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Hosted by Honora L. Englander
& Marc R. Larochelle

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Alcohol, Other Drugs, and Health: Current Evidence

MAY - JUNE 2024

INTERVENTIONS & ASSESSMENTS

Peer Support Services for Substance Use Disorders May Reduce Acute Care Utilization

Peer support services for substance use disorders (PS SUD) are increasingly in use and may improve health outcomes. Researchers conducted a case-control study of health service utilization comparing Pennsylvania Medicaid enrollees with at least two paid claims for PS SUD services (n=349) who were also receiving outpatient SUD treatment, with a group of patients receiving outpatient SUD services without PS SUD (n=698). Both groups utilized acute care (hospitalization or withdrawal management) in the 90 days prior to enrollment.

- The PS SUD cohort had decreased acute care utilization compared with the outpatient SUD cohort, both during enrollment (9 percent versus 21 percent, respectively), and 90 days post-enrollment (14 percent versus 17 percent).
- Patients receiving PS SUD had increased use of ancillary outpatient services (including rehabilitation and halfway housing), compared with those receiving outpatient SUD services-alone, both during enrollment (rehabilitation: 20 percent versus 16 percent; halfway housing: 20 percent versus 7 percent), and 90 days post-enrollment (rehabilitation: 19 percent versus 15 percent; halfway housing: 12 percent versus 8 percent).
- The proportion of patients continuing outpatient SUD treatment was higher 90 days post-enrollment in the PS SUD group (45 percent) than in the outpatient SUD group (0 percent).

Comments: In a high-risk patient population with SUD hospitalization in the last 90 days, receipt of PS SUD was associated with decreased acute care utilization and increased sustained engagement with outpatient SUD services, compared with patients who received only outpatient SUD services. Peer support services may help high-risk patients navigate outpatient resources and avoid acute decompensation or hospitalization.

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

Reference: Hutchison SL, MacDonald-Wilson KL, Karpov I, et al. Peer support to reduce readmission in Medicaid-enrolled adults with substance use disorder. *J Subst Abuse Treat.* 2023 Jan;144:108901.

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Opioid Craving Partially Mediates the Effect of Opioid Agonist Treatment on Likelihood of Non-prescribed Opioid Use

Non-prescribed opioid use among people receiving opioid use disorder (OUD) treatment can be risky. Researchers examined the effect of opioid craving on the impact of opioid agonist treatment (OAT) on self-reported non-prescribed opioid use among 270 people randomized to receive either buprenorphine/naloxone or methadone for 24 weeks. Past-24 hour opioid cravings were measured using the Brief Substance Craving Scale (higher scores indicating stronger cravings).

- Participants' mean age was 39 years; 34 percent were female; 67 percent were White.
- Receipt of buprenorphine/naloxone was associated with 0.6 fewer days per week of non-prescribed opioid use compared with receipt of methadone.
- The mean craving score was 3.86 among participants receiving buprenorphine/naloxone and 5.84 among those receiving methadone.
- The interaction between OAT type and opioid craving was non-significant.
- Opioid cravings partially mediated the effect of OAT on non-prescribed opioid use similarly among both groups (~24 percent).

Comments: Among this cohort of people with OUD, buprenorphine/naloxone receipt was associated with lower levels of craving and fewer days of non-prescribed opioid use than methadone. Cravings were a significant predictor of non-prescribed opioid use among participants in both treatment groups, suggesting that addressing cravings—via medication dose adjustments and/or therapies targeting coping skills—is important for decreasing the risk of non-prescribed opioid use among people receiving OAT.

Carrie Mintz, MD

Reference: McAnulty C, Bastien G, Ledjar O, et al. Mediating effect of craving on the impact of buprenorphine/naloxone and methadone treatment on opioid use: results from a randomized controlled trial. *Addict Behav.* 2024;154:108023.

HEALTH OUTCOMES

Adolescent Cannabis Use is Associated With Subsequent Anxiety Symptoms and Disorders

Cannabis use, anxiety symptoms, and anxiety disorders are common among adolescents, yet how they interact is not well understood. Adolescents are particularly vulnerable to the harmful effects of cannabis because of ongoing neurodevelopment, while its use is increasing among US adolescents due to legalization in many states. Researchers conducted a systematic review and meta-analysis of prospective studies of adolescents aged 13–19 to elucidate the temporal relationship between cannabis use, anxiety symptoms, and anxiety disorders.

