Alcohol, Other Drugs, and Health: Current Evidence

JANUARY-FEBRUARY 2019

TABLE OF CONTENTS

INTERVENTIONS & ASSESSMENTS

Telemedicine Can Be Used to Provide Access to Buprenorphine Treatment in Rural Areas, 1

Baclofen for Alcohol Use Disorder: Efficacy Unclear at Best, Harms Becoming Clearer, 1

HEALTH OUTCOMES

Awareness of Opioid Risks Does Not Reduce Non-medical Use by Youth, 2

Buprenorphine Dose Does Not Impact Severity of Neonatal Opioid Withdrawal Syndrome, 2

Evidence of an Association Between Alcohol Use and Gastroesophageal Reflux Disease, 3

Alcohol Consumption and Risk of Mortality in People With Nonalcoholic Fatty Liver Disease, 3

HIV & HCV

Antiretroviral and Opioid Agonist Treatment Improve Survival Among People With HIV Who Inject Drugs, 4

Early-Onset, Regular Marijuana Use Is Associated with Learning and Memory Impairment in People Living With HIV, 4

People Who Inject Drugs Have Low Knowledge of and Mixed Interest in HIV Pre-Exposure Prophylaxis, 5

Prescription Drugs & Pain

Chronic Pain, Alcohol and Other Drug Use, and Alcohol and Drug Overdoses Among Addiction Treatment Patients, 5

Chronic Opioid Therapy Risk Reduction Initiatives Did Not Reduce Opioid Overdose, 6

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INTERVENTIONS & ASSESSMENTS

Telemedicine Can Be Used to Provide Access to Buprenorphine Treatment in Rural Areas

Opioid use disorder and overdose are growing problems in rural areas. Opioid agonist treatment (OAT) is the most effective approach, but access is limited. In 2015, physicians at the University of Maryland created a telemedicine program in collaboration with a treatment center in rural Maryland. The treatment center was staffed by counselors, social workers, and a part-time nurse and provided intensive outpatient treatment and transitional housing. The physicians interviewed patients remotely and prescribed buprenorphine. This article reported on the 3-month outcomes of the first 177 patients treated.

- The mean age of the cohort was 35 years and 89% were male; 75% reported prior injection drug use. Most (72%) reported being abstinent from opioid use prior to referral to treatment.
- By the end of 3 months, 57% remained in treatment and 86% of them had opioid-negative urine drug tests.

Comments: This report shows how telemedicine can be used to provide pharmacotherapy to individuals who live in areas where there is little to no access to OAT. More needs to be done to encourage this type of collaboration to expand access to those who need treatment in underserved areas.

Darius A. Rastegar, MD

Reference: Weintraub E, Greenblatt AD, Chang J, et al. Expanding access to buprenorphine treatment in rural areas with the use of telemedicine. *Am J Addict.* 2018;27(8):612–617.

Baclofen for Alcohol Use Disorder: Efficacy Unclear at Best, Harms Becoming Clearer

Despite mixed evidence, baclofen continues to be used to treat alcohol use disorder (AUD) by some, particularly in France. Investigators analyzed data from French Health Insurance claims to assess the risk for hospitalization and death associated with initiating AUD medications.

- Some 165,334 patients started acamprosate, nalmefene, naltrexone, or baclofen between 2009 and 2015. Excluded were patients with medication treatment for opioid use disorder, an elevated one-year mortality risk, and with a neurological condition that could be associated with muscle spasms (that might be treated with baclofen).
- In analyses adjusted for sociodemographics, physician specialty, psychiatric medications, alcohol-related hospitalization, and comorbidity, baclofen—compared with the other medications—was associated with hospitalization (hazard ratio [HR], 1.1) and mortality (HR, 1.3).
- There was a dose-response relationship with higher doses of baclofen associated with greater risk.

(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.**

Baclofen for Alcohol Use Disorder: Efficacy Unclear at Best, Harms Becoming Clearer (continued from page 1)

Comments: Patients and clinicians are interested in a medication to treat AUD that has no liver toxicity and that has more than minimal efficacy. Baclofen is not that medication. Prior study results do not convincingly demonstrate efficacy, and the current study suggests very real harms.

