Alcohol, Other Drugs, and Health: Current Evidence

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Grayken Center for Addiction
Boston Medical Center

INTERVENTIONS & ASSESSMENTS

Characteristics of Medetomidine Withdrawal Among People With Concurrent Fentanyl Use

The potent α2-adrenergic agonist medetomidine has emerged as an adulterant in the unregulated US fentanyl supply in several communities. In some instances, people with non-medical fentanyl use have presented to the hospital with withdrawal symptoms that do not respond to opioid therapy and include severe autonomic hyperactivity (i.e., hypertension, tachycardia, vomiting, refractory delirium), suspected to be due to concurrent medetomidine withdrawal. This retrospective case series sought to characterize medetomidine withdrawal syndrome across three hospital systems in Philadelphia, PA, 2024–2025.

- Among 209 hospitalized patients who presented with fentanyl withdrawal and atypical autonomic instability, the median age was 38 years; 29 percent were female, and 64 percent identified as White.
- 162 patients (78 percent) required intensive care unit (ICU) admission, with 42 patients (20 percent) needing intubation. Tachycardia and hypertension were common, and most patients (74 percent) required dexmedetomidine infusions for autonomic hyperactivity.
- Common complications included encephalopathy (35 percent) and myocardial injury (29 percent). Seizure was uncommon (5 percent), and primarily affected patients with concurrent benzodiazepine use. Thirty-three percent of patients had a patient-directed discharge.
- Among a subset of 43 patients, urine toxicology with liquid chromatography–mass spectrometry confirmed 100 percent positivity for fentanyl and medetomidine metabolites.

Comments: This cohort of patients with medetomidine-adulterated fentanyl withdrawal experienced severe sympathetic hyperactivity, resulting in high rates of ICU admission, intubation, and patient-directed discharge . Clinicians should recognize this withdrawal syndrome and treat autonomic hyperactivity with early administration of α2-agonist therapy.

Delia Motavalli, MD* & Alexander Y. Walley, MD

* Contributing Editorial Intern and Addiction Medicine Fellow, Boston Medical Center

Reference: London KS, Huo S, Murphy L, et al. Severe fentanyl withdrawal associated with medetomidine adulteration: a multicenter study from Philadelphia, PA. *J Addict Med*. 2025 [Epub ahead of print]. doi: 10.1097/ADM.0000000000001560.

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HEALTH OUTCOMES

Among Individuals Receiving Buprenorphine, Prescribed Stimulant Receipt Does Not Increase the Risk of Opioid-related Overdose

In the US and Canada, the percentage of deaths involving both unregulated fentanyl and stimulants has increased in recent years. Researchers in British Columbia used a database of individuals who experienced an opioid-related overdose from 2015 to 2020 to investigate the association between receiving a prescription stimulant medication and fatal and non-fatal overdose among those receiving opioid agonist therapy (OAT; i.e., buprenorphine, methadone, or slow-release morphine). The authors adjusted analyses for a number of potential confounders, including sociodemographic characteristics, substance use patterns, and mental health diagnoses.

- There were 9395 individuals who received OAT in the cohort; of these, 683 (7 percent) were prescribed a stimulant. A total of 1746 fatal and non-fatal overdose events occurred over the study period (9.6 per 100 person-years); 37 (2 percent) were fatal.
- Dispensation of a stimulant was not associated with an increased risk of overdose overall.
- Secondary analyses found that among individuals receiving buprenorphine, dispensation of a stimulant was associated with reduced risk of overdose (adjusted hazard ratio [aHR], 0.47), while those receiving full agonist OAT (methadone or morphine) had a greater risk of overdose (aHR, 1.51).

Comments: This study provides some reassurance that prescribing stimulants to individuals receiving buprenorphine does not appear to increase the risk of fatal and non-fatal overdose. The increased risk observed among those receiving full-agonist medications warrants further study.

Darius A. Rastegar, MD

Reference: Young S, Fairbairn N, Cui Z, t al. Association between prescribed stimulant medications and overdose among individuals receiving opioid agonist therapy: a retrospective cohort study from British Columbia, Canada. *Addiction*. 2025;120:1184–1194.

Among People Admitted for an Overdose, Opioid Agonist Treatment is Associated With a Decreased Risk of Future Overdose

Overdose is a major risk for people who use drugs. This study assessed the impact of various treatment modalities on the risk of subsequent overdose in a cohort of people (N=4089) with a non-fatal opioid-related overdose admitted to a hospital or emergency department in Connecticut, May 2016–December 2017.

