Alcohol, Other Drugs, and Health: Current Evidence

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INTERVENTIONS & ASSESSMENTS

Models for Integrating Opioid Use Disorder Treatment into Primary Care

Primary care and the treatment of opioid use disorder (OUD) continue to be fragmented despite the development of several models addressing their integration. This scoping review identified current models of integrated care, and identified facilitators of and barriers to successful implementation. Starting with a literature review, the authors identified core components of each model and conducted interviews with key informants. Twelve models of care were identified:

- All models utilized medication for treatment of OUD, with most using buprenorphine/naloxone.
- Most, but not all, models performed outreach to prescribers (e.g., buprenorphine waiver trainings). Some provided additional support for nurses.
- A few models leveraged outreach to improve program acceptability within the community, incorporating primary-care based OUD treatment with other medical care (i.e., HIV and HCV treatment and prenatal/postpartum care).
- Most models had a clinical coordinator to manage aspects of OUD care. Some linked systems of care through coordinated efforts between locations, including bridging patients from one level of care to primary care (e.g., emergency department or inpatient to primary care-based buprenorphine/naloxone providers).
- All models provided linkage to additional behavioral health services; however, many were to off-site providers.

Comments: Models of OUD treatment integrated into primary care share the use of evidenced-based medication, linkage to additional medical/behavioral health care services, and facilitating training to support providers. There are at least 12 models available that programs can adapt and customize to their specific setting, but there has yet to be a trial that compares effectiveness of treatment outcomes between care models.

Brittany L. Carney, MS† and Alexander Y. Walley, MD, MSc

†Contributing editorial intern and DNP candidate, University of Massachusetts Medical School, Graduate School of Nursing

Reference: Korthuis PT, McCarty D, Weimer M, et al. Primary care-based models for the treatment of opioid use disorder: a scoping review. *Ann Intern Med*. 2017;166(4):268–278.

Pharmacologically Controlled Drinking in the Treatment of Alcohol Use Disorder: More Evidence Is Needed

This systematic review and meta-analysis summarized the evidence for 5 medications used to reduce alcohol use in non-abstinent adults with alcohol use disorder. The authors identified 32 randomized trials (published 1994–2015) with a total of 6036 patients. The primary outcome was total alcohol consumption, which was reported in 7 of the 9 nalmefene studies examined, 5 of the 14 naltrexone studies, 2 of the 4 topiramate studies, 1 of the 4 baclofen studies, and the 1 acamprosate study (all were compared with placebo).

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Pharmacologically Controlled Drinking in the Treatment of Alcohol Use Disorder: More Evidence Is Needed (continued from page 1)

- Twenty-six studies were deemed to have unclear or high risk of having incomplete outcome data and 17 to be at risk of selective outcome reporting.
- When total alcohol consumption was reported, nalmefene, baclofen, and topiramate showed superiority over placebo. No efficacy was observed for naltrexone and acamprosate.
- Data on heavy drinking days were more complete and the same results were observed, except for baclofen (not superior to placebo).
- No difference was found for any of the medications regarding mortality and serious adverse events.
- In indirect comparisons, topiramate was superior to nalmefene, naltrexone, and acamprosate.
- For all treatments except topiramate, effect sizes were small or inconsistent.

Comments: There is currently no high-quality evidence supporting pharmacological treatment to control drinking in patients with alcohol use disorder. The risks of incomplete outcome data or selective outcome reporting were identified by this report. In addition, no study demonstrated a benefit on health outcomes. More evidence is needed on this topic.

Nicolas Bertholet, MD, MSc

Reference: Palpacuer C, Duprez R, Huneau A, et al. Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network metaanalyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. *Addiction*. 2018;113(2):220–237.

Supplement N-acetylcysteine May Help With Drug Craving

N-acetylcysteine (NAC) is an over-the-counter supplement that has been identified in animal studies as a potential agent to help with drug craving. The authors conducted a systematic review of the literature and found 7 randomized controlled trials with 245 participants comparing NAC with placebo.

- The intervention periods ranged from 3 to 56 days. The studies looked at individuals with cocaine (2 studies), methamphetamine (1), nicotine (3), and cannabis (1) use disorders. NAC dosage ranged from 1200 to 3600 mg/day.
- Meta-analysis showed a significant clinical difference in drug craving between NAC and placebo groups. Hedges' g = 0.94, which suggests a large effect size.

