Alcohol, Other Drugs, and Health: Current Evidence

JANUARY-FEBRUARY 2021

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INTERVENTIONS & ASSESSMENTS

Medication for Opioid Use Disorder Reduces the Risk of Overdose More Than Treatment Without Medication

Opioid overdose is a leading cause of morbidity and mortality in the US and effective measures to mitigate this problem are urgently needed. Medications for opioid use disorder (MOUD), particularly methadone and buprenorphine, have been shown to reduce the risk of overdose. The impact of treatment without medication is less clear. Researchers used data from Maryland statewide claims and death records to compare opioid overdose death rates during treatment episodes that included MOUD (in this case, methadone or buprenorphine) in specialty care settings with treatment episodes that did not include MOUD.

- A total of 48,274 adults received outpatient treatment for OUD in 2015/2016; 50% had treatment episodes with MOUD, 28% had treatment episodes without medication, and 22% had both treatment episodes that did include MOUD and treatment episodes that did not include MOUD.
- Those who received MOUD were more likely to be female, older than 35, married, employed, not homeless, to not have reported an arrest in the past year, and to have been referred by a non-criminal justice source. There were no significant differences by race.
- Overdose death rates were lowest during receipt of MOUD (0.5/1000 person-years), followed by treatment without medication (4.1), after treatment without medication (13.2), and after MOUD (17.2).
- Weighted hazard ratio (HR) for overdose was significantly lower during receipt of MOUD versus treatment without medication (HR, 0.18). Periods after receipt of MOUD and non-medication treatment both had elevated risk, but were not significantly different from each other (HR, 5.45 and 5.85, respectively).

Comments: This study adds to the overwhelming evidence that methadone and buprenorphine reduce the risk of overdose among people with OUD. Other treatments reduce the risk, but less so. This reinforces the importance of including these medications as an option in all treatment settings, and doing a better job to recruit and retain people with OUD into evidence-based treatment.

Darius A. Rastegar, MD

Reference: Krawczyk N, Mojtabai R, Stuart EA, et al. Opioid agonist treatment and fatal overdose risk in a state-wide US population receiving opioid use disorder services. *Addiction*. 2020;115:1683–1694.

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Cannabidiol Shows Promise as a Treatment for Cannabis Use Disorder

Cannabis use is increasing in the US with some state laws permitting medicinal and/or recreational use. The incidence of cannabis use disorder (CUD) has also increased, but there are currently no FDA-approved pharmacologic treatments for CUD among adults. Cannabidiol is a cannabinoid that has effects different from D-9-tetrahydrocannabinol (THC) and more medicinal value. This randomized clinical trial among adults with CUD assessed the effect of various doses of oral cannabidiol* on cannabis use measured self-reported average days of cannabis use and urine drug screen (urinary THC:creatinine ratio).

- The 200mg dose of cannabidiol was not associated with cannabis use reduction.
- Compared with placebo, participants receiving 400mg of cannabidiol reduced cannabis use by 0.48 days per week, and their urinary THC:creatinine ratio decreased by -94·21 ng/mL.
- Compared with placebo, participants receiving 800mg of cannabidiol reduced cannabis use by 0.27 days per week, and their urinary THC:creatinine ratio decreased by -72·02 ng/mL.
- No serious side effects were noted.

* In the first phase of this adaptive Bayesian trial, participants received placebo or 1 of 3 different doses of oral cannabidiol (200mg, 400mg, or 800mg). In the second phase, new participants were randomized to placebo or the doses deemed most efficacious in the first phase (400mg and 800mg).

Comments: There are currently no pharmacologic treatment options for treating cannabis use disorder in adults. In this randomized trial, cannabidiol showed promise as a possible treatment.

Melissa B. Weimer, DO, MCR

Reference: Freeman TP, Hindocha C, Baio G, et al. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry*. 2020;7(10):865–874.

