Alcohol, Other Drugs, and Health: Current Evidence

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TABLE OF CONTENTS

Learn more on page 6

INTERVENTIONS & ASSESSMENTS

Effective Buprenorphine Initiation with Injectable Buprenorphine for Patients with Minimal-to-mild Opioid Withdrawal

Buprenorphine is a highly effective medication for opioid use disorder (OUD). Its partial opioid agonist properties require some consideration during initiation, particularly in the setting of highly potent synthetic opioids like fentanyl and fentanyl analogues. This non-randomized controlled trial studied the feasibility and acceptability of buprenorphine initiation with a seven-day extended-release buprenorphine injection for individuals with minimal-to-mild opioid withdrawal* treated in one of four US emergency departments.

- All patients (N=100) had positive urine drug test results for more than one opioid and negative for methadone; 70 percent tested positive for fentanyl and 39 percent tested positive for buprenorphine.
- Among patients with mild withdrawal (COWS 4–7; n=63), 6 percent experienced increased withdrawal following receipt of the injection; 3 percent experienced precipitated withdrawal.
- For patients with minimal withdrawal (COWS 0–3; n=37), 16 percent experienced increased withdrawal following receipt of the injection; 14 percent experienced precipitated withdrawal.
- Only individuals with fentanyl in their urine drug test experienced an increase in opioid withdrawal or precipitated opioid withdrawal.
- Most patients reported their overall experience with the treatment to be completely effective at seven days; 73 percent engaged in OUD treatment within seven days of receiving the injection.
- Adverse events occurred in 13 percent of patients, 5 percent requiring hospitalization; no opioid overdoses were reported within the 7 days of follow-up.

* Withdrawal was assessed via the Clinical Opiate Withdrawal Scale (COWS) with higher scores indicating increasing withdrawal.

Comments: This prospective trial is the first to describe the feasibility and acceptability of a buprenorphine seven-day injection for individuals with minimal-to-mild opioid withdrawal, including those exposed to fentanyl. It has high applicability and importance as a novel and safe initiation strategy for individuals with OUD with mild withdrawal at baseline. The findings also confirm prior guidance that it is safest to have some opioid withdrawal symptoms prior to buprenorphine initiation. Most importantly, this initiation strategy facilitated ongoing treatment engagement for OUD in most participants.

Melissa B. Weimer, DO, MCR

Reference: D'Onofrio G, Herring AA, Perrone J, et al. Extended-release 7-day injectable buprenorphine for patients with minimal to mild opioid withdrawal. *JAMA Netw Open*. 2024;7(7):e2420702.

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Alcohol-Related Intervention Increased Screening and Brief Intervention, but not Treatment Engagement, in Primary Care

Screening for unhealthy alcohol use is recommended in primary care, but optimal population-based implementation strategies have not been tested and may not have the expected impact on receipt of brief intervention or engagement in treatment for alcohol use disorder (AUD). Researchers conducted a stepped-wedge cluster randomized trial of an alcohol prevention and treatment intervention that included practice facilitation, electronic health record (EMR) decision support, and performance feedback. They assessed the proportion of patients who had unhealthy alcohol use and brief intervention documented in the EMR, and the proportion of patients with newly diagnosed AUD and EMR documentation of AUD treatment. No patient-reported outcomes were assessed.

- 333,596 primary care patients in 22 clinics had a mean age of 48 years; 58 percent were female and 70 percent were White.
- The proportion with EMR documentation of brief intervention was higher during the intervention period than with usual care (57 versus 11 per 100,000 patients per month).
- The proportion of EMR documentation of AUD treatment engagement was similar during the intervention period and usual care (1.4 versus 1.8 per 100,000 patients per month).
- Intermediate outcomes favored the intervention, including screening rates (83 percent versus 21 percent), new AUD diagnosis (34 versus 29 per 100,000), and AUD treatment initiation (7.8 versus 6.2 per 100,000).