- The average age was 41 years; 65 percent of the cohort was male, and 74 percent identified as non-Hispanic White.
- Overall, 56 percent of the cohort did not receive substance use disorder treatment in the 12 months following the index overdose; 35 percent received opioid agonist treatment (OAT; 25 percent buprenorphine, 13 percent methadone), and 21 percent received inpatient treatment (19 percent for withdrawal, 8 percent for extended inpatient treatment).
- Following the index overdose, 11 percent (n=467) experienced another opioid-related overdose within 12 months; 19 percent (n=87) of these overdoses had a fatal outcome, representing 2 percent of the overall sample.
- In adjusted survival analyses,* receipt of methadone or buprenorphine was associated with a decreased risk of subsequent overdose (adjusted hazard ratio [aHR], 0.41 and 0.72, respectively).

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Among People Admitted for an Overdose, Opioid Agonist Treatment is Associated With a Decreased Risk of Future Overdose *(continued from page 2)*

- Medically managed opioid withdrawal or extended inpatient treatment were not associated with a decreased risk of subsequent overdose (aHR, 1.08 and 0.90, respectively).
- No treatment modality was significantly associated with a decreased risk of fatal overdose.
- Exposure to benzodiazepines was associated with an increased risk of any overdose and of fatal overdose (aHR, 1.46 and 2.65, respectively).

* Adjusted for demographics, incarceration, receipt of opioids besides OAT, and receipt of benzodiazepines.

Comments: While this study likely lacked power to assess the impact of treatment modalities on fatal overdose, it underscores the critical importance of OAT for opioid use disorder. As only a minority of patients in this cohort received OAT, public health and policy interventions should support widespread access to OAT in order to prevent subsequent overdoses.

Nicolas Bertholet, MD, MSc

Reference: Howell BA, Black A, Lin HJ, et al. Receipt of addiction treatment after nonfatal opioid overdose and risk of subsequent overdose: A retrospective cohort study. *Drug Alcohol Depend.* 2025;273:112679.

Rising Opioid-related Overdose Mortality Rates in the American Indian and Alaska Native Communities, 1999–2021

Opioid-related overdose (OOD) mortality rates increased in the US from 1999 to 2021, following the four waves of the opioid crisis. American Indian (AI) and Alaskan Native (AN) populations were disparately affected. Researchers used observational, population-based data to quantify OOD mortality growth rates within the AI/AN population based on race, Hispanic ethnicity, age, and sex via segmented time series analysis.

- OOD mortality rates increased in the overall AI/AN population from 0.36 per 100,000 in 1999–2019 to 6.5 per 100,000 in 2019 –2021.
- OOD mortality growth rates were highest among 24–44 year-olds in 2019–2021.
- OOD mortality growth rates were similar in females and males in 2019–2021.
- Compared with the overall AI/AN population, the non-Hispanic AI/AN subpopulation demonstrated a greater OOD mortality growth rate, which was generally consistent across age groups.

Comments: The AI/AN community experienced a steep acceleration in OOD mortality rates from 2019–2021. The data suggest that two subpopulations are particularly at risk: adults 24–44 years old, and those of non-Hispanic ethnicity. A greater understanding of this population's vulnerabilities (stemming from structural racism, oppression, and health inequities) and strengths (including a holistic, community-based mindset) could inform culturally sensitive approaches to comprehensive treatment (i.e., medications for opioid use disorder and naloxone).

Emily Nields, DO

Reference: Bauer C, Hassan GH, Bayly R, et al. Trends in fatal opioid-related overdose in American Indian and Alaska Native communities, 1999–2021. Am J Prev Med. 2024;66(6):927–935.

A Canary in the Coal Mine: How Medicaid Cuts Could Impact Millions of Americans With Opioid Use Disorder

In 2020, during the COVID-19 public health emergency, the US Congress provided increased funding to states to maintain continuous Medicaid enrollment. In March 2023, Congress ended these funds and states resumed Medicaid eligibility redeterminations, described as "Medicaid unwinding." Researchers conducted a cross-sectional study using a difference-in-differences design to assess if Medicaid unwinding impacted buprenorphine treatment receipt among people with opioid use disorder. They used nationally representative buprenorphine dispensing data from retail pharmacies to measure and compare changes in buprenorphine prescriptions and insurance coverage from July 2017 to December 2022, and July 2023 to December 2023.

Compared with the earlier time period, in the latter time period…

- The number of days with active buprenorphine prescriptions decreased by 3.9 days.
- The probability of having no days with active buprenorphine prescriptions increased by 1.8 percent.
- The probability of having one or more active buprenorphine prescriptions paid for by private insurance increased by 1.9 percent.
- The probability of having one or more active cash-pay prescriptions increased by 0.9 percent.