Comments: NAC appears to be a promising agent for help with craving. It is available over-the-counter, is reported to be safe, and has minimal side effects. It remains to be seen whether the observed short-term reduction in craving translates into reduction in use and improvement in clinical outcomes.

Darius A. Rastegar, MD

Reference: Duailibi MS, Cordeiro Q, Brietzke E, et al. N-acetylcysteine in the treatment of craving in substance use disorders: systematic review and meta-analysis. *Am J Addict*. 2017;26:660–666.

HEALTH OUTCOMES

Causes of Death Among Patients With Opioid Use Disorder in a General Medical Setting

Most mortality and morbidity data on opioid use disorder (OUD) have come from publicly funded treatment center and population-level sources. In this study, researchers assessed all-cause and cause-specific mortality in 2576 patients aged 18 to 64 years with OUD. Patients were identified via ICD-9 codes from inpatient and outpatient visits to a large US university health system from 2006 to 2014. Mortality data were obtained through the National Death Index.

- Overall, 18% of patients died. Among decedents, the causes of death were drug or substance related (20%), drug or substance poisoning (17%), cardiovascular (17%), cancer (17%), infectious (14%), hepatitis C (12%), digestive system (12%), and liver disease (11%).
- The overall crude mortality rate was 48.6 per 1000 person-years and standardized mortality rate was 10.3 per 1000 person-years.
- Age, hepatitis C infection, and alcohol use disorder were associated with significantly higher risk of all-cause mortality among those with OUD.

Comments: The crude all-cause mortality rate in this sample is much higher than prior reports (e.g., 20.9 per 1000 person-years in one large systematic review and meta-analysis of 58 cohort studies), perhaps because the sample was drawn from a healthcare setting. A significant proportion (37%) of the deaths were directly related to substances. Although recorded ICD-9 codes for OUD may not always be accurate, the study reiterates the need for providers and health systems to improve efficient identification of OUD, provision of naloxone, and timely treatment for these patients.

Kevin L. Kraemer, MD, MSc

Reference: Hser YI, Mooney LJ, Saxon AJ, et al. High mortality among patients with opioid use disorder in a large healthcare system. *J Addict Med*. 2017;11(4):315–319.

Reduction in Cannabis Use Over Time Improves Functional Outcomes

People often use cannabis for its calming effects and as a sleep aid. However, chronic use and development of cannabis use disorder (CUD) may result in the opposite psychoactive effects. Abstinence is often the target of treatment initiatives, but little is known about how reduction in cannabis use may effect certain symptoms. This secondary analysis of a 12-week, multi-site trial of a medication for CUD examined the longitudinal association between reductions in cannabis use and anxiety, depression, sleep quality, and quality of life. The sample consisted of 302 individuals (152 reduced cannabis use, 150 increased use).

- The 2 groups did not differ in age, gender, educational achievement, or employment, but differed significantly regarding race/ethnicity with more black (36% versus 19%) and fewer "other" (4% versus 11%) participants in the reduction group compared with the increase group. Frequency of cannabis, alcohol, and tobacco use at baseline did not differ between the groups.
- Controlling for demographics, treatment condition, and time-varying tobacco and alcohol use, the authors found an association between reduction in cannabis use and improvement in anxiety, depression, and sleep quality, but not in quality of life.

Comments: Although the study period was only 12 weeks and changes in cannabis use were based on self-report, this study suggests that reductions in use over time may result in symptom control. More studies should test the effects of clinically applicable outcomes such as reduction in substance use rather than abstinence.

Jeanette M. Tetrault, MD

Reference: Hser YI, Mooney LJ, Huang D, et al. Reductions in cannabis use are associated with improvements in anxiety, depression, and sleep quality, but not quality of life. *J Subst Abuse Treat*. 2017;81:53–58.

Black Patients with Mental Health and Substance-Related Disorders Experience Longer Wait Times in the Emergency Department

Emergency Department (ED) crowding has been identified as a public health crisis in the US, with ED utilization increasing at a faster rate among patients with mental health and substance-related disorders than overall ED utilization. This cross-sectional study examined ED wait times among this population and evaluated the impact of race/ethnicity, insurance type, and geographical location on identified disparities.

