups (12% in the baclofen group and 11% in the placebo group).
- There were reductions in total alcohol use (-55.1 g/day in the baclofen group and -44.2 g/day in the placebo group) and heavy drinking days (-9.9 days in the baclofen group and -8.7 days in the placebo group) in both groups, but no difference between groups.
- There was a difference between groups on craving symptoms in

favor of the baclofen group, compared with placebo.

Comments: This is the second null trial of high-dose baclofen published in a year. The choice of primary outcome (maintenance of abstinence for 20 weeks) is surprising, as this is particularly difficult for patients attending specialty centers to attain. Even though there was an effect on craving symptoms in favor of baclofen, there were no significant differences in alcohol use between groups.

Nicolas Bertholet, MD, MSc

Reference: Reynaud M, Aubin HJ, Trinquet F, et al. A randomized, placebo-controlled study of high-dose baclofen in alcohol-dependent patients—the ALPADIR study. *Alcohol Alcohol.* 2017;52(4):439-446.

HEALTH OUTCOMES

Heroin Is Increasingly the Initial Opioid Used by Individuals Who Develop Opioid Use Disorder

The past few decades have seen an increase in opioid use disorder and overdose in the US. This epidemic was initially fueled by a rise in opioid prescribing and non-medical use of prescription opioids, resulting in efforts to limit prescribing. Many people with non-medical use of prescription opioids have transitioned to heroin because of easier access and lower cost. Researchers used reports of the specific opioid first regularly used from interviews of individuals entering substance use disorder treatment as part of the nationwide Survey of Key Informants' Patients (SKIP) program to analyze changes over time.

- In 2005, 8.7% of opioid initiates began with heroin; this rose to 33.3% in 2015.
- In 2005, 42.4% of initiates began with hydrocodone and 42.3% with oxycodone; this fell to 24.1% and 27.8%, respectively, in 2015.
- Individuals who initiated with heroin were younger and less likely to have a college education, be white, or reside in non-urban areas, but the differences were relatively small.

Comments: This study is limited by its focus on individuals seeking treatment and may not be representative of others with opioid use. Nonetheless, it suggests that heroin (or what is being distributed as heroin) is increasingly becoming the opioid with which people initiate use. This is likely a spillover effect of the increasing use of heroin in general and the decreased availability of prescription opioids. The increase in relatively inexperienced individuals using substances with variable and unpredictable potency is likely contributing to the alarming increase in the rates of overdose.

Darius A. Rastegar, MD

Reference: Cicero TJ, Ellis MS, Kasper ZA. Increased use of heroin as an initiating opioid of abuse. *Addict Behav.* 2017;74:63-66.

“Moderate” Drinking Linked to Hippocampal Atrophy and Cognitive Dysfunction

Consumption of lower-risk amounts of alcohol has been associated with a decreased risk of dementia, although a mechanism for this effect beyond the presumed effects on cardiovascular disease is unclear. Investigators randomly selected 527 adults from the population-based Whitehall II study of cardiovascular health to investigate the association between weekly alcohol consumption (determined 6 times over 30 years), grey matter density and white matter integrity (magnetic resonance imaging after 30 years), and cognitive dysfunction (a variety of tests 6 times over 30 years).

- Compared with no drinking in analyses adjusted for potential confounders, alcohol consumption—starting at any use—was associated with hippocampal atrophy in a dose-dependent fashion:
 - non-significant increases at 0.6–<4 (14g) drinks/week (odds ratio [OR], 1.5) and 4–<8 drinks/week (OR, 2.0).
 - significant increases at the other levels of drinking: 8–<12 drinks/week (OR, 3.4), 12–<17 drinks/week (OR, 3.6), and ≥17 drinks/week (OR, 5.8).
- Greater consumption was associated with smaller hippocampal volume, less anterior corpus callosum white

matter integrity, and lower lexical fluency. The latter decreased by 14% over 30 years among those drinking 4–8 drinks/week and there were no benefits of lower amounts compared with abstinence.

Comments: Recent studies with improved methods have suggested that the benefits of lower-risk amounts of alcohol seen in many observational studies for cardiovascular disease and total mortality do not exist. This study now calls into question benefits from alcohol on dementia. Alcohol has long been known to be a neurotoxin. These findings—bolstered by a dose-response association and plausible mechanism—suggest that at just over 1 drink a day, there is hippocampal atrophy and cognitive dysfunction. As methodologically improved research emerges, it is folly to continue to trust prior observational studies suggesting that a carcinogenic neurotoxin has widespread health benefits. At the very least, this current study should raise concerns that “moderate” and heavier drinking might harm the brain.