- A meta-analysis of six studies found that adolescents with cannabis use were more likely to be diagnosed with a subsequent anxiety disorder (odds ratio [OR], 2.14), compared with those without cannabis use.
- In a systematic qualitative review of 12 additional studies, eight studies confirmed a prospective association between cannabis use and subsequent anxiety symptoms and one found an association with subsequent anxiety disorder diagnosis. Three studies detected no significant association.

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Adolescent Cannabis Use is Associated With Subsequent Anxiety Symptoms and Disorders *(continued from page 2)*

- None of the studies detected an association between anxiety symptoms and subsequent cannabis use.

Comments: Adolescents and their parents should be educated that cannabis use is associated with increased risk of anxiety symptoms and disorders. More research is needed to better understand cannabis dose effects, the role of individual components of cannabis, and the differ-

ential impact among gender, racial, and ethnic identities that face intersectional stress and stigma..

Safina Adatia, MD, MSc* & Alexander Y. Walley, MD, MSc

* Contributing editorial intern and addiction medicine fellow, Boston Medical Center

Reference: Lowe DJE, Sorkhou M, George TP. Cannabis use in adolescents and anxiety symptoms and disorders: a systematic review and meta-analysis. *Am J Drug Alcohol Abuse*. 2024;50(2):150–161.

Stimulant Therapy for Adolescent ADHD Not Associated With Subsequent Non-medical Stimulant Use

Attention-deficit/hyperactivity disorder (ADHD) is a risk factor for substance use disorder. Prescription stimulant medications are highly effective for treating ADHD, but there is concern that adolescents with ADHD who are treated with stimulants may escalate to non-medical stimulant use over time. This US-based, prospective, multi-cohort study investigated the association between young adults who have received stimulant ADHD therapy, and future non-medical use of prescription stimulants and/or cocaine use from ages 18 to 24, compared with ADHD controls (participants with ADHD who received non-stimulant therapy) and population controls.

- Multi-cohort panels of 11,905 US 12th graders were surveyed at the time of baseline data collection and biennially thereafter for six years.
- At baseline, 10 percent of participants reported lifetime receipt of stimulant medication for ADHD; 3 percent reported lifetime receipt of non-stimulant therapy for ADHD; and 87 percent reported receipt of neither.

- There was no significant difference in prevalence or incidence of past-year non-medical use of prescription stimulants and cocaine use between all groups.

Comments: Negotiating ADHD treatment options can be complex, particularly when weighing the risk of potentially addictive stimulant therapy against the risk(s) associated with untreated ADHD (including predisposition to substance use disorder). This study did not demonstrate increased incidence or prevalence of non-medical use of prescription stimulants and/or cocaine use in young adults with a history of prescription stimulant therapy for ADHD in adolescence. This finding (and a similar retrospective evidence base) may lend reassurance to prescribers, patients, and caregivers when electing to utilize prescription stimulants as clinically indicated for ADHD.

Emily Nields, DO

Reference: McCabe VV, Veliz PT, Wilens TE, et al. Adolescents' use of medications for attention-deficit/hyperactivity disorder and subsequent risk of nonmedical stimulant use. *J Adolesc Health*. 2024;75(1):188–191.

Stigma in Healthcare Settings is Associated With Reduced Healthcare Access Among Women Who Inject Drugs

Few studies focus on the distinct experiences and health outcomes of women who inject drugs. Researchers performed a cross-sectional study analyzing the association between experience of healthcare stigma and healthcare access among women who inject drugs using a subset of Australian survey data collected between October and December 2021 (N=232). "Reduced healthcare access" was defined as the following: delaying care, not disclosing drug use, downplaying the need for pain medication, looking for alternative health services, or not attending follow-up appointments.

- Of the women included in this study, 75 percent injected drugs weekly or more and 40 percent had shared needles in the past month.
- While 20 percent of women reported not experiencing any stigma or discrimination related to drug use in the past year, 90 percent had engaged in at least one strategy to avoid experiencing stigma in a healthcare setting.

- Variables that predicted reduced healthcare access were reduced well-being, negative treatment by a health worker in the past year, higher injecting frequency, being employed, and LGBTQ identity.

