Alcohol, Other Drugs, and Health: Current Evidence

SEPTEMBER-OCTOBER 2018

TABLE OF CONTENTS

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INTERVENTIONS & ASSESSMENTS

Weekly and Monthly Subcutaneous Buprenorphine Are Not Inferior to Daily Sublingual Buprenorphine for Treatment of Opioid Use Disorder

Buprenorphine is an opioid partial agonist with known efficacy across a range of outcomes including decreased overdose, illicit opioid use, HIV transmission, and increased treatment retention for individuals with opioid use disorder (OUD). Until recently, buprenorphine with or without naloxone was only available in sublingual formulations for daily use. Longer-term depot formulations (i.e., biodegradable subcutaneous devices that deliver the medication over time) may have advantages for adherence, diversion, and unintended exposures. This study was a multisite, double-blind, double-dummy, active-controlled phase-3 randomized non-inferiority trial of sublingual buprenorphine compared with weekly and monthly depot buprenorphine for 24 weeks among 428 participants with moderate to severe OUD.

- Subcutaneous buprenorphine treatment was not inferior to sublingual buprenorphine treatment for both primary endpoints:
  - Response rates (no evidence of illicit opioid use for 8 of 10 time-points) were 14% for sublingual buprenorphine and 17% for subcutaneous buprenorphine.
  - Proportion of opioid-negative urine tests were 28% for sublingual buprenorphine and 35% for subcutaneous buprenorphine.

Comments: Although the response rates were low, these data support depot buprenorphine as an additional treatment option for individuals with moderate to severe OUD. Cost, insurance coverage, and restrictions on which pharmacies can dispense depot buprenorphine may impact adoption. Further work is needed to understand if depot buprenorphine provides theorized benefits for adherence and diversion in different patient populations.

Marc R. Larochelle, MD, MPH

Reference: Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial. *JAMA Intern Med*. 2018;178(6):764-773.

Adjusting Methadone Dose Based on Plasma R-Methadone Levels Does Not Improve Retention

Methadone is a racemic mixture comprised of 50% R-methadone and 50% S-methadone. R-methadone is considered to be responsible for the mu-opioid agonist properties of methadone, while S-methadone blocks the N-methyl-D-Aspartate receptor and may be responsible for adverse effects. Researchers sought to determine whether providing doses such that patients' plasma levels of R-methadone remained within a target therapeutic window of 80-250ng/mL improved treatment retention at 6 and 12 months. They randomized 308 patients receiving methadone from 13 treatment centers in Italy. Intervention participants had their methadone dose titrated weekly based on plasma R-methadone concentrations while the control participants received dose titration as usual. Participants were not blinded.

- Treatment retention at 6 and 12 months was high in both groups, but not better in the intervention group than control (81% and 72% in intervention, 91% and 80% in control at

(continued page 2)

Alcohol, Other Drugs, and Health: Current Evidence **is a project of the Boston Medical Center produced in cooperation with the Boston University Schools of Medicine and Public Health. Initially supported by a grant from the National Institute on Alcohol Abuse and Alcoholism, the newsletter is currently supported by grant no. R25-DA013582 from the National Institute on Drug Abuse (NIDA). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIDA or the National Institutes of Health.**

Adjusting Methadone Dose Based on Plasma R-Methadone Levels Does Not Improve Retention (continued from page 1)

6 and 12 months, respectively).

- Participants with R-methadone levels in the target range at baseline and 6 months had significantly better treatment retention at 12 months than those who did not (94% versus 80%).
- Correlation between methadone dose and plasma R-methadone concentration was low.

Comments: Although patients with plasma R-methadone levels in a range of 80-250ng/mL were more likely to be retained in treatment, dose adjustments based on plasma concentrations of R-methadone did not improve and may have worsened retention. The clinical utility of R-methadone plasma testing to determine dose remains unproven.