Richard Saitz, MD, MPH

Reference: Topiwala A, Allan CL, Valkanova V, et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ*. 2017;357:j2353.

Opioid Agonist Treatment During Incarceration Saves Lives After Prison Release

Prison inmates with opioid use disorder (OUD) have a very high risk of death from overdose during the first 4 weeks post-release. This national prospective cohort study examined mortality rates among inmates with OUD released from 39 prisons in England; 8645 had received opioid agonist treatment (OAT; i.e., methadone or buprenorphine) while incarcerated and 6496 had not.

- Of the 160 deaths in the year after release, 64% were drug-related poisonings (DRP).
- During the first 4 weeks following release, OAT receipt reduced all-cause mortality (hazard ratio [HR], 0.25) and death from DRP (HR, 0.15). Adjustment for age, multiple risk, and community factors did not reduce these effects. However, this protective effect dissipated after 4 weeks.
- The OAT group was twice as likely to enter community treatment as the untreated group, but no association was detected between community treatment and mortality.

Comments: This large study suggests that receiving OAT during incarceration attenuates the high risk of death in the month after release among inmates with OUD. Most of the benefit appears to come from reductions in drug-related poisonings, likely because OAT preserves opioid tolerance, which is protective against overdose. Although selection bias is a concern in this non-randomized study, OAT is often reserved for the most severe cases; hence, this investigation likely underestimates the true mortality benefit of OAT for this population. The forced detoxification of inmates with OUD is a cruel punishment unjustly served on top of their adjudicated sentence; this study admonishes us that it is frequently lethal to them as well.

Peter D. Friedmann, MD, MPH

Reference: Marsden J, Stillwell G, Jones H, et al. Does exposure to opioid substitution treatment in prison reduce the risk of death after release? A national prospective observational study in England. *Addiction*. 2017;112(8):1408–1418.

Exposure to Alcohol Content Posted by Peers on Social Media Increases Alcohol Initiation and Heavy Drinking

Adolescents may be exposed to alcohol messages on social media and the impact of this exposure—whether and how it affects underage drinking—is unknown. The authors conducted a longitudinal study of 658 US high school students to investigate the impact of exposure to alcohol content on social media on drinking initiation and heavy alcohol use.

- More than 20% of students reported exposure to alcohol-related content posted by peers and 7.5% reported having posted alcohol-related content themselves.
- Exposure to friends' alcohol-related social media content was associated with more favorable impressions of alcohol one year later.
- More favorable impressions of alcohol were associated with higher rates of alcohol initiation and heavy drinking.

Comments: There has been enormous growth in adolescents' use of social media in the past decade. Unlike face-to-face communication, messages posted on social media can be curated and controlled. In this regard, social media combines aspects of mass media (i.e., advertising) with more traditional peer interactions, both of which are known to influence teen alcohol use. Social media has the potential to amplify messages, and adolescents who see this content may be more likely to overestimate pro-drinking social norms. Strategies that present teens with actual data on drinking rates and attitudes may be an effective prevention mechanism.

Sharon Levy, MD, MPH

Reference: Nesi J, Rothenberg WA, Hussong AM, Jackson KM. Friends' alcohol-related social networking site activity predicts escalations in adolescent drinking: mediation by peer norms. *J Adolesc Health*. 2017;60(6):641–647.

People With Low Socio-Economic Status and Alcohol Consumption Have a Greater Risk of Poor Health Outcomes

The majority of epidemiological studies have shown that the health effects of alcohol consumption are modified by people's socio-economic status (SES). There are limited scientific data, however, on the specific mechanisms that cause the differences. Researchers used data on alcohol intake collected in the Scottish Health Surveys from 50,236 people to investigate whether the harmful effects of alcohol consumption differ by SES (factors include: education level, social class, household income, and area-based deprivation).

- Without considering alcohol intake, people with lower SES were overall at much greater risk for poor health outcomes than those in higher SES categories.
- Compared with people with "light" consumption (1–10 units/week for men, 1–7 units/week for women), the risk of alcohol-attributable hospital admission or death for people who reported "moderate" consumption (11–20 units/week for men; 8–13 units/week for women) was higher for all but more so among those with lower SES (hazard ratio, 1.35 in higher-SES groups and 2.95 in lower-SES groups).

