Alcohol, Other Drugs, and Health: Current Evidence

MARCH-APRIL 2023

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INTERVENTIONS & ASSESSMENTS

Receipt of Lisdexamphetamine Associated With Decreased Risk of Hospitalization and Death in a Cohort of People With Stimulant Use Disorder

Despite increasing prevalence and mortality associated with stimulant use disorders—particularly methamphetamine—treatment options remain limited. Researchers used Swedish national registry data to follow 14,000 persons aged 16–64 with a stimulant use disorder diagnosis. They examined associations of prescription stimulant use and other psychotropic medication use with hospitalization and mortality.

- Among participants (70 percent male, mean age 35), 28 percent were prescribed stimulant medications or atomoxetine; 44 percent were prescribed benzodiazepines. Co-occurring psychiatric illnesses, including co-occurring substance use disorders (SUDs), were common, as were prescriptions for other psychotropic medications.
- During the follow-up period (mean 4 years), 75 percent of participants experienced SUD-related hospitalization(s), and 10 percent died.
- Receipt of the medication lisdexamphetamine was associated with decreased odds of SUD-related hospitalization (adjusted hazard ratio [aHR], 0.82), hospitalization due to any cause or death (aHR, 0.86), and all-cause mortality (aHR, 0.43). Receipt of methylphenidate was also associated with decreased odds of all-cause mortality (aHR, 0.56).
- Receipt of benzodiazepines was associated with increased odds of SUD-related hospitalization (aHR, 1.17), any hospitalization or death (aHR, 1.20), and all-cause mortality (aHR, 1.39).
- Researchers did not assess whether observed associations varied by type of stimulant use disorder (e.g., methamphetamine, cocaine, prescription stimulant, etc).

Comments: Receipt of lisdexamphetamine was associated with decreased odds of hospitalization and death in a large cohort of Swedish persons with stimulant use disorder. Benzodiazepine use was associated with increased odds of these outcomes. Medications that have previously demonstrated potential for treatment of stimulant use disorder in randomized controlled trials, including naltrexone and bupropion, were not associated with beneficial outcomes in this study. These results support the need for randomized controlled trials to test the efficacy of lisdexamphetamine for the treatment of stimulant use disorders.

Carrie Mintz, MD

Reference: Heikkinen M, Taipale H, Tanskanen A, et al. Treatments and hospitalization and death in individuals with amphetamine use disorders in a Swedish nationwide cohort of 13965 patients. *JAMA Psychiatry*. 2023;80(1):31–39.

***Alcohol, Other Drugs, and Health: Current Evidence* is a project of the Grayken Center for Addiction at Boston Medical Center, produced in cooperation with Boston University. Initially supported by a grant from the National Institute on Alcohol Abuse and Alcoholism, the newsletter was supported by grant no. R25-DA013582 (PI: Jeffrey Samet) from the National Institute on Drug Abuse (NIDA) until July 2022. The content is solely the responsibility of the authors and does not necessarily represent the official views of Boston Medical Center, NIDA, or the National Institutes of Health.**

HEALTH OUTCOMES

Relaxed Federal Methadone Take-home Policy Not Associated With Methadone-related Deaths

Strictly regulated methadone take-home dose policies at US opioid treatment programs have been critiqued for limiting access to flexible treatment, but they may also provide important protection against methadone-related overdose. The US COVID-19 emergency response included relaxation of these regulations. This research letter described changes in methadone-related and non-methadone-related overdose deaths in the US from January 2019 to August 2021.

- Interrupted time series analysis showed that overdose deaths not involving methadone increased by 78 deaths per month before March 2020, by 1078 deaths per month in March 2020, and by 69 deaths per month after March 2020.
- Methadone-related deaths per month were stable prior to March 2020; they increased by 94 deaths in March 2020, and remained stable after March 2020.
- The percentage of overdose deaths involving methadone declined 0.06 percent per month before March 2020, increased by 0.69 percent per month in March 2020, and declined 0.05 percent per month after March 2020.

Comments: This study documents a substantial increase in non-methadone-related overdose deaths at the beginning of the COVID-19 pandemic, and a modest increase in methadone-related deaths. Both before and after March 2020, non-methadone-related deaths rose significantly while methadone-related deaths did not. These data support continuation of the COVID-19 related federal take-home policy changes to improve access to methadone in the US.