Richard Saitz, MD, MPH

Reference: Chaignot C, Zureik M, Rey G, et al. Risk of hospitalisation and death related to baclofen for alcohol use disorders: Comparison with nalmefene, acamprosate, and naltrexone in a cohort study of 165 334 patients between 2009 and 2015 in France. *Pharmacoepidemiol Drug Saf*. 2018;27:1239–1248.

HEALTH OUTCOMES

Awareness of Opioid Risks Does Not Reduce Non-medical Use by Youth

Despite the current epidemic of opioid addiction with its roots in aggressive pain treatment, non-medical use of prescription opioids (NMUPO) for pain remains common among youth. This community survey examined the relationships between knowledge of opioid risks, perceived riskiness, past NMUPO, and willingness to engage in NMUPO among 972 youth aged 15–23 recruited on a college campus.

- 32% of participants reported past NMUPO.
- Compared with youth without NMUPO, willingness to engage in NMUPO was correlated with having engaged in NMUPO in the past (adjusted odds ratio [aOR], 1.81), and inversely correlated with risk perception (aOR, 0.75).
- Simple knowledge of opioid risks was not associated with willingness to engage in NMUPO.

Comments: Reducing NMUPO among youth is a critical aspect to ending the opioid epidemic. Understanding decisional factors that drive NMUPO among youth is important for developing effective interventions. The results of this survey demonstrate that knowledge of the harmful effects of opioids does not strongly impact decision-making. Findings suggest that increasing risk perception is a logical target for intervention.

Sharon Levy, MD

Reference: Voepel-Lewis T, Boyd CJ, McCabe SE, et al. Deliberative prescription opioid misuse among adolescents and emerging adults: opportunities for targeted interventions. *J Adolesc Health*. 2018;63:594–600.

Buprenorphine Dose Does Not Impact Severity of Neonatal Opioid Withdrawal Syndrome

Maternal exposure to opioid agonist treatment can result in neonatal opioid withdrawal syndrome (NOWS) in the newborn. This retrospective analysis examined severity of NOWS among mother-newborn dyads presenting to a single institution over a 16-year period. The primary outcomes were requirement for morphine treatment (yes/no), peak neonatal opioid withdrawal score, peak morphine dose, time to morphine start, days receiving morphine, and total duration of hospital stay.

(continued page 3)

Buprenorphine Dose Does Not Impact Severity of Neonatal Opioid Withdrawal Syndrome (continued from page 2)

- Of 89 mother-infant dyads included in the study, NOWS incidence requiring morphine was 44%.
- For infants requiring morphine, there was a mean 55 hours to morphine start, mean 16 days receiving morphine, and mean of 20 days hospital stay.
- NOWS requiring morphine treatment occurred in 49% and 41% of infants of mothers receiving ≤8 mg/day buprenorphine versus >8 mg/day, respectively.
- There were no associations of maternal buprenorphine dose with peak NOWS score, NOWS severity requiring morphine, time to morphine start, peak morphine dose, or days receiving morphine. Only exclusive breastfeeding was significantly associated with neonatal outcomes, specifically lower odds of morphine treatment (odds ratio, 0.24).

Comments: Although this study was limited by small sample size and possibility of changes to NOWS treatment protocols over the 16-year study period, these data suggest that buprenorphine dose does not impact severity of NOWS among infants born to mothers prescribed buprenorphine during pregnancy.

Jeanette M. Tetrault, MD

Reference: Wong J, Saver B, Scanlan JM, et al. Does maternal buprenorphine dose affect severity or incidence of neonatal abstinence syndrome? *J Addict Med*. 2018;12(6):435–441.

Evidence of an Association Between Alcohol Use and Gastroesophageal Reflux Disease

There is mixed evidence of an association between alcohol use and gastroesophageal reflux disease (GERD). In this systematic review and meta-analysis, researchers summarized the current epidemiologic evidence based on observational studies.

- 26 cross-sectional and case control studies were identified and included in the meta-analysis.
- In general, people with alcohol consumption had an increased risk of GERD (odds ratio [OR], 1.48) when compared with people who had no or occasional alcohol consumption. Specifically, and using the same comparison group, individuals drinking <3–5 times/week were 1.29 times more likely, and those drinking >3-5 times/week were 2.12 times more likely to develop GERD.
- Dose-response analyses—conducted on 3 studies that had >2 categories of alcohol exposure—showed a linear association between alcohol consumption and GERD. The OR for a unit of alcohol/day increment (one unit =12.5 g, just under one standard drink in the US) was 1.16.