Payel J. Roy, MD† & Alexander Y. Walley, MD, MSc

† Contributing editorial intern and addiction medicine fellow, Boston Medical Center, Boston, MA, USA

Reference: Mannaioni G, Lanzi C, Lotti M, et al. Methadone dose adjustments, plasma R-methadone levels and therapeutic outcome of heroin users: a randomized clinical trial. *Eur Addict Res*. 2018;24(1):9–18.

HEALTH OUTCOMES

For Your Health, No Amount of Alcohol Is Safe

Alcohol use is a leading health risk factor. Its impact is complex and includes purported benefits at low levels for certain health conditions. Using data from 694 individual and population-level studies in 195 countries and territories, researchers evaluated the global impact of alcohol use and estimated the levels of consumption that minimize an individual's total attributable risk on health.

- In 2016, alcohol was the seventh leading risk factor for death and disability worldwide.
- Among those aged 15–49, alcohol use was the leading risk factor, accounting for 2.3% of disability-adjusted life-years (DALYs) and 3.8% of deaths among women, and 8.9% of DALYs and 12.2% of deaths among men.
- The burden changed over the lifespan: tuberculosis, road injuries, and self-harm were leading causes of death attributable to alcohol among 15-49 year-olds, while cancer was the leading cause among people over 50.
- A J-shaped curve showing positive effects for lower levels of alcohol use was found only for ischemic heart disease, with a minimum relative risk at 0.9 standard drinks (10g ethanol) per day. For all other outcomes (including all cancers), risk increased with any alcohol consumption.
- Protective effects were offset by cancer risks. Consuming zero standard drinks a day minimized the overall risk for all health outcomes.

Comments: This analysis provides a global view; the exact distribution of each alcohol-attributable illness will vary by locale. Nonetheless, Alcohol use contributes largely to global death and disability, particularly among men. These results indicate that the safest level of drinking is none, which should encourage health agencies to revise current recommendations. We should not drink alcohol because we think that it is good for our health.

Nicolas Bertholet, MD, MSc

Reference: GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2018; 392(10152):1015–1035.

Low Amounts of Average Alcohol Consumption Associated With Less Heart Disease, More Stroke

Despite myriad known risks, whether or not alcohol has any health benefits continues to be an open question. Investigators analyzed data from a European prospective cohort study of men and women aged 35–70—which included 17,594 incident cases of cardiovascular disease ascertained by questionnaire, medical records, and registries—and 16,244 randomly selected controls. Analyses were adjusted for age, height, body mass index, smoking, hypertension, and physical activity. There were 9307 first non-fatal and 1699 fatal coronary heart disease (CHD) events, and 5855 non-fatal and 733 fatal strokes.

- Average alcohol consumption at study entry was associated with less non-fatal (hazard ratio [HR] 0.94 for every additional 12 grams/day of alcohol) and fatal CHD (e.g. HR 0.83 at 5-15 g/d) but was not associated with stroke (no amount of alcohol was protective for stroke).
- Alcohol consumption averaged over decades was also protective for non-fatal CHD but not for non-fatal stroke.
- Wine and beer were protective for non-fatal CHD, beer was associated with more non-fatal stroke (wine was not), and spirits were associated with neither.

Comments: These are the sorts of results that raise serious questions about the validity and utility of observational studies of alcohol's purported health benefits. Results are inconsistent by alcohol type and cardiovascular outcome. The more studies that are done and published, the more questions are raised about whether alcohol has any health benefits at all.

Richard Saitz, MD, MPH

Reference: Ricci C, Wood A, Muller D, et al. Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke: EPIC-CVD case-cohort study. *BMJ*. 2018;361:k934.

Patient Factors Associated With Substance Use Disorder Treatment in Primary Care

General medical settings are an ideal place to identify and treat substance use disorders. The authors of this study sought to determine the patient-level predictors of initiation of medication for alcohol use disorder (AUD) or opioid use disorder (OUD) in primary care. This was a secondary data analysis of a randomized controlled trial that tested the effectiveness of a dual intervention strategy combining organizational readiness and collaborative care to integrate evidence-based treatment of AUD and OUD into primary care in a federally qualified health center. The mean age of participants was 42; 79% were male, 44% were white, and 43% described themselves as "other or multiple races."