Joseph Merrill, MD, MPH

References: Jones CM, Compton WM, Han B, et al. Methadone-involved overdose deaths in the US before and after federal policy changes expanding take-home methadone doses from opioid treatment programs. *JAMA Psychiatry*. 2022;79(9):932–934.

Benzodiazepine Use Did Not Have an Adverse Impact on Treatment Retention in an Open-access Methadone Program

Concurrent medical and non-medical use of benzodiazepines is common among individuals receiving methadone for opioid use disorder (OUD), and is associated with an increased risk of overdose. However, guidelines recommend that providers not withhold medications for OUD (including methadone) from people with benzodiazepine use because of these concerns. Researchers investigated the impact of baseline benzodiazepine exposure on 12-month retention in a US open-access methadone program (i.e., a program offering low-barrier access to methadone).

- Between January 2015 and February 2017, 2698 patients initiated methadone in this program. The majority were male (63%) and non-Hispanic white (77%); the mean age was 37 years.
- At intake, 545 (18%) of patients tested positive for benzodiazepines; these individuals were more likely to be female, white, non-Hispanic, of higher education, unemployed, and receiving disability benefits.
- At 12 months, 171 individuals with benzodiazepine exposure (31%) remained in treatment compared with 757 of the patients without exposure (31%). In multivariable analyses, there was no difference in treatment retention when controlling for covariates (hazard ratio, 1.03).

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Benzodiazepine Use Did Not Have an Adverse Impact on Treatment Retention in an Open-access Methadone Program (continued from page 2)

Comments: Overall retention is this program was relatively low, probably reflecting the low-barrier approach to treatment entry. Nonetheless, people who are receiving methadone should be counseled on the risks of concurrent benzodiazepine use, but it should not be a reason to deny access to methadone, or to create barriers to OUD treatment.

Darius A. Rastegar, MD

Reference: Morford KL, Tetrault JM, Zhou B, et al. The impact of benzodiazepine exposure on treatment retention in an open-access methadone program: a retrospective cohort study. *Drug Alcohol Depend*. 2022;241:109707.

Prior Authorization Policies Are Associated With Shorter Duration of Buprenorphine Treatment

Buprenorphine is a very effective treatment for opioid use disorder and longer duration of treatment with buprenorphine improves outcomes. Despite its effectiveness and relative safety, many insurers have prior authorization policies that create barriers to buprenorphine receipt. Researchers used 2006–2014 Medicaid claims data to investigate the association between prior authorization requirements and buprenorphine treatment duration of ≥180 days, as well as concurrent prescribing of benzodiazepines and opioid analgesics.

- During the study period, there were 294,031 buprenorphine treatment episodes that met study inclusion criteria. Nearly half had a duration of ≥180 days (47%). Most of these episodes did not include receipt of concurrent prescriptions for benzodiazepines (75%) or opioid analgesics (76%).
- Prior authorization requirement was associated with significantly fewer treatment episodes of ≥180 days, with an 11% reduction in year 1 of policy implementation, 9% reduction in year 2, 15% reduction in year 3, and 10% reduction in year 4.
- Prior authorization policies were not associated with concurrent prescribing of benzodiazepines or opioid analgesics.

Comments: Prior authorization policies are ostensibly intended to improve quality of care and prevent unsafe practices. However, these policies create more work for clinicians and insurers while—at least in the case of buprenorphine—impeding the delivery of high-quality care and almost certainly harming patients.

Darius A. Rastegar, MD

Reference: Landis RK, Opper I, Saloner B, et al. Buprenorphine treatment episode duration, dosage, and concurrent prescribing of benzodiazepines and opioid analgesics: the effects of Medicaid prior authorization policies. *Drug Alcohol Depend*. 2022;241:109669.

Screening, Brief Intervention, and Referral to Treatment in Adolescence Provides Lasting Benefit into Young Adulthood

Screening, brief intervention, and referral to treatment (SBIRT) has been shown to reduce substance use in adolescents, but the US Preventive Services Task Force has concluded that there is insufficient evidence to recommend it. This study randomized adolescent patients (ages 12–18; N=1871) to 1 of 3 SBIRT groups within a US pediatric practice: pediatrician-delivered SBIRT, embedded behavioral health counselor delivered-SBIRT, or treatment as usual (control). Researchers followed up after 7 years to assess outcomes related to substance use, mental health diagnoses, and healthcare utilization. They combined the two SBIRT groups and compared outcomes with the control group.