Comments: This study provides insight into the consequences of healthcare stigma experienced by women who inject drugs. Lower well-being scores, higher injecting frequency, and LGBTQ identity may negatively impact healthcare access because of higher rates of stigma in these groups. Fear of stigma negatively impacting employment may lead to reduced healthcare access among employed women who inject drugs. We must do more to eliminate policies and behaviors that perpetuate stigma related to drug use in order to provide optimal care to this high-risk group of patients.

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Reference: Brener L, Cama E, Broady T, et al. Experiences of stigma and subsequent reduced access to health care among women who inject drugs. *Drug Alcohol Rev*. 2024 [Epub ahead of print]. doi:10.1111/dar.13806

British Columbia's "Safer Opioid Supply" Policy Associated With Increased Opioid-related Hospitalizations

In March 2020, British Columbia instituted a "Safer Opioid Supply" policy that allowed prescription of strong oral opioids—and later injectable fentanyl—to persons at high risk of opioid overdose. In this policy analysis, investigators compared population-level changes in opioid-related outcomes from 2016 to 2022 in British Columbia with two Canadian provinces that did not institute the policy (Manitoba and Saskatchewan). Analyses were adjusted for differences in demographics, economic conditions, and COVID-19 public health policies.

- Opioid prescriptions increased by 52 percent after policy implementation in British Columbia, but remained stable in comparison provinces.
- Opioid-related hospitalization trends were similar between British Columbia and comparison provinces before policy implementation, but following implementation British Columbia had a 63 percent relative increase in opioid-related hospitalizations (an increase of 3.2 hospitalizations quarterly per 100,000 population compared with the corresponding increases in the comparison provinces).

- There was no significant association between the policy change and opioid-related deaths, or the number of prescribers.

Comments: Prior smaller studies have demonstrated some benefits for "Safer Opioid Supply" program participants, but this population-level study suggests that increased opioid prescribing may have contributed to disproportionate increases in opioid-related hospitalizations in British Columbia. If prescribed opioids are diverted, the increased prescribing could cause unintended harms. It is also possible that changes in unregulated opioid supplies during the study period were different in British Columbia and other provinces, accounting for the increase in hospitalizations. Additional research is warranted to better understand the risks and benefits of "Safer Opioid Supply" programs.

Aaron D. Fox, MD

Reference: Nguyen HV, Mital S, Bugden S, McGinty EE. British Columbia's Safer Opioid Supply policy and opioid outcomes. *JAMA Intern Med.* 2024;184(3):256–264.

Benzodiazepine Discontinuation is Associated With Increased Mortality and Other Negative Outcomes

Benzodiazepine medications are commonly prescribed and their use may be associated with harms, including overdose death. However, discontinuation of benzodiazepine medications may be risky. This retrospective study used 2013–2019 commercial US health insurance claims data to examine the risk of death and other outcomes associated with benzodiazepine discontinuation among individuals who were prescribed benzodiazepines at a stable dose for over a year at baseline and followed for another year, stratified by presence of an additional opioid prescription. The analysis adjusted for a number of potential confounders including age, sex, benzodiazepine dose, psychiatric and substance use disorders.

- Of the 297,853 individuals prescribed benzodiazepines included in this study, 40 percent had at least one opioid medication prescription within the last 30 days of the baseline period. Of these patients, 60,297 (20 percent) experienced benzodiazepine discontinuation during the one-year follow-up. The methods of discontinuation were not specified.
- In adjusted analyses among all patients, benzodiazepine discontinuation was associated with an increased risk of

mortality (risk ratio [RR], 1.6).

- Benzodiazepine discontinuation was also associated with an increased risk of nonfatal overdose (RR, 1.2), emergency department use (RR, 1.2), and suicidal ideation (RR, 1.4), regardless of opioid medication receipt.

Comments: Benzodiazepine medications, like opioids, should be prescribed judiciously. However, as is also the case with opioid medications, it appears that benzodiazepine discontinuation can be risky. Other factors that may influence risk include the reason for discontinuation, how this was done (e.g., rapid versus slow taper), and receipt of other medications and supports during the taper period.

Lia Penn, MD* & Darius A. Rastegar, MD

*Contributing editorial intern and addiction medicine fellow, Johns Hopkins Medicine

Reference: Maust DT, Petzold K, Strominger J, et al. Benzodiazepine discontinuation and mortality among patients receiving long-term benzodiazepine therapy. *JAMA Network Open.* 2023;6(12):e2348557.