HEALTH OUTCOMES

Teen Vaping Associated With Increased Risk of Later Combustible Cigarette Use

Research has demonstrated an association between e-cigarette use (vaping) and initiation of combustible cigarette (tobacco) use among youth. This study used data from a US national sample (N=3426, age 15–27) to examine the magnitude of this association among youth with e-cigarette use from 2017 to 2019, when "pod mod" devices—which deliver high nicotine concentrations—had the largest share of the market.

- Compared with youth who had never had e-cigarette use, those who initiated it in 2018 were 7 times more likely to initiate combustible cigarette use in 2019 (adjusted odds ratio [aOR], 7.29), and 8 times more likely to have current combustible cigarette use (aOR, 8.26).
- Other predictors of combustible cigarette use included male gender, household tobacco use, and sensation seeking.

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Teen Vaping Associated With Increased Risk of Later Combustible Cigarette Use (continued from page 2)

Comments: E-cigarette use during adolescence greatly increases the risk of later combustible cigarette use. The popularity of vaping is a concern because the vast majority of adults with combustible cigarette use initiated it in their teen years. While e-cigarettes were introduced to the marketplace as a solution to the public health problem of smoking, the popularity of "pod mod" devices among adolescents may result in these devices introducing a greater number people to smoking than the number of those they help to quit.

Sharon Levy, MD

Reference: Hair EC, Barton AA, Perks SN, et al. Association between e-cigarette use and future combustible cigarette use: evidence from a prospective cohort of youth and young adults, 2017–2019. *Add Behav*. 2021;112:106593.

Regular Cocaine Use Associated With Adverse Cardiovascular and Respiratory Outcomes

Cocaine use has been associated with adverse cardiovascular and pulmonary outcomes, but previous research has been limited by cross-sectional analysis and failure to adjust for important confounders, especially tobacco use. This study used data on 426,112 patients treated at a health system in Ohio from 1999 to 2018 to investigate the association between "regular" cocaine use* and adverse cardiovascular and pulmonary outcomes. Researchers adjusted their analyses for age, sex, race, median income of zip code of residence, body mass index, and tobacco use.

- A total of 8244 individuals met criteria for regular cocaine use and were compared with 8244 control individuals with similar demographic variables.
- Cocaine use was associated with an increased risk of myocardial infarction (adjusted odds ratio [aOR], 2.9), cerebrovascular accidents (aOR, 2.5), and heart arrhythmia (aOR, 1.3), but not subarachnoid hemorrhage (aOR, 1.1).
- Cocaine use was also associated with respiratory outcomes, including an increased risk of pneumonia (aOR, 2.9), COPD (aOR, 2.5), and asthma (aOR, 2.3).
- Cocaine use was associated with higher all-cause mortality (aOR, 3.9).

* Defined as having a diagnosis of cocaine use disorder, or ≥2 cocaine-positive urine drug tests.

Comments: This study strongly suggests a relationship between cocaine use and a number of adverse health outcomes, but could not account for frequency or route of use. Evidence for causation would be strengthened by studies demonstrating a dose-response relationship between cocaine use and adverse outcomes.

Darius A. Rastegar, MD

Reference: Winhusen T, Theobald J, Kaelber DC, Lewis D. The association between regular cocaine use, with and without tobacco co-use, and adverse cardiovascular and respiratory outcomes. *Drug Alcohol Depend*. 2020;214:108136.

Prescription of Opioids and Gabapentinoids Associated With Subsequent Overdose, Especially at High Doses and in Combination

Gabapentinoid prescriptions have increased substantially over the last 2 decades, and there is increasing evidence of a heightened risk of overdose among patients prescribed these medications, especially in combination with opioids. This prospective cohort study evaluated the association between receipt of gabapentinoid and/or opioid medications* and overdose over 12 months. Participants (N = 71,000) were Medicare beneficiaries with a diagnosis of fibromyalgia, low back pain, neuropathy, or osteoarthritis who were newly prescribed either medication (or both) following a 6-month period without a prescription for either. Results were adjusted for sociodemographic markers, disability, a medical comorbidity index, co-occurring psychiatric disorders, benzodiazepine prescriptions, and healthcare access and utilization. People with previously diagnosed substance use disorder or overdose were excluded.