Comments: This intervention resulted in substantial improvements in rates of screening, brief intervention, and AUD evaluation, but only modest gains in documented AUD diagnosis and initiation of treatment. The weakest link in this population-based approach was ongoing engagement in alcohol-related treatment, which did not improve with the intervention, and where innovative approaches are needed. While implementation trials solely using EMR data can provide key insights into gaps in treatment, they lack potentially informative patient-level measures of help-seeking and drinking behavior.

Joseph Merrill, MD, MPH

Reference: Lee AK, Bobb JF, Richards JE, et al. Integrating alcohol-related prevention and treatment Into primary care: a cluster randomized implementation trial. *JAMA Intern Med*. 2023;183(4):319–328.

HEALTH OUTCOMES

Providing Medication for Opioid Use Disorder During Incarceration Halves the Risk of Overdose in the Two Weeks After Release

Many individuals with opioid use disorder (OUD) experience incarceration and are at high risk for overdose during the initial period following release from prison or jail. Medications for OUD (MOUD)—specifically methadone and buprenorphine—have been shown to reduce the risk of overdose. In this retrospective observational study in New York City, researchers used data from 31,382 incarceration events between 2011 and 2017 and compared those where MOUD was provided during the last three days of incarceration with those where it was not.

- There were 17,119 incarceration events where MOUD was provided in the last three days of incarceration and 14,263 where it was not.
- Individuals receiving MOUD prior to release were more likely to be female, unhoused, and have cocaine use and injection drug use.

(continued, page 3)

Providing Medication for Opioid Use Disorder During Incarceration Halves the Risk of Overdose in the Two Weeks After Release *(continued from page 2)*

- Receiving MOUD in the last three days of incarceration was associated with a reduced risk of an emergency department visit for non-fatal overdose within 14 days of release (adjusted hazard ratio, 0.49). There was no significant association at 15–28, 29–56, or 57–365 days after release.

Comments: This study adds to a growing body of evidence demonstrating the benefits of providing continuous MOUD to individuals with OUD who are experiencing incarceration. It also underscores the need for linkage to evidence-based OUD care following release from prison or jail.

Darius A. Rastegar, MD

Reference: Cherian T, Lim S, Katyal M, et al. Impact of jail-based methadone or buprenorphine treatment on non-fatal overdose after incarceration. *Drug Alcohol Depend*. 2024;259:111274.

No Association between Cannabis and Non-prescription Opioid Use among People Receiving Medications for Opioid Use Disorder

One of the reasons cited for the legalization of cannabis for medical and non-medical use is that it might decrease unhealthy opioid use through substitution effects. To date, however, evidence on this is mixed, and the co-use of cannabis and opioids is common. Researchers conducted a meta-analysis of longitudinal cohort studies of the relationship between cannabis use and non-medical opioid use among people with opioid use disorder (OUD) receiving medications for OUD (i.e., methadone, buprenorphine, and intramuscular naltrexone); cross sectional and retrospective studies were excluded.

- Ten trials were analyzed; they included 8367 people with OUD; of these, 76 percent, 21 percent, and 2 percent were treated with methadone, buprenorphine, and naltrexone, respectively. The average follow-up time was 9.7 months.
- In the pooled meta-analysis, there was no association between cannabis use and non-medical opioid use (odds ratio, 1.00).
- The lack of association persisted after removal of two trials that were outliers, and a subgroup analysis based on people receiving methadone and buprenorphine only.

Comments: This meta-analysis of longitudinal studies found no association between cannabis and non-medical opioid use among people receiving pharmacologic treatment for OUD. In the context of treatment, clinical trials could better assess relationships between cannabis and non-medical opioid use.

Timothy S. Naimi, MD, MPH

Reference: Costa GP, Nunes JC, Heringer DL, et al. The impact of cannabis on non-medical opioid use among individuals receiving pharmacotherapies for opioid use disorder: a systematic review and meta-analysis of longitudinal studies. *Am J Drug Alcohol Abuse*. 2024;50(1):12–26.