PRESCRIPTION DRUGS & PAIN

Among Patients Receiving Long-term Opioid Therapy, Stimulant-positive Drug Tests Were Not Associated With Subsequent Harm

Guidelines for prescribing opioid medications for chronic pain state that non-prescribed substance use—including that of stimulants, cocaine, and methamphetamine—contribute to the risks associated with long-term opioid therapy (LTOT). This study investigated the associations between stimulant-positive urine drug tests (UDT) and subsequent (within 90 days) emergency department (ED) visits, overdose deaths, and discontinuation of LTOT among 600 patients prescribed LTOT with 1:1 matching of HIV positive and negative adults.

- Of the 600 patients, 547 (91 percent) had at least one recorded UDT from 2012 to 2019; of these, 270 (49 percent) had at least one stimulant-positive UDT. Of 6088 UDTs recorded, 24 percent were stimulant-positive.
- Individuals with at least one stimulant-positive UDT were more likely to have had an ED visit during the study period (28 percent versus 9 percent), but stimulant-positive UDTs were not associated with ED visits within 90 days.
- There were 22 opioid overdose deaths during the follow-up period; none were within 90 days of a stimulant-positive UDT.
- Stimulant-positive UDTs were associated with discontinuation of LTOT.

Comments: This study suggests that providers should not reflexively discontinue LTOT in individuals who have a UDT positive for non-prescribed stimulants. Rather, these results should prompt a discussion of stimulant use, its impact on the patient's health, and ways in which risks can be minimized.

Darius A. Rastegar, MD

Reference: Appa A, McMahan VM, Long K, et al. Stimulant use and opioid-related harm in patients on long-term opioids for chronic pain. *Drug Alcohol Depend.* 2024;256:111065.

Daily Cannabis Use Associated With Decreased Pain Tolerance

Medical cannabis use is commonly viewed as a reasonable pain management solution by the public, but the current evidence reflects conflicting results. This retrospective cohort study compared pain tolerance thresholds in participants who reported daily cannabis use with individuals who reported daily inhaled nicotine use, daily cannabis and inhaled nicotine use, and no cannabis/nicotine use (control group). All participants received a painful stimulus (the cold pressor test [CPT]), with time-to-reported pain as the primary outcome measure.

- Individuals with daily cannabis use demonstrated a significant reduction in pain tolerance with a median CPT time of 46 seconds, compared with the control group median CPT time of 105 seconds.
- Participants with daily inhaled nicotine use demonstrated a similar result to those with daily cannabis use with median CPT time of 45 seconds, but this result had marginal statistical significance.

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Daily Cannabis Use Associated With Decreased Pain Tolerance *(continued from page 5)*

- Overall, participants with both daily cannabis and nicotine use demonstrated a significant reduction in pain tolerance with the lowest median CPT time (26 seconds).

Comments: This study contributes to a growing body of evidence that daily cannabis use may result in increased pain sensitivity and chronic pain (or central sensitization). The authors postulate that opponent processing (desensitization of CB1 and CB2 receptors resulting in the brain's dysphoric complementary mechanism to function in overdrive) may play a role in cannabis-induced hyperalgesia. In turn, patients may be driven to escalate

their use and risk developing cannabis use disorder. Given the implications, medical cannabis use should be approached with caution. The relationship between individuals with inherently decreased pain tolerance and subsequent cannabis use deserves further inquiry.

Emily Nields, DO

Reference: Zhang-James Y, Wyon E, Grapsas D, Johnson B. Daily cannabis use may cause cannabis-induced hyperalgesia. *Am J Addict.* 2023;32(6):532–538.

Listen to the second episode of Season 2 of our podcast, “Behind the Evidence,” supported by the Grayken Center for Addiction at Boston Medical Center.

Hosted by addiction medicine specialists Honora L. Englander, MD (Oregon Health & Science University) and Marc R. Larochelle, MD, MPH (Boston Medical Center/ Boston University Chobanian & Avedisian School of Medicine), each episode of “Behind the Evidence” offers thoughtful discussion of one or more recent significant publications in the clinical addiction literature. Through author interviews and expert insights, “Behind the Evidence” will appeal to clinicians, as well as anyone who is interested in the latest developments in addiction medicine research.

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