- Most patients received monotherapy (59% opioid-only and 27% gabapentinoid-only), while 14% received both medications.
- Compared with patients prescribed opioids only who had early medication discontinuation (i.e., discontinued within a month of initiation, 41% of the cohort), patients prescribed gabapentinoids alone—regardless of dose or duration—had a 40% increased risk of overdose over the 12-month follow-up. A similar overdose risk was observed in the group prescribed only low-dose opioid medications.
- Compared with the opioid-only early discontinuation group, receipt of low-dose opioid medications co-prescribed with both high- and low-dose gabapentinoids was associated with a 250% increased risk of overdose. Patients co-prescribed high-dose opioids and moderate-dose gabapentinoids saw a 7-fold risk increase.

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Prescription of Opioids and Gabapentinoids Associated With Subsequent Overdose, Especially at High Doses and in Combination (continued from page 3)

* Opioid average daily doses defined as: low (< 50 morphine milligram equivalent [MME]), moderate (50–90 MME), and high (> 90 MME). Gabapentinoid standardized daily doses (SDD) defined as: low (< 2 SDD [i.e., gabapentin < 600 mg or pregabalin < 300 mg]), moderate (2–3 SDD [i.e., 600 ≤ gabapentin < 900 mg or 300 ≤ pregabalin < 450 mg]), and high (>3 SDD [i.e., gabapentin ≥ 900 mg or pregabalin ≥ 450 mg]).

Comments: This study provides evidence of heightened risk of overdose in a dose-dependent and additive manner following new prescriptions for gabapentinoid and opioid medications. This study should give clinicians significant pause when considering a new prescription for gabapentinoids, especially in combination with opioid medications, and when prescribing for an off-label application where evidence of benefit is limited at best.

Morgan Younkin, MD, MPH† and Darius A. Rastegar, MD

† Contributing Editorial Intern and Addiction Medicine Fellow, Boston Medical Center.

Reference: Zhou L, Bhattacharjee S, Kwoh CK, et al. Dual-trajectories of opioid and gabapentinoid use and risk of subsequent drug overdose among Medicare beneficiaries in the United States: a retrospective cohort study. *Addiction*. 2020 [Epub ahead of print]. doi: 10.1111/add.15189.

Black and Hispanic Women Were Less Likely Than White Women to Receive Medications for Opioid Use Disorder During Pregnancy

Methadone and buprenorphine (i.e., medications for opioid use disorder [MOUD]) are recommended for treating opioid use disorder (OUD) during pregnancy. Investigators used data from a statewide Massachusetts quality improvement initiative to examine whether maternal race/ethnicity were associated with receiving MOUD during pregnancy and several other infant outcomes. Among 1710 deliveries to women with OUD in 24 hospitals, maternal and infant outcomes for non-Hispanic White women were compared with non-Hispanic Black and Hispanic women using multivariable mixed-effects regression models.

- During pregnancy, 68% of the cohort received MOUD and had no non-prescribed opioid use, 20% received MOUD and had non-prescribed opioid use, and 13% had non-prescribed opioid use and received no MOUD.
- Compared with non-Hispanic White women, non-Hispanic Black and Hispanic women were less likely to receive MOUD (adjusted odds ratio [aOR], 0.34 and 0.43, respectively).
- A greater percentage of non-Hispanic White women received buprenorphine than non-Hispanic Black or Hispanic women.
- Infant outcomes—including pharmacologic treatment of neonatal opioid withdrawal syndrome, in-hospital care, and whether they were discharged home with a biological parent—were not significantly associated with race/ethnicity.

Comments: Most women with OUD in this cohort received MOUD during pregnancy, but non-Hispanic Black and Hispanic women were less likely than non-Hispanic White women to receive treatment. Consistent with other studies, receipt of buprenorphine was greatest among the non-Hispanic White group. Medicaid and MOUD availability in Massachusetts likely positively influenced receipt of MOUD in this study, but reasons for differences based on race/ethnicity deserve additional exploration.

