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Alcohol, Other Drugs, and Health: Current Evidence

SEPTEMBER-OCTOBER 2020

INTERVENTIONS & ASSESSMENTS

Few Adolescent-serving Addiction Treatment Centers in the US Offer Medication for Opioid Use Disorder

This study used data from the 2017 National Survey of Substance Abuse Treatment Services to report on medication for opioid use disorder (MOUD) availability for adolescents (interpreted to mean <18 years of age), and examined whether program characteristics are associated with medication availability.

- 3537 of 13,585 treatment facilities (26%) offered adolescent-serving programs.
- Adolescent programs were less likely to offer MOUD compared with adult programs (odds ratio [OR], 0.53). MOUD was offered in 23% of adolescent programs versus 36% of adult programs.
- Non-profit status, hospital affiliation, accepting private insurance, accreditation, location in the Northeast, and offering inpatient services were all associated with greater likelihood of offering MOUD in adolescent-serving facilities.

Comments: This study reinforces previous findings that adolescents are less likely to receive MOUD than adults, despite recommendations from the American Academy of Pediatrics. Hospital-affiliated treatment facilities had better alignment with national guidelines than commercial programs. As a group, youth are underserved, even though, as with any disorder, early treatment improves outcomes. For substance use disorders, treatment during youth has the potential to save lives and reduce the enormous societal expenditures on treating addiction and its complications in adulthood.

Sharon Levy, MD

Reference: Alinsky RH, Hadland SE, Matson PA, et al. Adolescent-serving addiction treatment facilities in the United States and the availability of medications for opioid use disorder. *J Adolesc Health*. 2020;67(4):542-549.

Brief Interventions May Be Effective for Lower-risk Non-cannabis Substance Use

Brief interventions (BI) alone, and as part of screening and referral to treatment (SBIRT), have been shown to be effective for certain types of unhealthy alcohol use, but studies in a variety of settings have failed to show consistent effects on the use of other substances. Two recent studies provided promising results for individuals with lower-risk substance use.

Karno et al studied SBIRT in 718 adults with an affective or psychotic disorder who reported any past 90-day use of cannabis or stimulants, or ≥1 heavy drinking days. Participants were randomly assigned to either SBIRT delivered by trained clinicians, or a health education session (control).

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Brief Interventions May Be Effective for Lower-risk Non-cannabis Substance Use (continued from page 1)

- Compared with the control group, participants who received SBIRT had significantly fewer heavy drinking days at 3-month follow-up (odds ratio [OR], 0.53) and less frequent stimulant use (OR, 0.58), but cannabis use did not differ (OR, 0.93). At 6 months, heavy drinking days and stimulant use remained significantly lower. At 12 months, only stimulant use was significantly lower.
- There were no significant differences in rates of abstinence or receipt of addiction-focused treatment.

Bertholet et al conducted a pilot trial in a primary care clinic among 61 individuals with lower-risk substance use, defined as a score of 2 or 3 on the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). Participants were randomly assigned to one of the following: 1) a brief negotiated interview delivered by trained health educators; 2) adaptation of motivational interviewing delivered by master's degree-level counselors; or 3) no BI.

- At 6-month follow-up, participants in the 2 BI groups reported significantly fewer days of use of their primary substance, compared with the group that received no BI. When stratified by primary substance, the difference was significant for "cocaine, opioids and other," but not for cannabis.
- Identification rates of any primary substance on follow-up hair analyses were lower in the 2 BI groups, but the difference was not significant.
- There were no significant differences in substance-related problems.

Comments: These studies suggest that brief interventions may be effective for lower-risk use of substances other than cannabis. This is consistent with previous studies showing BI to be effective for unhealthy alcohol use that does not meet criteria for alcohol use disorder. It is important to note that these interventions were delivered by trained staff and not by patients' regular clinicians.

Darius A. Rastegar, MD

References: Karno MP, Rawson R, Rogers B, et al. Effect of screening brief intervention and referral to treatment for unhealthy alcohol and other drug use in mental health treatment settings: a randomized controlled trial. *Addiction*. 2020 [Epub ahead of print]. doi: 10.1111/add.15114.
Bertholet N, Meli S, Palfai TP, et al. Screening and brief intervention for lower-risk drug use in primary care: a pilot randomized trial. *Drug Alcohol Depend*. 2020;213:108001.