Comments: This study confirms the observations of experienced clinicians that alcohol use is associated with GERD; the dose-response analyses support the idea that it is causal. Nevertheless, the methodology of the included studies necessarily means that firm conclusions cannot be made. Future studies should be prospective ones using validated measures of exposure to better understand this association.

Nicolas Bertholet, MD, MSc

Reference: Pan J, Cen L, Chen W, et al. Alcohol consumption and the risk of gastroesophageal reflux disease: a systematic review and meta-analysis. *Alcohol Alcohol*. 2019;54(1):62–69.

Alcohol Consumption and Risk of Mortality in People With Nonalcoholic Fatty Liver Disease

The majority of chronic liver disease in the US is nonalcoholic fatty liver disease (NAFLD), which is strongly related to obesity and glucose intolerance. People with alcohol-related chronic liver disease should avoid alcohol consumption, but it is unclear how "moderate" alcohol intake affects the health of those with NAFLD. The authors analyzed results from the National Health and Nutrition Examination Survey from 1988 to 2010, relating reported alcohol intake with risk of mortality, as derived from the National Death Index. The investigators excluded participants with "significant alcohol use" (undefined), viral hepatitis, or increased transferrin saturation. A total of 4568 participants with NAFLD were included in the analysis.

- Compared with those who reported abstinence, and with adjustments for age, race, sex, smoking, physical activity, education level, diabetes, and fiber and polyunsaturated fatty acid intake, participants reporting an average alcohol consumption of 0.5–1.5 drinks in a day had lower mortality (hazard ratio [HR], 0.64).
- Participants reporting ≥1.5 drinks in a day had higher mortality (HR, 1.45).

Comments: People with NAFLD who reported low average alcohol consumption experienced a decrease in all-cause mortality (probably due mainly to a decrease in cardiovascular disease mortality), while those with heavier

(continued page 4)

Alcohol Consumption and Risk of Mortality in People With Nonalcoholic Fatty Liver Disease (continued from page 3)

consumption experienced increased mortality. However, participants who reported "significant alcohol use" were excluded from the analysis, which would be expected to lead to an underestimation of an increase in mortality risk associated with heavy alcohol intake.

R. Curtis Ellison, MD

Reference: Hajifathalian K, Torabi Sagvand B, McCullough AJ. Effect of alcohol consumption on survival in nonalcoholic fatty liver disease: a national prospective cohort study. *Hepatology*. 2018 [Epub ahead of print]. doi: 10.1002/hep.30226.

HIV AND HCV

Antiretroviral and Opioid Agonist Treatment Improve Survival Among People With HIV Who Inject Drugs

People who inject drugs (PWID) have an increased risk of acquiring HIV. Researchers recruited "network units"—PWID who have HIV along with ≤5 uninfected injection partners—in Ukraine, Indonesia, and Vietnam. Network units were randomly assigned to receive either: 1) standard care (referrals to existing HIV and opioid agonist treatment [OAT] clinics and standard harm-reduction services—including risk counseling, treatment of other infections, and syringe-service programs); or 2) the intervention (standard care plus systems navigation and psychosocial counseling sessions to facilitate initiation and engagement with HIV care and OAT). Included in the analysis were 502 PWID who had HIV along with 806 uninfected injection partners. They were followed for 12–24 months.

- At week 26, the intervention participants were more likely to be receiving antiretroviral treatment (73% versus 36%), to have a suppressed HIV viral load (36% versus 16%), and to be receiving OAT (38% versus 24%), compared with controls.
- Mortality was significantly lower in the intervention group, compared with controls (5.6 versus 12.1 deaths per 100 person-years; hazard ratio, 0.47).
- There were 7 new HIV infections among the injection partners in the control group compared with none in the intervention group; this difference was not statistically significant.

Comments: This feasibility study shows that a fairly straightforward intervention that focuses on engagement with HIV care and OAT can help improve the health and decrease mortality of PWID who also have HIV. This intervention likely also reduces further transmission, but the study was not powered to assess this.