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A Canary in the Coal Mine: How Medicaid Cuts Could Impact Millions of Americans With Opioid Use Disorder

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Comments: These findings suggest that Medicaid unwinding was associated with disruptions in buprenorphine receipt. The results raise concerns about how the proposed changes in the "One Big Beautiful Bill Act"—which is projected to cause 10.9 million people to lose Medicaid coverage over the next 10 years—will impact people who rely on Medicaid for buprenorphine. The bill may lead to a reversal in the recently observed decreases in US overdose deaths.

Susan L. Calcaterra, MD, MPH, MS

Reference: Constantin J, Kenney GM, Simon K, Chua KP. Medicaid unwinding and changes in buprenorphine dispensing. *JAMA Netw Open*. 2025;8(5):e258469.

PRESCRIPTION DRUGS & PAIN

Decreasing Opioid Dose Trajectory in Patients Prescribed Opioids Long Term Associated with Adverse Clinical Outcomes

Observational studies have documented the association between high-dose opioid prescribing and adverse clinical outcomes—including opioid overdose—while rapid reduction in prescribed opioid dose has also been associated with adverse outcomes. This large retrospective cohort study in Victoria, Australia linked opioid prescribing records with emergency department (ED) and hospital admission data to model distinct dose trajectories for primary care patients receiving long-term opioid therapy (LTOT; >90 days), and to assess the associations between dose trajectories and admission for emergency and hospital care over 18 months.

- Overall, 39,767 of 511,934 primary care patients (14 percent) were prescribed LTOT between January 2018 and May 2022.
- Three stable dose trajectories (low-dose, medium-dose, and high-dose) and two decreasing dose trajectories (rapid decrease from low-dose, and gradual decrease from medium-dose) were identified using trajectory modelling techniques.
- Compared with the "medium stable dose" group, the incidence risk ratio (IRR) of mental health-related ED visits increased by 35 percent for the "gradual decrease from intermediate dose" group and by 31 percent in the "rapid decrease from low dose" group.
- The risk of hospital admission was increased for the "gradual decrease from intermediate dose" group (IRR, 1.57) compared with the "medium stable dose" group.

Comments: This large observational study is consistent with other studies documenting adverse consequences associated with LTOT de-prescribing, especially mental health consequences. Reasons for de-prescribing in this cohort were unknown and could include unmeasured confounders explaining the association with adverse outcomes, just as reasons for opioid dose escalation could explain the adverse outcomes associated with higher prescribed opioid doses. Guidelines and policies should balance the risks of both opioid prescribing and de-prescribing.

Joseph Merrill, MD, MPH

Reference: Xia T, Picco L, Rowland B, et al. Opioid dose trajectories and associations with opioid- and nonopioid-related emergency department presentations and hospital admissions. *Pain*. 2025;166(10):e460–e467.

Among Individuals With Opioid Use Disorder, Initiation of Extended-release Naltrexone Did Not Increase Pain Intensity

Individuals with opioid use disorder (OUD) have high rates of chronic pain. The efficacy of opioid agonist medications for chronic pain is questionable at best, and previous studies found that individuals with chronic pain who start extended-release naltrexone (XR-NTX) do not report increased pain. This study was a secondary analysis of an observational study in Norway comparing individuals with OUD who chose to start XR-NTX and those who were prescribed opioid agonist therapy (OAT). The goal was to see if initiation of XR-NTX had an effect on pain intensity, and whether pain intensity had an effect on treatment outcomes at six months.

- There were 160 participants receiving XR-NTX who completed at least one pain questionnaire; 79 (49 percent) completed six-month follow-up. There were 151 patients receiving OAT; 122 (81 percent) completed six-month follow-up.