- Compared with people with "light" consumption living in advantaged areas, the hazard ratios for alcohol-attributable hospital admission or death for people with "excessive" consumption (≥ 51 units/week for men, ≥ 36 units/week for women) were 6.12 in advantaged areas and 10.22 in deprived areas.

Comments: Unfortunately, the authors of this study had limited information on participants' access to health care and patterns of alcohol consumption, and no data on the types of beverages. While the study showed marked differences in adverse health outcomes according to SES, the estimated amount of alcohol consumed and the factors considered inadequately explain the differences in health effects. The specific reasons why people with lower SES have worse health overall after alcohol consumption remain unclear.

R. Curtis Ellison, MD

Reference: Katikireddi SV, Whitley E, Lewsey J, et al. Socioeconomic status as an effect modifier of alcohol consumption and harm: analysis of linked cohort data. *Lancet Public Health*. 2017;2(6):e267–e276.

Does "Light" Drinking Increase the Risk of Cancer?

There are a number of types of cancer for which risk is clearly increased among people with heavy drinking. Researchers conducted a meta-analysis of data from 60 high-quality cohort studies to identify an association between lower-risk alcohol consumption and the risk of cancer incidence and mortality.

- "Very light" consumption (≤ 0.5 standard drink/day) was

associated with an increased incidence of female breast cancer (relative ratio [RR], 1.04), but also with a decreased risk of mortality from female breast cancer (RR, 0.79). It was also associated with a decreased incidence of lung cancer (RR, 0.89).

- "Light" consumption (≤ 1 drink/day) was associated with an increased incidence of female breast cancer (RR, 1.09),

(continued page 5)

Does “Light” Drinking Increase the Risk of Cancer? (continued from page 4)

female and male colorectal cancer (RR, 1.04), and female and male malignant melanoma (RR, 1.44). It was also associated with a decreased incidence of lung cancer (RR, 0.91).

- “Moderate” consumption (1–2 drinks/day) was associated with an increased incidence of male colorectal cancer and female breast cancer, whereas it was also associated with a decreased incidence of both female and male hematologic malignancy. It was associated with an increased risk of mortality from female colorectal cancer (RR, 2.51, based on 1 study) and female breast cancer (RR, 1.04, based on 2 studies), but with a reduced risk of mortality from male kidney cancer (RR, 0.46). It was not associated with mortality for other cancers.

Comments: This well-done analysis supports most previous epidemiologic evidence on the association between “light” to “moderate” alcohol consumption and cancer. The main weaknesses of the study related to the lack of evaluation of a number of known confounders. Further, the authors did not describe the effects of alcohol consumption on total mortality. Thus, it remains difficult for scientists to use this study to provide scientifically sound guidelines regarding the health consequences of alcohol consumption.

R. Curtis Ellison, MD

Reference: Choi YJ, Myung SK, Lee JH. Light alcohol drinking and risk of cancer: a meta-analysis of cohort studies. *Cancer Res Treat.* 2017 [Epub ahead of print]. doi: 10.4143/crt.2017.094.

HIV AND HCV

Harm Reduction Strategies and Opioid Agonist Treatment Decrease HCV Incidence

Worldwide, over 10 million people who inject drugs (PWID) are chronically infected with hepatitis C (HCV). Few published studies examine incidence patterns, temporal trends, and disease etiology. HCV-negative PWID were selected from pooled epidemiologic data from population-based cohort studies from cities in the US (Boston, Baltimore, and San Francisco), Canada (Montreal), the Netherlands (Amsterdam), and Australia (Sydney and Melbourne). The authors of this study calculated overall and within-city HCV incidence trends, HCV rates 1985–2011, and temporal trends in exposure behaviors. Poisson regression models estimated trends in HCV incidence over calendar-time. Survival models identified risk factors for HCV incidence across cities and estimated independent effects of city and calendar period on HCV infection risk.

- 1391 HCV-negative PWID were followed prospectively for 1644.5 person-years of observation (PYO); 371 incident HCV infections resulted in an overall incidence of 22.6 per 100 PYO.
- Incidence was highest in Baltimore (32.6/100 PYO),

San Francisco (24.7/100 PYO), and Montreal (23.5/100 PYO); lowest in Melbourne and Amsterdam (7.5/100 PYO and 13.1/100 PYO, respectively); and moderate in Sydney (21.4/100 PYO).

- Higher rates of syringe and equipment sharing and lower prevalence of opioid agonist therapy were associated with HCV incidence in cities with the highest incidence. In the multivariable model, risk for infection dropped by 18% for every 3-year increase in calendar-time (adjusted hazard ratio, 0.8).