Receipt of Benzodiazepine Medications Not Commonly Associated With Long-term Use or Dose Escalation in a Danish Cohort

Benzodiazepine receptor agonists (BZRAs)—including benzodiazepines and Z-drugs—are commonly prescribed medications for insomnia and anxiety, but carry risk of physiologic dependence and unhealthy use. BZRAs are therefore generally recommended only for short-term use, although the prevalence of long-term receipt of BZRA medications and whether it is associated with dose escalation is not well understood. Researchers followed more than 4,000,000 persons aged 20–80 years from a Danish registry to examine: 1) the frequency and correlates of long-term receipt of BZRAs; and 2) the risk of dose escalation over time. BZRAs were sub-categorized as hypnotic benzodiazepines, anxiolytic benzodiazepines, or Z-drugs.

- Overall, 22 percent of the cohort (n=950,767) received BZRA medications. Of these individuals, 15 percent received them for more than one year; 3 percent were prescribed BZRAs for more than seven years.
- Z-drugs were the most common BZRA subtype to result in long-term use (18 percent for one year, 4 percent for seven years).
- Co-occurring substance use disorder was associated with increased likelihood of long-term BZRA receipt at one and seven years.

(continued, page 4)

Receipt of Benzodiazepine Medications Not Commonly Associated With Long-term Use or Dose Escalation in a Danish Cohort *(continued from page 3)*

- Among persons with long-term continuous receipt of BZRAs, 7 percent experienced dose escalations higher than recommended guidelines.
- Co-occurring substance use disorder, dementia, and female gender were associated with BZRA dose escalation.

Comments: This study provides evidence that BZRA prescriptions do not necessarily result in long-term use or dose escalations. Given differences in population characteristics and provision of health care between Denmark and other countries, however, extrapolating these findings to other populations should be made with caution. Future research is needed to examine BZRA prescription patterns in the US and elsewhere.

Carrie Mintz, MD

Reference: Rosenqvist TW, Wium-Andersen MK, Wium-Andersen IK, et al. Long-term use of benzodiazepines and benzodiazepine-related drugs: a register-based Danish cohort study on determinants and risks of dose escalation. *American J Psychiatry*. 2024;181(3):246–254.

Primary Care Patients With Substance Use Disorder More Likely to Have Undiagnosed Hypertension and Diabetes

Using electronic health record data from a large, urban US healthcare system, investigators conducted a cross-sectional study comparing rates of undiagnosed hypertension and diabetes in primary care patients with and without substance use disorder (SUD).*

- Of 315,935 patients, only 7991 (3 percent) had documented SUD diagnoses.
- Among patients with SUD, 47 percent had diagnosed hypertension and 3 percent had undiagnosed hypertension; 22 percent had diagnosed diabetes and 12 percent had undiagnosed diabetes.
- Among patients without SUD, 51 percent had diagnosed hypertension and 1 percent had undiagnosed hypertension; 31 percent had diagnosed diabetes and 6 percent had undiagnosed diabetes.
- In adjusted analyses, patients with SUD had greater odds of having undiagnosed hypertension (adjusted odds ratio [aOR], 1.81) and undiagnosed diabetes (aOR, 1.93), compared with those without SUD.
- Having an HIV diagnosis was also independently associated with greater odds of undiagnosed hypertension (aOR, 8.80) and undiagnosed diabetes (aOR, 3.4), compared with patients without an HIV diagnosis.

* Undiagnosed hypertension was defined as having ≥2 blood pressure readings of ≥140/90 without a hypertension diagnosis or being prescribed antihypertensive medication. Undiagnosed diabetes was defined as having a hemoglobin A1c reading ≥6.5 without a diabetes diagnosis or being prescribed diabetes medication. Types of SUD included: "alcohol use, opioid use, cannabis dependence, sedative use, cocaine use, other stimulant use, hallucinogen use, inhalant use, other psychoactive substance use, and unspecified SUD."