HEALTH OUTCOMES

Higher-Potency Cannabis Use Associated With Cannabis Use Problems and Generalized Anxiety Disorder in Young Adults

Cannabis use is associated with poor mental health outcomes, and higher cannabis potency may be associated with greater mental health risks. This cross-sectional study examined the association of higher-potency cannabis use and substance use and mental health measures in a UK birth cohort of 24-year old participants who reported past-year cannabis use (N=1087). The main exposure variable of most commonly used cannabis type was self-assessed and dichotomized by higher potency ("skunk/other stronger types of herbal cannabis") and lower potency ("herbal cannabis/marijuana" or "hashish/resin/solid" or "other").

- Higher-potency cannabis use was significantly associated with an increased frequency of cannabis use (adjusted odds ratio [aOR], 4.38), and increased odds of cannabis use problems (aOR, 4.08) and generalized anxiety disorder (aOR, 1.92), compared with lower-potency cannabis use.

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Higher-Potency Cannabis Use Associated With Cannabis Use Problems and Generalized Anxiety Disorder in Young Adults (continued from page 2)

- Higher-potency cannabis use was NOT associated with use of other illicit substances, alcohol use disorder, major depression, and psychotic experiences, after adjusting for childhood sociodemographic factors, mental health measures during adolescence, and frequency of cannabis use.

Comments: Higher-potency cannabis use was associated with increased frequency of cannabis use, cannabis use problems, and generalized anxiety disorder in this cross-sectional study, but the direction of causation is unclear. Given the growing availability of high-potency cannabis, further study of its risks is needed.

Tae Woo (Ted) Park, MD

Reference: Hines LA, Freeman TP, Gage SH, et al. Association of high-potency cannabis use with mental health and substance use in adolescence. *JAMA Psychiatry*. 2020;77(10):1044–1051.

Canadian Geospatial Analysis Finds Association Between Cannabis Use and Major Congenital Anomalies

In Canada, roughly two thirds of pregnant women presenting to cannabis dispensaries are recommended cannabis products to treat pregnancy-related nausea, despite the fact that animal studies have suggested a relationship between cannabis and serious birth defects. Canada presents an ideal opportunity to study these relationships in human populations given its national birth registry on congenital defects and nationwide survey data on cannabis use. Using data obtained between 1998 and 2009, the authors employed geospatial regression analyses to explore the association between prenatal cannabis exposure and teratogenicity.

- Mapping showed cannabis use was more common in the northern Territories of Canada.
- All congenital anomalies, cardiovascular defects, orofacial clefts, Downs syndrome, and gastroschisis were found to be more common in the northern Territories of Canada, compared with the Provinces, (odds ratio, 1.16) and rose as a function of cannabis exposure.
- By geospatial analysis model, cannabis was significant both alone as a main effect and in all its first and second-order interactions with both tobacco and opioids.

Comments: This sophisticated geospatial analysis in Canada suggests a distinct association between cannabis use and major congenital anomalies. Although potential confounding may contribute to this association, these findings—taken with cellular and animal studies that similarly suggest an association—should be explored further.

Jeanette M. Tetrault, MD

Reference: Reece AS, Hulse GK. Canadian cannabis consumption and patterns of congenital anomalies: an ecological geospatial analysis. *J Addict Med*. 2020;14(5):e195-e210.

Prenatal Exposure to Buprenorphine or Methadone Is Not Clearly Associated with Children's Cognitive Outcomes

Buprenorphine and methadone are associated with improved substance use, pregnancy, and infant outcomes and are the standard of care for pregnant persons with opioid use disorder (OUD). Mixed results from retrospective cohort studies have suggested a potential negative association between prenatal exposure to buprenorphine or methadone and longer-term cognitive outcomes. This meta-analysis pooled data from 16 retrospective studies to examine this association while considering important potential confounding variables, including maternal education and employment and other substance exposure.

- Maternal characteristics associated with cognitive outcomes in children were highly imbalanced between groups that were exposed to and not exposed to buprenorphine and methadone:
  - 67% of exposed versus 34% not exposed had less than high school education.
  - 19% of exposed versus 67% not exposed were employed.
  - 89% of exposed versus 40% not exposed had tobacco use.
- Pooled results suggest that if children were selected at random from exposed and unexposed groups, 66% of the time the child exposed to buprenorphine or methadone would have lower cognitive development scores.
- Cognitive development score differences did not persist when restricting the sample to studies balanced on tobacco exposure.

Comments: Prenatal exposure to buprenorphine or methadone is not clearly associated with cognitive outcomes when accounting for potential confounding. Furthermore, the comparison group in these cohort studies was not restricted to mothers with OUD, questioning the clinical relevance of these studies. A more appropriate comparison group in future studies would be children of mothers with OUD during pregnancy who had not been treated with methadone or buprenorphine. Buprenorphine and methadone should be offered to all pregnant persons with OUD.