- Of 6534 ED visits, the majority were made by non-Hispanic whites (66%), followed by non-Hispanic blacks (19%) and other non-Hispanic races (3%).
- 39% of all ED visits were substance use-related.
- Private insurance, Medicare, and Medicaid beneficiaries accounted for 22%, 18%, and 25% of ED visits

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Black Patients with Mental Health and Substance-Related Disorders Experience Longer Wait Times in the Emergency Department (continued from page 3)

respectively; 23% of individuals did not have health insurance.
- After adjusting for patient and hospital-level factors, ED wait time was 23% longer for non-Hispanic blacks compared with non-Hispanic whites.
- ED wait time did not differ by insurance type or geographic location.

Comments: Racial disparities were observed in this study, with ED wait times found to be significantly longer for non-Hispanic black patients with mental health and substance-related disorders compared with non-Hispanic whites with similar disorders. These findings highlight the need for urgent corrective ED, community-based and culturally competent interventions to both improve care for this patient population and help address ED overcrowding.

Seonaid Nolan, MD

Reference: Opoku ST, Apenteng BA, Akowuah EA, Bhuyan S. Disparities in emergency department wait time among patients with mental health and substance-related disorders. *J Behav Health Serv Res*. 2017 [Epub ahead of print]. doi: 10.1007/

Association Between Alcohol Consumption and Gastric Cancer

While heavy alcohol intake has been found to increase the risk of upper aero-digestive tract cancers, results are less clear for gastric cancer. This meta-analysis is notable because it was based on a large number of participants from 75 studies, used appropriate analytic methods, and provided dose-dependent results according to type of beverage.

- For total alcohol consumption, the dose-response results show a curvilinear association between alcohol intake and gastric cancer, with a 4% increase in risk per standard drink (12.5 g alcohol).
- In beverage-specific analyses, for beer, a non-linear association was found with a 7% increase in risk per drink. For liquor, there was a linear association (relative risk [RR], 1.03 per drink); and for wine, the RR was 0.99.

Comments: When comparing high versus lower levels of alcohol intake on a linear basis, the authors found a 25% increase in gastric cancer. However, the association was non-linear, and using spline analyses the increase was only 4% per standard drink. Further, beverage-specific analyses found no change in risk of gastric cancer for wine consumers, polyphenols in wine that may mitigate some adverse effects of alcohol.

R. Curtis Ellison, MD

Reference: Wang PL, Xiao FT, Gong BC, Liu FN. Alcohol drinking and gastric cancer risk: a meta-analysis of observational studies. *Oncotarget*. 2017;8:99013–99023.

HIV AND HCV

People Living With HIV Have Increased Non-fatal Overdose Risk With Each Additional Medication

People living with HIV (PLWH) are exposed to many medications and their potential risks. In this study of 250 adult PLWH, researchers assessed the association of an increasing number of sedating, non-sedating (both opioid and non-opioid), non-antiretroviral (ARV), and overall medications with the self-reported outcomes of lifetime and past-year non-fatal overdose.

- At baseline, participants were prescribed a median of 10 medications (2 sedating); 80% received sedating medications, 50% received opioid prescriptions, and 42% were co-prescribed opioid and non-opioid sedating medications. The most common non-opioid sedating medications were gabapentin (22%), mirtazapine (16%), trazodone (14%), hydroxyzine (12%), and diphenhydramine (10%). The most common benzodiazepine was clonazepam (7%).
- 45% of participants reported lifetime non-fatal overdose and 7% reported past-year non-fatal overdose.
- Odds of lifetime non-fatal overdose were significantly higher with each additional sedating medication (odds ratio [OR], 1.3), any opioid (OR, 2.3), and any opioid agonist treatment medication (OR, 4.8).
- Odds of past-year non-fatal overdose were higher with each additional sedating (OR, 1.2) and non-ARV (OR, 1.1) medication and any opioid agonist treatment (OR, 2.7).

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People Living With HIV Have Increased Non-fatal Overdose Risk With Each Additional Medication (continued from page 4)

Comments: Polypharmacy is common among PLWH and has the potential for increased harm as this population ages. The increased risk with opioid agonist treatment is likely because PLWH with opioid use disorder are perhaps more likely to both overdose and be initiated on opioid agonist treatment. The study is limited by absence of information about current medications at the time of non-fatal overdose. Nonetheless, it suggests that providers should carefully assess the risks and benefits of all medications among PLWH.

Kevin L. Kraemer, MD, MSc

Reference: Kim TW, Walley AY, Heeren TC, et al. Polypharmacy and risk of non-fatal overdose for patients with HIV infection and substance dependence. *J Subst Abuse Treat.* 2017;81:1-10.