- Of the 392 participants enrolled in the study, 23% initiated brief behavioral treatment and 13% initiated medications for AUD or OUD.
- Patient factors associated with initiation of medications for AUD or OUD were: older age (odds ratio [OR], 1.07), being female (OR, 3.05), having a *DSM-IV* diagnosis of heroin abuse or dependence (with or without alcohol abuse or dependence, compared with alcohol dependence only [OR, 3.03]), and having received at least one session of behavioral treatment (OR, 6.42).

Comments: Aside from the need to replicate these findings and trying harder to initiate treatment for younger men with AUD only, encouraging behavioral treatment to improve medication initiation has some promise. But the most striking finding that needs serious efforts is the small proportion of patients who initiated medications for AUD or OUD, particularly in a study that included attention to organizational context. Further innovation will be needed to address this major deficit.

Jeanette M. Tetrault, MD

Reference: Ober AJ, Watkins KE, McCullough CM, et al. Patient predictors of substance use disorder treatment initiation in primary care. *J Subst Abuse Treat*. 2018;90:64–72.

Involuntary Residential Drug Treatment Is Associated With an Increased Risk of Overdose

Despite a lack of evidence supporting this strategy, people who use drugs are sometimes forced into drug treatment, often as an alternative to incarceration. Researchers used data from a longitudinal study of 671 people with injection drug use (PWID) in Tijuana, Mexico to investigate the association between involuntary drug treatment (IDT) and **recent** non-fatal overdose. Participants were interviewed every 6 months and asked about treatment and overdose in the intervening period. Most drug treatment in the area is provided by at residential centers that do not provide opioid use disorder medications.

- Over a 6-year period, 32% of participants reported at least one non-fatal overdose and 15% reported IDT at least once.
- On multivariable analysis, IDT was associated with recent non-fatal overdose (adjusted odds ratio [aOR], 1.76). Tranquilizer use (aOR, 1.92), using a "hit

(continued page 4)

Involuntary Residential Drug Treatment Is Associated With an Increased Risk of Overdose (continued from page 3)

doctor" (i.e., someone who assists with injections, aOR, 1.68), daily injection use (aOR, 1.05), and younger age were also associated with overdose.

Comments: It is likely that treatment without opioid use disorder medications increases the risk of overdose regardless of whether it is voluntary or involuntary. It is possible that involuntary treatment with opioid use disorder medications, particularly long-acting injectable medications (i.e., buprenorphine or naltrexone), may reduce the risk of overdose. But regardless, it is wrong to force someone into treatment; forcing them into treatment without opioid use disorder medications is not only unjust, it is dangerous.

Darius A. Rastegar, MD

Reference: Rafful C, Orozco R, Rangel G, et al. Increased non-fatal overdose risk associated with involuntary drug treatment in a longitudinal study with people who inject drugs. *Addiction*. 2018;113:1056–1063.

Child Involvement in Family Member Alcohol and Tobacco Use Associated With Child Substance Use

This longitudinal study examined whether child involvement in family member substance use (i.e., getting, opening, or pouring alcoholic drinks; getting or lighting cigarettes) influenced that child's likelihood of substance use beyond known family factors such as parental substance use and family rules. Families (N=224) with children aged 10–18 years were surveyed 7 times between 2002 and 2011.

- 34% of families reported that children had gotten or opened alcoholic drinks; 21% reported that children had gotten or lit cigarettes for family members.
- Child involvement in family use was associated with alcohol (odds ratio [OR], 4.29), cigarette (OR, 7.16), and marijuana use (OR, 7.64).
- Better family management (clear family rules, parental monitoring, and praise for good behavior) was associated with a lower likelihood of alcohol (OR, 0.27) and marijuana (OR, 0.45), but not cigarette use.