Darius A. Rastegar, MD

Reference: Miller WC, Hoffman IF, Hanscom BS, et al. A scalable, integrated intervention to engage people who inject drugs in HIV care and medication-assisted treatment (HPTN 074): a randomised, controlled phase 3 feasibility and efficacy study. *Lancet*. 2018;392:747–759.

Early-Onset, Regular Marijuana Use Is Associated with Learning and Memory Impairment in People Living With HIV

Early-onset (<18 years of age) marijuana use may result in deficits in cognitive functioning. Individuals living with HIV experience cognitive impairment and also have disproportionately high rates of marijuana use. This cross sectional study of adults living with HIV examined the associations between regular marijuana use (defined as ≥3 times/week), onset age of regular marijuana use, HIV biomarkers, and neurocognitive test performance.

- 69 participants had been living with HIV for a mean of 11 years; 73% were male, 77% were African American, and 90% had a high school degree or a GED.
- There were no significant differences in measured neurocognitive impairment between people with late onset (at ≥18 years old) regular marijuana use and those who did not use marijuana regularly.
- People with early onset regular marijuana use were more likely to demonstrate impairment in the cognitive domains of learning (odds ratio [OR], 8.46) and memory (OR, 3.95), but less likely to demonstrate impairment in attention/working memory (OR, 0.11) when compared with people who did not use marijuana regularly.
- Cognitive function was not associated with HIV disease markers (viral load, current CD4 count, nadir CD4 count), nor were there interactions between these biomarkers and marijuana use group.

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Early-Onset, Regular Marijuana Use Is Associated with Learning and Memory Impairment in People Living With HIV (continued from page 4)

Comments: The potential for early onset, regular marijuana use to exacerbate memory impairment among people with HIV may have clinical implications, including compromised adherence to critical antiretroviral medication regimens. The balance of risks and potential benefits of marijuana use remain unclear.

Jeoffrey Hill, MD† and Marc R. Larochelle, MD, MPH

† Contributing editorial intern and Addiction Medicine Fellow, Boston Medical Center/Boston University School of Medicine

Reference: Skalski LM, Towe SL, Sikkema KJ, Meade CS . Memory impairment in HIV-infected individuals with early and late initiation of regular marijuana use. *AIDS Behav*. 2018;22(5):1596–1605.

People Who Inject Drugs Have Low Knowledge of and Mixed Interest in HIV Pre-Exposure Prophylaxis

People who inject drugs (PWID) have high rates of sexual and injection-related HIV risk behavior, but HIV pre-exposure prophylaxis (PrEP) uptake among PWID remains low. Researchers conducted semi-structured interviews with HIV-uninfected PWID (n=33) and key informants (providers and community-based organization staff, n=12) to assess PrEP knowledge and interest among PWID.

- PWID who participated were young (mean age=33), male (55%), and white (67%).
- PrEP knowledge among PWID was low.
- Key informants identified the following contributors to low knowledge:
  - Marketing efforts targeting other populations (e.g. men-who-have-sex-with-men) that do not feel relevant to PWID.
  - Barriers faced by providers in discussing PrEP, including time constraints and competing clinical priorities.
  - Low provider willingness to offer PrEP to PWID due to stigma and assumptions about medication adherence.
- Interest in PrEP among PWID was mixed. Low interest was driven by a low perception of HIV risk, but significant discrepancies between perceived risk and self-reported risk behaviors were identified.

Comments: Recent HIV outbreaks have demonstrated how quickly HIV can spread through injection networks in the era of short-acting fentanyl, making increased PrEP utilization by PWID an urgent priority. Low PrEP knowledge and inaccurate self-assessment of HIV risk are two important targets for future interventions to increase PrEP uptake. Educational interventions for PWID must be tailored to this population in terms of content and access (i.e. availability at sites where PWID already access services). Interventions should also support increased PrEP counseling and prescribing capacity among providers who work with PWID.

Jessica L. Taylor, MD

Reference: Bazzi AR, Biancarelli DL, Childs E, et al. Limited knowledge and mixed interest in pre-exposure prophylaxis for HIV prevention among people who inject drugs. *AIDS Patient Care STDs*. 2018;32(12):529–537.