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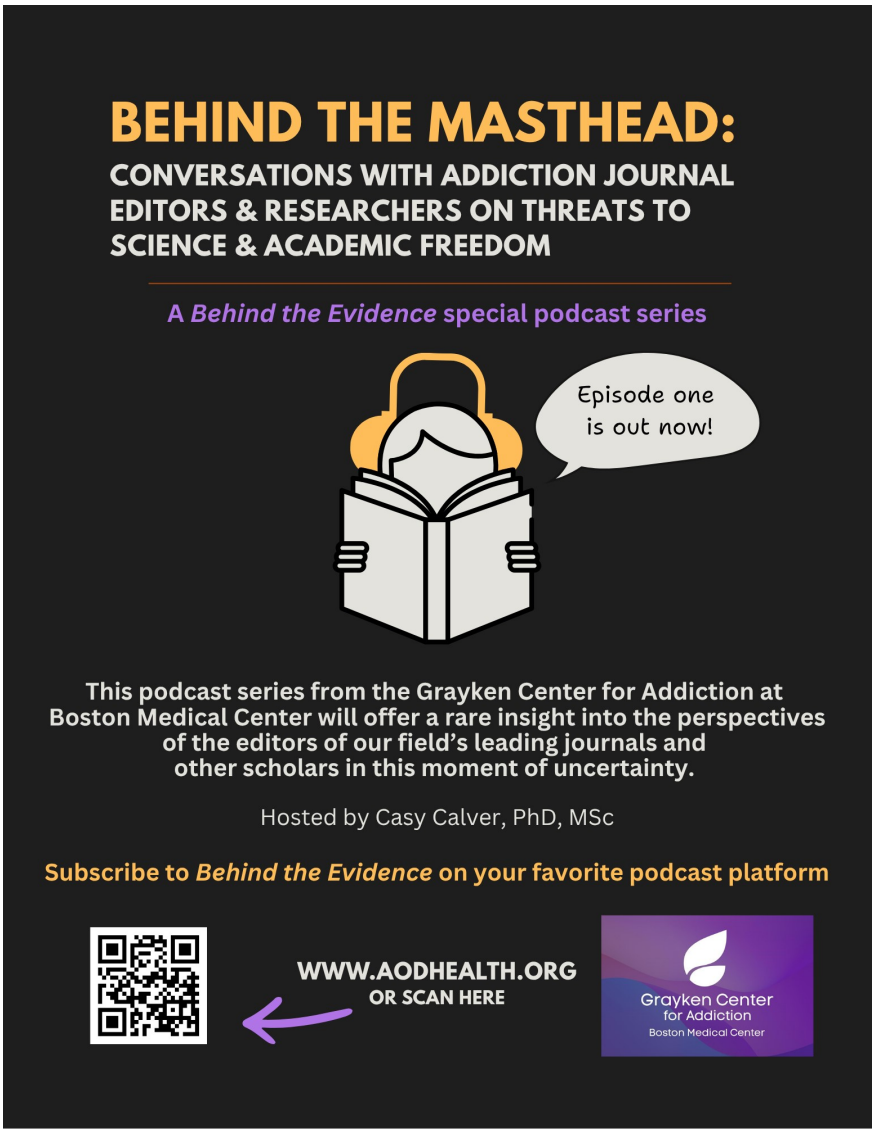
Among Individuals With Opioid Use Disorder, Initiation of Extended-release Naltrexone Did Not Increase Pain Intensity (continued from page 4)

- In the XR-NTX group, there was a significant reduction in pain intensity from baseline to follow-up among patients with low and low-to-moderate pain, but not among patients with high levels of pain. In the OAT group, the reduction in pain intensity was not significant.
- In the XR-NTX group, there was no significant association between baseline pain intensity and treatment retention.

Comments: This study adds to growing evidence that opioid agonist medications are not an effective treatment for chronic pain. While treatment retention was better among patients receiving OAT compared with XR-NTX, this study suggests that chronic pain should not be a reason to choose OAT over XR-NTX.

Darius A. Rastegar, MD

Reference: Juya F, Solli KK, Holtan L, et al. Pain intensity in patients using extended-release naltrexone or opioid agonists and its effect on extended-release naltrexone treatment outcomes. *Am J Addict*. 2025;34(5):528–535.



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.

Co-Editors-in-Chief
Jeffrey H. Samet, MD, MA, MPH
Emily C. Williams, PhD

About the journal: *ASCP* provides a forum for clinically relevant research and perspectives that contribute to improving the quality of care for people with unhealthy alcohol, tobacco, or other drug use and addictive behaviors across a spectrum of clinical settings. ***ASCP* is the official journal of the Grayken Center for Addiction at Boston Medical Center.**

We are seeking submissions to our upcoming special series:

"Beyond the four walls:
Innovative approaches to promoting equity in addiction treatment"

This Collection seeks to highlight innovative approaches to substance use and substance use disorder (SUD) treatment initiation and sustained care that extend beyond traditional clinical contexts.

The editors are interested in all submissions that address the above goals but would particularly like to encourage research conducted in such settings in the Global South and in countries where research into substance use and SUD care has been historically low.

Submissions are desired by 15 December 2025.

2024 Impact Factor: 3.7

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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