Comments: These findings are in line with other work showing that child involvement in family alcohol use predicts an increased risk of child substance use, suggesting that this practice could be a potential target for family-based interventions. Public health messaging urging parents to refrain from involving children in substance use may also be helpful in reducing teen substance use.

Sharon Levy, MD, MPH

Reference: Bailey JA, Epstein M, Steeger CM, Hill KG. Concurrent and prospective associations between substance-specific parenting practices and child cigarette, alcohol, and marijuana use. *J Adolesc Health*. 2018;62(6):681–687.

HIV AND HCV

Increases in Unhealthy Drinking Are Associated With Poorer Outcomes for People Living With HIV

Unhealthy drinking among people living with HIV (PLWH) is associated with HIV disease progression and poorer disease management. There are limited data on the effect of changes in patterns of alcohol use over time and HIV outcomes. Researchers used data from the Veterans Aging Cohort Study to investigate the association between changes in Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) scores and HIV outcomes among PLWH. The sample included 33,224 PLWH who had at least 2 AUDIT-C measurements within 9–15 months and a CD4 cell count or HIV viral load (VL) measurement following each AUDIT-C measurement.

- At baseline, approximately one half of observations had an AUDIT-C score of 0 and ~10% had a score of ≥4. Participants with higher AUDIT-C scores had lower CD4 cell counts and higher VL.
- AUDIT-C scores remained relatively stable, with a mean change of 0.08 points, and overall CD4 counts and VL improved over time. On analyses adjusted for other factors including demographics, psychiatric disorders, other substance use, and baseline medication adherence, improvements in CD4 count and VL were highest among those with stable AUDIT-C scores and lowest among those with the largest increases.

Comments: This study adds to previous observations documenting the harms of unhealthy alcohol use for PLWH. It remains to be seen whether interventions targeting alcohol use disorders can improve outcomes in this population.

Darius A. Rastegar, MD

Reference: Williams EC, McGinnis KA, Bobb JF, et al. Changes in alcohol use associated with changes in HIV disease severity over time: a national longitudinal study in the Veterans Aging Cohort. *Drug Alcohol Depend*. 2018;189:21–29

Injectable Naltrexone Improves Post-release Viral Suppression Among Incarcerated People Living With HIV

Many incarcerated people living with HIV (PLWH) achieve viral suppression in jail/prison, but post-release they may experience low linkage to HIV care, high rates of return to substance use, and unstable housing, all of which can undermine adherence to antiretroviral therapy (ART). This double-blind, placebo-controlled randomized trial examined the efficacy of XR-NTX in 100 incarcerated PLWH who also had alcohol use disorder. Outcomes were viral suppression to <200 copies/mL and <50 copies/mL 6 months after release.

- Overall, XR-NTX was associated with viral suppression at <200 copies/mL (48% versus 65%) and <50 copies/mL (31% versus 57%) at 6 months.
- Receipt of 3- and 6-month injections was 57% and 15% respectively for XR-NTX and 45% and 18% respectively for placebo.
- Receipt of ≥3 injections of XR-NTX was associated with viral suppression at <200 copies/mL and <50 copies/mL (adjusted odds ratio, 3.26 and 6.34 respectively).
- Reduced alcohol consumption and white race were additional factors associated with viral suppression at <50 copies/mL.

Comments: Though limited by a high attrition rate, this study confirms the important role of treating alcohol use disorder in improving HIV treatment outcomes. Future research should focus on the implementation and evaluation of strategies to improve alcohol use disorder treatment retention among HIV infected individuals in the period following release from a correctional facility.

Jeffrey Morgan† and Seonaid Nolan, MD

† Contributing editorial intern and Research Coordinator for the British Columbia Centre on Substance Use

Reference: Springer SA, Di Paola A, Barbour R, et al. Extended-release naltrexone improves viral suppression among incarcerated persons living with HIV and alcohol use disorders transitioning to the community: results from a double-blind, placebo-controlled trial. *J Acquir Immune Defic Syndr*. 2018;79(1):92–100.