- Compared with the control group, participants who received SBIRT were less likely to have a substance use-related diagnosis at follow-up (24% versus 19%, respectively).
- Participants in the SBIRT groups had lower odds of inpatient hospitalization, compared with the control group (odds ratio, 0.59).
- Compared with patients in the control group, those who received SBIRT who had at least one visit had fewer visits to primary care (incidence rate ratio [iRR], 0.90) and psychiatry (iRR, 0.64), and more visits to addiction medicine services (iRR, 1.52).

Comments: It can be difficult to document reductions in substance use and associated harms in adolescents, whose use is often sporadic. This study adds important evidence to the burgeoning literature documenting the effectiveness of adolescent SBIRT in improving SUD and mental health outcomes. This is especially important in the US, because access to healthcare via insurance is more uniform in the adolescent years, whereas coverage is not guaranteed in adulthood.

Corey McBrayer, DO, MPH* & Sharon Levy, MD

* Rich Saitz Editorial Intern & Grant Medical Center Addiction Medicine Fellow, OhioHealth.

Reference: Sterling S, Parthasarathy S, Jones A, et al. Young adult substance use and healthcare use associated with screening, brief intervention and referral to treatment in pediatric primary care. *J Adolesc Health*. 2022;71(4S):S15–S23.

Alcohol Use Patterns in Adolescence Associated With Alcohol and Other Drug Overdose in Adulthood

Alcohol and other drug overdoses are a significant public health problem and a common cause of death among young adults. This study assessed whether alcohol use at age 15–16 years is a risk factor for alcohol or drug overdose, or poisoning requiring medical attention, by the age of 32–33 in a population-based Finnish cohort study. The study was limited to 7714 individuals with no history of overdose prior to the age of 15–16 years. Information on overdose was collected from nationwide registers.

- By the age of 32–33, 183 overdose diagnoses were recorded among assessed individuals.
- In adjusted analyses,* the following were associated with an increased risk of any overdose at age 32–33:
  - ◊ First alcohol intoxication at age ≤12 (hazard ratio [HR], 4.5).
  - ◊ First alcohol intoxication at age 13 or 14 (HR, 2.1).
  - ◊ High alcohol tolerance** (HR, 3.1).
  - ◊ Frequent alcohol intoxication† (HR, 1.9).
- First alcohol intoxication at age ≤12, and high alcohol tolerance were associated with an increased risk of intentional overdose (HR, 5.2 and 4.4, respectively).

* Analyses were adjusted for "behavioral and emotional problems," non-medical drug use, and family background.
** Defined as number of standard drinks (12g ethanol) to become intoxicated (≥7 drinks for females or 9 for males).
† Defined as reporting being intoxicated ≥3 times in the last 30 days.

Comments: This cohort study suggests that specific alcohol use patterns in adolescence are associated with increased risk of alcohol and other drug-related overdose later in life. Overdose prevention efforts could include early identification and intervention during adolescence/young adulthood for people with early onset of alcohol consumption, frequent alcohol intoxication, and high alcohol tolerance.

Nicolas Bertholet, MD, MSc

Reference: Koivisto MK, Miettunen J, Levola J, et al. Alcohol use in adolescence as a risk factor for overdose in the 1986 Northern Finland Birth Cohort Study. *Eur J Public Health*. 2022;32(5):753–759.

Receipt of Buprenorphine in Pregnancy Associated With a Lower Risk of Adverse Neonatal Outcomes Than Methadone

Opioid use disorder (OUD) is a major cause of morbidity among pregnant persons and their offspring. Both methadone and buprenorphine are effective in the treatment of OUD, but it is unclear whether one is superior to the other in terms of maternal or fetal morbidity. This study examined US Medicaid data for pregnant persons from 2000 to 2018 and compared rates of neonatal abstinence syndrome (NAS), preterm birth, low birth weight, and small for gestational age (SGA) among infants exposed in utero to buprenorphine or methadone in early and late pregnancy. The authors also compared maternal outcomes.