Comments: The results of this study of temporal trends in HCV incidence in large, urban areas are consistent with prior reports that harm reduction strategies and access to opioid agonist treatment (in areas where opioids are the primary injected drug) reduce HCV infection among PWID.

Jeanette M. Tetrault, MD

Reference: Morris MD, Shiboski S, Bruneau J, et al. Geographic differences in temporal incidence trends of hepatitis C virus infection among people who inject drugs: the InC3 Collaboration. *Clin Infect Dis.* 2017;64:860–869.

Persistent Unhealthy Drinking Is Associated With More Advanced HIV Disease Severity

Unhealthy alcohol use is common among people living with HIV. Previous studies have found a deleterious impact of drinking on HIV disease progression, probably mediated through effects on treatment adherence and the immune system. However, many previous studies have been limited by a focus on drinking measures at a single time point. Researchers used data from 3539 participants in the Veterans

Aging Cohort Study (VACS) between 2002 and 2010 to examine the relationship between alcohol use trajectories and HIV disease severity over time.

- Based on Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) scores, the authors identified 4

(continued page 6)

Persistent Unhealthy Drinking Is Associated With More Advanced HIV Disease Severity

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distinct alcohol use trajectories: “abstainers” (24%), “lower risk” (44%), “moderate risk” (24%), and “higher risk” (8%).

- Based on the VACS index—a composite measure that predicts mortality and other clinical outcomes—the cohort was divided into 4 disease trajectories: “low risk” (2%), “moderate” (46%), “high” (36%) and “extreme” (16%).
- In multivariable analysis, higher-risk AUDIT-C trajectory was significantly associated with higher-risk VACS index trajectory.

Comments: This study adds to previous research showing a deleterious association between unhealthy alcohol use and HIV outcomes. However, this study cannot tell us much about the reasons for this association and it remains to be seen whether interventions targeting alcohol use in this population can improve clinical outcomes.

Darius A. Rastegar, MD

Reference: Marshall BDL, Tate JP, McGinnis KA, et al. Long-term alcohol use patterns and HIV disease severity. *AIDS*. 2017;31:1313–1321.

PRESCRIPTION DRUGS & PAIN

Referral to and Engagement in Substance Use Disorder Treatment After Aberrant Urine Drug Test Varies by Substance Detected

Urine drug tests (UDTs) are recommended when patients are prescribed long-term opioid therapy (LTOT). Positive results can lead to opioid discontinuation, but substance use disorder (SUD) treatment patterns after discontinuation have not been studied. Researchers examined a cohort of 600 Veterans Administration patients (300 with and 300 without prior SUD diagnoses) who discontinued LTOT—169 had discontinuation triggered by an aberrant UDT—to compare subsequent treatment referral and engagement based on the substance that led to discontinuation. Patients with SUD treatment within one year prior to opioid discontinuation were excluded.

- In the year following discontinuation, 43% of patients were referred for SUD treatment and 20% engaged in a new SUD treatment episode.
- In adjusted models, patients testing positive for cocaine were more likely than patients testing positive for drugs other than cocaine to be referred for SUD treatment (adjusted odds ratio [aOR], 3.32) and engage in SUD treatment (aOR, 2.44).
- Patients testing positive for cannabis were less likely than patients testing positive for drugs other than cannabis to be referred for SUD treatment (aOR, 0.44) and engage in SUD treatment (aOR, 0.42).

Comments: While a retrospective chart review cannot capture the nature of SUD treatment-related patient-clinician interactions after an aberrant UDT, the data suggest that SUD referral and uptake vary by substance found on urine testing. Cocaine-positive UDTs appear to reflect more significant SUDs requiring treatment from a provider (referral) and patient (uptake) perspective. The evolving legal status of cannabis, its potential pain relief and/or opioid sparing properties, and low patient interest in SUD treatment referral and entry raise questions about cannabis testing policies during LTOT.

Joseph Merrill, MD, MPH

Reference: Nugent SM, Dobscha SK, Morasco BJ, et al. Substance use disorder treatment following clinician-initiated discontinuation of long-term opioid therapy resulting from an aberrant urine drug test. *J Gen Intern Med*. 2017 [Epub ahead of print]. doi: 10.1007/s11606-017-4084-0.

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Alcohol, Other Drugs, and Health: Current Evidence
Boston University School of Medicine/Boston Medical Center
801 Massachusetts Ave., 2nd floor
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aodhce@bu.edu



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