Marc R. Larochelle, MD, MPH

Reference: Nelson LF, Yocum VK, Patel KD, et al. Cognitive outcomes of young children after prenatal exposure to medications for opioid use disorder: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(3):e201195.

Oral Antibiotics Decrease Readmissions Among People Who Inject Drugs Admitted With Invasive Infections Leaving Against Medical Advice

People who inject drugs (PWID) are at risk for serious infectious complications requiring hospitalization for prolonged intravenous (IV) antibiotics. Individuals with substance use disorder (SUD) are at increased risk for leaving the hospital against medical advice (AMA) due to poorly treated withdrawal symptoms, lack of initiation of treatment for SUD, or other factors—which may pose challenges to antibiotic completion. This retrospective, observational, single-site study assessed 90-day readmission rates among 293 PWID hospitalized with serious infections related to injection drug use. All participants received an infectious disease consultation and, based on clinical care decisions and patients choice to leave AMA, 1 of 3 antibiotic treatment strategies: 1) Full course of IV antibiotics in-hospital; 2) partial course of IV antibiotics without a prescription for oral antibiotics at discharge; or 3) partial course of IV antibiotics with a prescription for oral antibiotics at discharge.

- 90-day all-cause readmission rates were highest among patients leaving AMA without a prescription for oral antibiotics (68%) compared with those receiving IV antibiotic treatment (32%) and those receiving partial oral antibiotic treatment (33%).
- Risk of 90-day readmission was highest among patients who did not receive oral antibiotic treatment at discharge (adjusted hazard ratio [aHR], 2.32), and not different among PWID who received oral antibiotic therapy at discharge (aHR, 0.99).
- Surgical source control (aHR, 0.57) and addiction medicine consultation (aHR, 0.57) were both associated with reduced 90-day readmission rates.

Comments: Although this was an observational study from a single site and only included patients who were seen by infectious disease teams, these data add to a growing literature suggesting the need for improvements for treatment of PWID who are hospitalized with serious infectious complications. Patients who choose not to remain inpatient should be given a prescription for oral antibiotics to complete the course of treatment.

Jeanette M. Tetrault, MD

Reference: Marks LR, Liang SY, Muthulingam D, et al. Evaluation of partial oral antibiotic treatment for persons who inject drugs and are hospitalized with invasive infections. *Clin Infect Dis*. 2020;ciaa365. doi: 10.1093/cid/ciaa365.

Does Initiation of Opioid Agonist Therapy Affect the Use of Other Substances?

Opioid agonist therapy (OAT) with methadone or buprenorphine reduces unhealthy opioid use and the harms associated with it. Its effect on the use of other substances is less clear. Researchers used data from 3 ongoing prospective cohort studies of people who use drugs in Vancouver, Canada to compare self-reported substance use trends before and after engaging in OAT. This analysis included 1107 participants who initiated OAT after study enrollment and had at least 1 study visit after initiation.

- For heroin and non-medical use of prescription opioids (NMUPO), there was a significant decrease in per-year increase in use trends post-OAT treatment initiation, compared with pre-treatment trends:
  - Heroin: adjusted odds ratio (aOR), 1.19 pre-treatment versus 0.80 post-treatment.
  - NMUPO: aOR, 1.04 pre-treatment versus 0.87 post-treatment.
- For benzodiazepines, there was a trend of declining use pre-treatment (per-year increase aOR, 0.84) that continued and strengthened post-treatment (aOR, 0.73).
- For daily alcohol use, there was a trend of declining use pre-treatment (per-year increase aOR, 0.91) that reversed post-treatment (aOR, 1.03).
- For stimulants and cannabis, there were no significant changes in post-treatment use trends, compared with pre-treatment use trends.

Comments: The focus on urine drug testing for individuals receiving OAT may lead providers to overlook unhealthy alcohol use. While the rates and changes in alcohol use were relatively modest, this study suggests that we need to pay more attention to this. It would be interesting to see if the effects of extended-release naltrexone are different in this respect.

Darius A. Rastegar, MD

Reference: Dong H, Hayashi K, Milloy MJ, et al. Changes in substance use in relation to opioid agonist therapy among people who use drugs in a Canadian setting. *Drug Alcohol Depend*. 2020;212:108005.