Aaron D. Fox, MD

Reference: Peeler M, Gupta M, Melvin P, et al. Racial and ethnic disparities in maternal and infant outcomes among opioid-exposed mother-infant dyads in Massachusetts (2017-2019). *Am J Public Health*. 2020;110(12):1828–1836.

Medicaid Expansion Not Clearly Associated With Population-level Increases in Opioid Agonist Treatment

Opioid agonists buprenorphine and methadone are the standard of care for treatment of opioid use disorder, yet they are markedly underused. Access to opioid agonist medications may be limited in the US by health insurance availability and the design of health benefits. This retrospective study examined the impact of Medicaid expansion through the Affordable Care Act on statewide dispensing of buprenorphine and methadone.

- On average, Medicaid expansion was associated with…
  - a non-significant 14% increase in methadone dispensed through opioid treatment programs.
  - a non-significant 4% increase in buprenorphine dispensed.
- In the states with the most buprenorphine-waivered providers pre-expansion, Medicaid expansion was associated with a significant 33% increase in buprenorphine dispensed.

Comments: This study did not identify a clear association between Medicaid expansion and state-level buprenorphine or methadone dispensing. Insurance coverage may be important but insufficient to expanding opioid agonist treatment. Additional targets include improving provider supply and treatment accessibility through regulatory and health care delivery reforms.

Marc R. Larochelle, MD, MPH

Reference: Gertner AK, Robertson AG, Jones H, et al. The effect of Medicaid expansion on use of opioid agonist treatment and the role of provider capacity constraints. *Health Serv Res*. 2020;55:383–392.

HIV & HCV

Methamphetamine Use Associated With High Rates of HIV Seroconversion Among Sexual and Gender Minorities Who Have Sex With Men

Methamphetamine use increases sexual libido, decreases sexual inhibitions, and reduces the need for sleep; these factors may drive risky sexual behaviors that increase HIV transmission. Methamphetamine use is on the rise among sexual and gender minorities who have sex with men (SGMSM). Using baseline and 12-month data (2017–2018) from the Together 5000 US internet-based cohort study, researchers assessed rates of HIV seroconversion among 4786 SGMSM aged 16–49, comparing individuals with and without methamphetamine use.

- Across the study cohort, 2.47 per 100 persons had HIV seroconversion between baseline and 12 months.
- 9% of the cohort had "persistent"* methamphetamine use, 2% initiated use during the study period, and 3% discontinued use between baseline and 12 months.
- 36% of those with HIV seroconversion were people with "persistent" methamphetamine use.
- Compared with people who did not have methamphetamine use, the odds of HIV seroconversion were 7.11 greater among those with "persistent" use and 3.95 greater for those who initiated use during the study period. People who discontinued methamphetamine use did not have a significant difference in odds of HIV seroconversion, compared with those without use.

* Defined as methamphetamine use in the 3 months before baseline and in the 12 months of follow-up.

Comments: In this large internet-based cohort study of sexual and gender minorities that have sex with men, the 12-month HIV seroconversion rate was very high and strongly associated with methamphetamine use. Healthcare providers should regularly test SGMSM patients for HIV infection, screen for methamphetamine use, and offer ready access to HIV treatment and prevention medications. This study did not consider the role of other substance use, which may be interwoven with methamphetamine use for many SGMSM individuals.

Raagini Jawa, MD, MPH† & Alexander Y. Walley, MD, MSc

† Contributing Editorial Intern and Infectious Disease and Addiction Medicine Fellow, Boston Medical Center.

Reference: Grov C, Westmoreland D, Morrison C, et al. The crisis we are not talking about: one-in-three annual HIV seroconversions among sexual and gender minorities were persistent methamphetamine users. *J Acquir Immune Defic Syndr*. 2020;85(3):272–279.

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