Injection Drug Use Is Associated With Tuberculosis Among People With HIV

HIV and tuberculosis (TB) are important and linked causes of morbidity and mortality worldwide. People with injection drug use (PWID) are at risk for HIV infection, but less is known about their risk for TB. Investigators used public health data from the United Kingdom to investigate the association of injection drug use with TB among adults living with HIV.

- Between 2000 and 2014, 102,202 adults were diagnosed with HIV, among whom 5649 (6%) also had TB.
- The overall TB incidence was 344/100,000 person-years (PY). The incidence among PWID was significantly higher: for the men, it was 876/100,000 PY, and for women, 605/100,000 PY.
- In multivariable analysis, compared with men who have sex with men, PWID had increased rates of TB (incidence rate ratio [IRR] for men 5.47, for women 4.59). The only other demographic group with a comparable rate was black Africans born in high-incidence countries (IRR, 4.27).

Comments: As with any observational study, association does not establish causation. It is possible that this association is due to other unmeasured factors; a few that come to mind are smoking, living conditions, and past incarceration. Nevertheless, this study shows that PWID are at higher risk for TB and should be targeted for screening.

Darius A. Rastegar, MD

Reference: Winter JR, Stagg HR, Smith CJ, et al. Injecting drug use predicts active tuberculosis in a national cohort of people living with HIV. *AIDS*. 2017;31(17):2403-2413.

Marijuana as a Modifiable Cardiovascular Risk Factor in People Living With HIV

The literature offers conflicting data on the effects of marijuana on HIV disease progression, CD4 count, and HIV viral load. People living with HIV have a 2-fold increase in cardiovascular disease compared with age-matched HIV-uninfected controls, which is only partially explained by the presence of traditional cardiovascular risk factors, antiretroviral therapy effect, and healthcare disparities. This 20-year prospective cohort study of 558 men living with HIV examined the associations between heavy marijuana use and HIV disease markers and health outcomes, including cardiovascular endpoints.

- The median baseline age of participants was 41 years; 66% were white; and 70% had >12 years of education. At >50% of the biannual follow up visits, 20% of participants reported daily or weekly marijuana use (defined as "heavy use").
- There was no association between heavy marijuana use and HIV disease markers.
- There were no associations between heavy marijuana use and progression to AIDS, cancer diagnosis, or mortality.
- Heavy marijuana use was associated with increased cardiovascular events between the ages of 40 and 60 (odds ratio, 2.5) after adjusting for age, tobacco smoking, HIV viral load, and traditional cardiovascular risk factors.

Comments: Although these results should be replicated in other cohorts, heavy marijuana use may be a modifiable cardiovascular risk factor among people living with HIV and should be discussed as part of routine preventive care.

Jeanette M. Tetrault, MD

Reference: Lorenz DR, Dutta A, Mukerji SS, et al. Marijuana use impacts midlife cardiovascular events in HIV-infected men. *Clin Infect Dis*. 2017;65(4):626–635.

PRESCRIPTION DRUGS & PAIN

Prescribing Opioids With Other Psychotropic Medications Increases the Risk of Neonatal Withdrawal Symptoms

Twenty percent of the global population is affected by chronic pain. Opioid prescribing, including to pregnant women, has increased substantially in the past 2 decades, and many fetuses are exposed to opioids concomitantly with other psychotropic medications. This report examined the relative risk of neonatal withdrawal symptoms among infants whose mothers received prescriptions for psychotropic medications in addition to opioids, compared with those whose mothers received opioids alone.

- Among infants whose mothers were prescribed opioids (other than methadone or buprenorphine) in the last 45 days of pregnancy, the absolute risk of neonatal withdrawal symptoms was 1%.
- Risk increased 30-60% among infants whose mothers were co-prescribed antidepressants, benzodiazepines, or gabapentin.
- Risk doubled in infants whose mothers received prescriptions for ≥2 psychotropic medications.

Comments: Opioid prescribing to pregnant women infrequently results in neonatal withdrawal symptoms, but the risk increases substantially when other psychotropic medications are co-prescribed. Physicians who provide care to pregnant women should be aware of these risks and take steps to minimize them when possible. Physicians that care for newborns should be aware of the increased risk of neonatal withdrawal symptoms in infants that were exposed to opioids and psychotropic medications in utero.

Sharon Levy, MD, MPH

Reference: Huybrechts KF, Bateman BT, Desai RJ, et al. Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: cohort study. *BMJ*. 2017;358:j3326.

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