- In early pregnancy, 10,704 pregnant persons were exposed to buprenorphine and 4387 to methadone. In late pregnancy, 11,272 were exposed to buprenorphine and 5056 to methadone (9976 and 4597, respectively, in the 30 days before delivery).
- NAS occurred in 69 percent of infants exposed to methadone versus 52 percent of those exposed to buprenorphine (relative risk, 0.73).
- For early pregnancy, the rates of adverse outcomes were significantly higher in infants exposed to methadone compared with buprenorphine: preterm birth (25 versus 14 percent), low birth weight (15 versus 8 percent), and SGA (15 versus 12 percent).
- For late pregnancy, the rates of adverse outcomes were likewise higher among infants with methadone exposure compared with buprenorphine: preterm birth (25 versus 14 percent), low birth weight (14 versus 8 percent), and SGA (16 versus 13 percent).
- No difference was found in maternal outcomes, including rates of cesarean section and severe complications.

Comments: While this study is important and can inform anticipatory guidance for pregnant persons with OUD, it is vital that individuals with OUD receive the medication that works best for them. Both methadone and buprenorphine are effective and can be used during pregnancy.

Corey McBrayer, DO, MPH* & Darius A. Rastegar, MD

* Rich Saitz Editorial Intern & Grant Medical Center Addiction Medicine Fellow, OhioHealth.

Reference: Suarez EA, Huybrechts KF, Straub L, et al. Buprenorphine versus methadone for opioid use disorder in pregnancy. *N Engl J Med*. 2022;387(22):2033–2044.

Most Current Guidelines for the Treatment of Infective Endocarditis Fall Short of Evidence-based Treatment for Opioid Use Disorder

Infective Endocarditis (IE) is common among people who inject drugs (PWID), and rates of IE in this population are increasing. Many guidelines outline duration of IV antibiotic treatment and patients' appropriateness for surgery. Researchers reviewed and compared 10 medical guidelines published 2007–2020 for management of IE in PWID.

- Six of the 10 guidelines include considerations for reduced treatment intensity among PWID, including a shortened course of antibiotics or the use of oral antibiotics.
- Five of the 10 guidelines discuss the increased risk of reinfection among PWID, and 2 guidelines (including those of the American Heart Association [AHA]*) recommend avoiding surgery among PWID.
- Only 1 guideline specifically mentions the prescribing of medication for OUD, and only 3 mention treatment of OUD or an addiction medicine consult.
- All guidelines use some stigmatizing language (e.g., "abuser," "addict").
- Management of withdrawal is not addressed in any guidelines.**

* In 2021, the AHA assembled an expert writing group that issued a scientific statement (2022) on the management of IE among PWID endorsing evidence-based treatment, harm-reduction measures, and thorough considerations for surgery in this population ("Indications for surgery in PWID with IE are the same as in patients with IE who do not inject drugs").
** The 2022 AHA statement recommends using medication for the treatment of withdrawal (buprenorphine and methadone).

Comments: Many guidelines include considerations about reducing standards of care for the treatment of IE among PWID, while few include recommendations about how to address the underlying substance use disorder that led to IE and which increases the risk of recurrence. This orientation—along with the prevalent use of stigmatizing language—reflects a relative lack of substance use expertise and perspective in the formulation of IE guidelines (a gap that the AHA has taken steps to remedy). Evidence-based recommendations about how to address substance use disorder among PWID could facilitate more effective treatment of IE and reduce the risk of recurrence.

Corey McBrayer, DO, MPH* & Timothy S. Naimi, MD, MPH

* Rich Saitz Editorial Intern & Grant Medical Center Addiction Medicine Fellow, OhioHealth.

References: Selitsky L, Racha S, Rastegar D, Olsen Y. Infective endocarditis in people who inject drugs: a scoping review of clinical guidelines. *J Hosp Med*. 2023;18 (2):169–176.
Baddour LM, Weimer MB, Wurcel AG, et al. Management of infective endocarditis in people who inject drugs: a scientific statement from the American Heart Association. *Circulation*. 2022;146(14):e187–e201.

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Contact Information:
Alcohol, Other Drugs, and Health: Current Evidence
Boston Medical Center
801 Massachusetts Ave., 2nd floor
Boston, MA 02118
aodhce@bu.edu

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