PRESCRIPTION DRUGS & PAIN

Discontinuation of Opioid Analgesics is Particularly Risky for Those With Mental Illness or Substance Use Disorders

Opioid analgesic prescribing has recently come under scrutiny in light of the overdose epidemic. Focused efforts encourage careful risk versus benefit evaluations when prescribing opioids and cessation when the risks exceed the benefits. Some studies show increases in deaths from suicide and overdose after opioid cessation. This large observational cohort study of mostly male US veterans (N=1.3 million) with an outpatient prescription for an opioid analgesic over 2 years assessed death from overdose or suicide based on length of time from opioid cessation, and length of opioid treatment.

- Overall, 57% of patients stopped receiving opioids during the time-frame; most had prescriptions for either <30 days (32%) or >400 days (37%).
- Patients who stopped opioids were mostly prescribed short-acting medications (70%); 15% had a documented substance use disorder and 43% had a documented mental health diagnosis (versus 14% and 49%, respectively, among patients who continued opioids).
- Opioid discontinuation was associated with an increased risk of death from overdose or suicide regardless of the length of opioid treatment, although risk increased with the longer the patient was prescribed opioids (hazard ratios [HRs]: 1.67 [≤30 days], 2.80 [31-90 days], 3.95 [91-400 days], and 6.77 [>400 days]).
- Death rates for overdose or suicide increased both after the initiation of and with the cessation of opioids, but these risks reduced after 3 months. Patients with substance use disorders (HR, 2.48) and mental health diagnoses (HR, 1.54) were at most risk for suicide or overdose.

Comments: Discontinuation of prescription opioid analgesic medications is a common clinical practice, particularly after surgery or acute injury, yet most prescribers receive little-to-no formal training in it. This study shows the importance of additional education in this area so that prescribers can support patients and offer evidence-based treatments when needed, particularly among patients who are prescribed longer-term opioid medications, or who have mental illness or substance use disorders. Importantly, the study did not report the racial or ethnic background of the patients, nor the specialty of the opioid prescriber; these data may further illuminate treatment and training gaps.

Melissa B. Weimer, DO, MCR

Reference: Oliva EM, Bowe T, Manhapra A, et al. Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation. *BMJ*. 2020;368:m283.

Increased Pain Sensitivity in Patients with Chronic Pain Who Developed Opioid Use Disorder

The clinical relevance of increased pain sensitivity in patients prescribed opioids for chronic pain is unclear. If increased pain sensitivity predicted the development of opioid use disorder (OUD) in this group, it could provide a more objective criterion for risk stratifying patients who are being considered for chronic opioid therapy. This study hypothesized that differences in pain sensitivity might explain vulnerability to OUD among patients receiving opioids for chronic pain. A secondary hypothesis was that pain catastrophizing might mediate these differences.

- Pain sensitivity was measured in 20 patients receiving chronic opioid therapy who had not developed signs or symptoms of OUD after at least 18 months of opioid treatment, and in 20 patients who developed OUD while taking prescription opioids and were being treated with buprenorphine.
- Patients without a diagnosis of OUD reported higher baseline pain intensity scores and were taking full agonist opioids rather than buprenorphine.
- Those who developed OUD showed increased sensitivity to a heat test of central sensitization, but not to a cold pressor test. For both tests, those who developed OUD subjectively rated the maximal intensity of pain higher than those not developing OUD.
- Scores measuring pain catastrophizing were not different between the 2 groups and did not mediate differences in pain sensitivity.

Comments: Some measures of pain sensitivity were increased in patients who developed OUD during opioid treatment for chronic pain and were being treated with buprenorphine. While these differences could be due to pre-existing pain sensitivity putting patients at risk of OUD, other possible explanations include differences in current pain severity, current medication use (buprenorphine versus full agonists), or the increased pain sensitivity might be a complication of OUD. Prospective assessment of patients initiating opioids for chronic pain would be necessary to assess the predictive power of pain sensitivity as a risk factor for OUD in this population.

Joseph Merrill, MD, MPH

Reference: Compton PA, Wasser T, Cheatle MD. Increased experimental pain sensitivity in chronic pain patients who developed opioid use disorder. *Clin J Pain*. 2020;36:667-674.

ADDICTION SCIENCE & CLINICAL PRACTICE

Call for Papers

Addiction Science & Clinical Practice (*ASCP*), founded in 2002 by the National Institute on Drug Abuse (NIDA) and now published by leading open-access publisher BioMed Central, is seeking submissions for an upcoming **special series on the opioid use disorder (OUD) care continuum**, specifically articles describing broad research and data supported by the National Drug Abuse Treatment Clinical Trials Network (CTN): its past effort in developing MOUD treatment and current effort in improving MOUD treatment quality.

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