Comments: This sample's low prevalence of documented SUD highlights the need for better SUD screening in primary care. Furthermore, the association between SUD and undiagnosed medical comorbidities raises questions about the quality of care that these patients receive. Stigma toward patients with SUD among primary care practitioners (PCPs) may contribute to these disparities, but time pressures on PCPs are likely also a factor. As PCPs are increasingly encouraged to treat SUD, interdisciplinary clinical teams and realistic reimbursement models will be necessary to support this work.

Aaron D. Fox, MD

Reference: Lindenfeld Z, Chen K, Kapur S, Chang JE. Comparing rates of undiagnosed hypertension and diabetes in patients with and without substance use disorders. *J Gen Intern Med*. 2024;39(9):1632–1641.

Legalization of Cannabis in Canada Was Associated With a Decline in Beer Sales

Canada legalized non-medical cannabis use in 2018; this has led to increased use of cannabis, which may have an impact on the use of other drugs. Researchers used data on beer sales from 2012 to 2020 and spirits from 2016 to 2020 to investigate the impact of cannabis legalization on alcohol sales using an interrupted time series design, adjusting for seasonal patterns.

- Beer sales in Canada declined by 96 hectoliters/100,00 population in the first month after legalization and by an additional 4 hectoliters/100,000 each month thereafter for an average monthly decline of 136 hectoliters/100,000.*
- Overall, there was a 3 percent decline in beer sales between September 2018 and February 2020.

(continued, page 5)

Legalization of Cannabis in Canada Was Associated With a Decline in Beer Sales *(continued from page 4)*

- There was no significant change in sales of spirits from January 2016 to February 2020.

* 1 hectoliter = 26.4 US liquid gallons.

Comments: This study suggests that some individuals may be replacing beer consumption with cannabis use. It is not clear what effect this has on health outcomes on an individual level; if it is reducing heavy use, then it may have a positive effect, but it may be primarily replacing lower-risk drinking.

Darius A. Rastegar, MD

Reference: Mital S, Bishop L, Bugden S, et al. Association between non-medical cannabis legalization and alcohol sales: quasi-experimental evidence from Canada. *Drug Alcohol Depend*. 2024;257:111137.

Increased Distance From Cannabis Retailers Associated With Reduction in Past 30-day Cannabis Use Among California Adolescents

Recent cannabis legalization in many US states and the subsequent increase in cannabis retailers have potentially increased adolescent access to cannabis. Using a statewide sample of California adolescents (N=1406), researchers modeled the association between self-reported past 30-day cannabis use and home address distance from the nearest licensed and unlicensed cannabis retailers. Model covariates included gender, age, ethnicity/race, neighborhood socioeconomic status index, and a perceived social norms scale.

- The average distance from a cannabis retailer was nine miles from any retailer, 10 miles from a licensed retailer, and seven miles from an unlicensed retailer.
- Every five-mile increase in distance was associated with a 4 percent reduction in past 30-day cannabis use (adjusted incidence rate ratio [IRR], 0.96) for any cannabis retailer and licensed retailers.
- Increased cannabis use was associated with being Black (IRR, 1.5) or "Other/Multiracial" (IRR, 1.7)—both compared with being White—being older in age (IRR, 1.2), and having higher scores on the perceived social norms scale (IRR, 1.5).
- When stratifying by race, the association was only significant among Hispanic/Latinx individuals, with a 9 percent reduction in past 30-day cannabis use for every five-mile increase in distance from the nearest retailer.

Comments: These results suggest that despite the 21-year age limit for cannabis sales, proximity to cannabis retailers may increase adolescent cannabis use, with a stronger effect among Hispanic/Latinx individuals. For clinicians, it is important to recognize that cannabis legalization, marketing, and zoning laws are among the environmental factors that contribute to risk for cannabis use and its associated health consequences among adolescents.

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* 2023–24 Rich Saitz Editorial Intern & Addiction Medicine Fellow, University of Iowa Hospitals and Clinics

Reference: Albers L, Rogers CJ, Steinberg J, et al. Proximity to cannabis retailers and recent cannabis use among a diverse sample of California adolescents. *Subst Use Misuse*. 2024;59(5):643–650.

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