PRESCRIPTION DRUGS & PAIN

Chronic Pain, Alcohol and Other Drug Use, and Alcohol and Drug Overdoses Among Addiction Treatment Patients

While drug overdose is the leading cause of accidental death in the US, the contributions of pain and alcohol (particularly when combined with other central nervous system depressants) have not yet been well described. The authors examined whether past nonfatal overdose was more likely among residential addiction treatment patients with pain, and examined the characteristics of alcohol or drug* overdose among those with and without pain. Cross sectional, self-reported data were analyzed from 739 patients at a large residential treatment center in Michigan between 2014 and 2016.

- The median age of participants was 37 years with most being male (74%), white (67%), and recommended for residential treatment by the criminal justice system (95%).
- 72% of the study sample reported pain (69% chronic pain only, 8% acute pain only, 23% both acute and chronic pain).
- Among people with alcohol use, approximately 83% of participants reported at least 1 previous nonfatal alcohol overdose (median=5). Past chronic pain and drug use were associated with an increased likelihood of nonfatal alcohol overdose.
- Among participants with drug use, 54% reported at least 1 previous episode of nonfatal drug overdose (median=1). Non-medical prescription opioid use, depression, and younger

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Chronic Pain, Alcohol and Other Drug Use, and Alcohol and Drug Overdoses Among Addiction Treatment Patients (continued from page 5)

age were associated with an increased likelihood of nonfatal drug overdose.
- Individuals with pain were also more likely to combine numerous drugs with alcohol prior to overdose, compared with those without pain.

*Defined as "lifetime history of heroin, methadone, nonprescribed opioids/narcotic analgesics, barbiturates, sedatives, hypnotics, tranquilizers, amphetamines, ecstasy, cannabis, hallucinogens, phencyclidine, ketamine, inhalants, or 'any other drugs.'"

Comments: This study has important limitations that impact its generalizability, including its single-site, cross-sectional, self-reported study design and an inability to distinguish the timing between overdose and pain onset. However, the findings emphasize a high prevalence of nonfatal alcohol overdose among the study's patient population and suggest pain to be a significant contributing factor. Addiction treatment and overdose prevention interventions should incorporate appropriate assessment and treatment of pain, including education about the risks of polysubstance use.

Seonaid Nolan, MD

Reference: Fernandez AC, Bush C, Bonar EE, et al. Alcohol and drug overdose and the influence of pain conditions in an addiction treatment sample. *J Addict Med*. 2019;13(1):61–68.

Chronic Opioid Therapy Risk Reduction Initiatives Did Not Reduce Opioid Overdose

Little is known about the effects of primary care-based opioid dose reduction and risk stratification/monitoring (RSM) interventions on the risk of opioid overdose. This study used an interrupted time series analysis to compare: 1) opioid overdose rates among patients in clinics that implemented a dose reduction intervention followed by a RSM intervention; with 2) overdose rates among patients in clinics without the sequential interventions.

- From 2006 to 2014, 22,673 intervention patients (in 26 group practice clinics) and 8469 control patients (in diverse contracted care practices) experienced 311 fatal or non-fatal opioid overdoses.
- In the primary analysis, neither the opioid dose reduction nor the RSM intervention were associated with reduced opioid overdose rates among patients receiving chronic opioid therapy.
- In planned secondary analyses, overdose rates decreased significantly in intervention settings during the dose reduction phase (relative annual change, 0.83), but not in the control settings. No changes in overdose rates were seen during the RSM intervention phase.

Comments: These data are limited by potential differences in the intervention and control settings, although efforts were made to control for patient differences. Since the study only examined overdose rates among patients currently prescribed opioids, possible effects on overdose among patients whose opioids were discontinued are not included, and the design did not allow reporting of any differential opioid discontinuation rates between settings. Studies of the effects of opioid dose reduction and discontinuation on opioid overdose among patients receiving chronic opioid therapy are urgently needed.

Joseph Merrill, MD, MPH

Reference: Von Korff M, Saunders K, Dublin S, et al. Impact of chronic opioid therapy risk reduction initiatives on opioid overdose. *J Pain*. 2019;20(1):108–117.

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