PRESCRIPTION DRUGS & PAIN

Sources of Opioids for Non-medical Use Differ in Older Adults

Non-medical use of prescription opioid (NMUPO) patterns and sources of opioids have been widely described in adolescents and young adults; however, older adults are experiencing increasing rates of NMUPO and overdose death. This study used combined data from the 2009–2014 National Survey on Drug Use and Health to examine patterns of NMUPO, prescription opioid use disorder (POUD) symptoms, and most recent source of opioids across age groups.

- People aged ≥65 years were more likely to receive opioids from physicians (48%, with 39% from a single physician), compared with those 50–64 years (39%, with 33% from a single physician) and those in lower age groups (22–24% for those <25 years).
- Compared with those <65 years, older adults were less likely to use theft (5%), purchase (9%), or friends/family for free (23%) to obtain opioids.
- Among those >50 years with NMUPO, POUD symptoms were associated with obtaining opioids from purchase, a single physician, and multiple sources.

Comments: Older adults with NMUPO, especially those over 65 years, are much more likely to obtain opioids from a single physician, compared with younger people. Typical safety strategies such as prescription drug monitoring program checks or urine drug testing may be less effective in identifying these older patients with NMUPO or POUD. Although rates of NMUPO and POUD are lower in older people, increasing rates of opioid problems and the different opioid source patterns described here argue for innovative tactics to treat this population.

Joseph Merrill, MD, MPH

Reference: Schepis TS, McCabe SE, Teter CJ. Sources of opioid medication for misuse in older adults: results from a nationally representative survey. *Pain*. 2018;159(8):1543–1549.

ADDICTION SCIENCE & CLINICAL PRACTICE

Call for Papers

Addiction Science & Clinical Practice (*ASCP*), founded in 2002 by the National Institute on Drug Abuse (NIDA) and now published by leading open-access publisher BioMed Central, is seeking submissions of the following article types:
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Jeffrey H. Samet, MD, MA, MPH

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18th Annual Chief Resident Immersion Training (CRIT) Program in Addiction Medicine

Accepting applications through **January 25, 2019**
www.bumc.bu.edu/crit

What: This is a four-day immersion training for internal and family medicine incoming chief residents on state-of-the-art methods to diagnose, manage, and teach about addiction medicine. Additional spaces are available for faculty mentors of chief residents as well as junior faculty members.
When: April 28 - May 1, 2019
Where: Wylie Inn and Conference Center, Beverly, MA
Cost: The grant supports up to 15 full chief resident scholarships that cover tuition, travel and accommodations. Faculty mentors and junior faculty are responsible for covering their travel and accommodations.
Sponsors: National Institute on Drug Abuse (NIDA) and Boston University School of Medicine.
For more information or to apply: Visit www.bumc.bu.edu/crit or contact Marlene Lira (marlene.lira@bmc.org, 617-414-6924)

8th Annual Fellow Immersion Training (FIT) Program in Addiction Medicine

Accepting applications through **January 25, 2019**
www.bumc.bu.edu/fit

What: The Fellow Immersion Training (FIT) program is a four-day intensive, immersion training that equips incoming and current clinical subspecialty fellows (e.g., Infectious Disease, Pain, Gastroenterology) with state-of-the-art skills and content to integrate addiction medicine into research and clinical care.
When: April 28 - May 1, 2019
Where: Wylie Inn and Conference Center, Beverly, MA
Cost: There is no tuition for fellows. Accommodations and travel for fellows are funded.
Sponsors: National Institute on Drug Abuse (NIDA) and Boston University School of Medicine.
For more information or to apply: Visit www.bumc.bu.edu/fit, or contact Kristina King (kristina.king@bmc.org, 617-414-6632).

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

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