



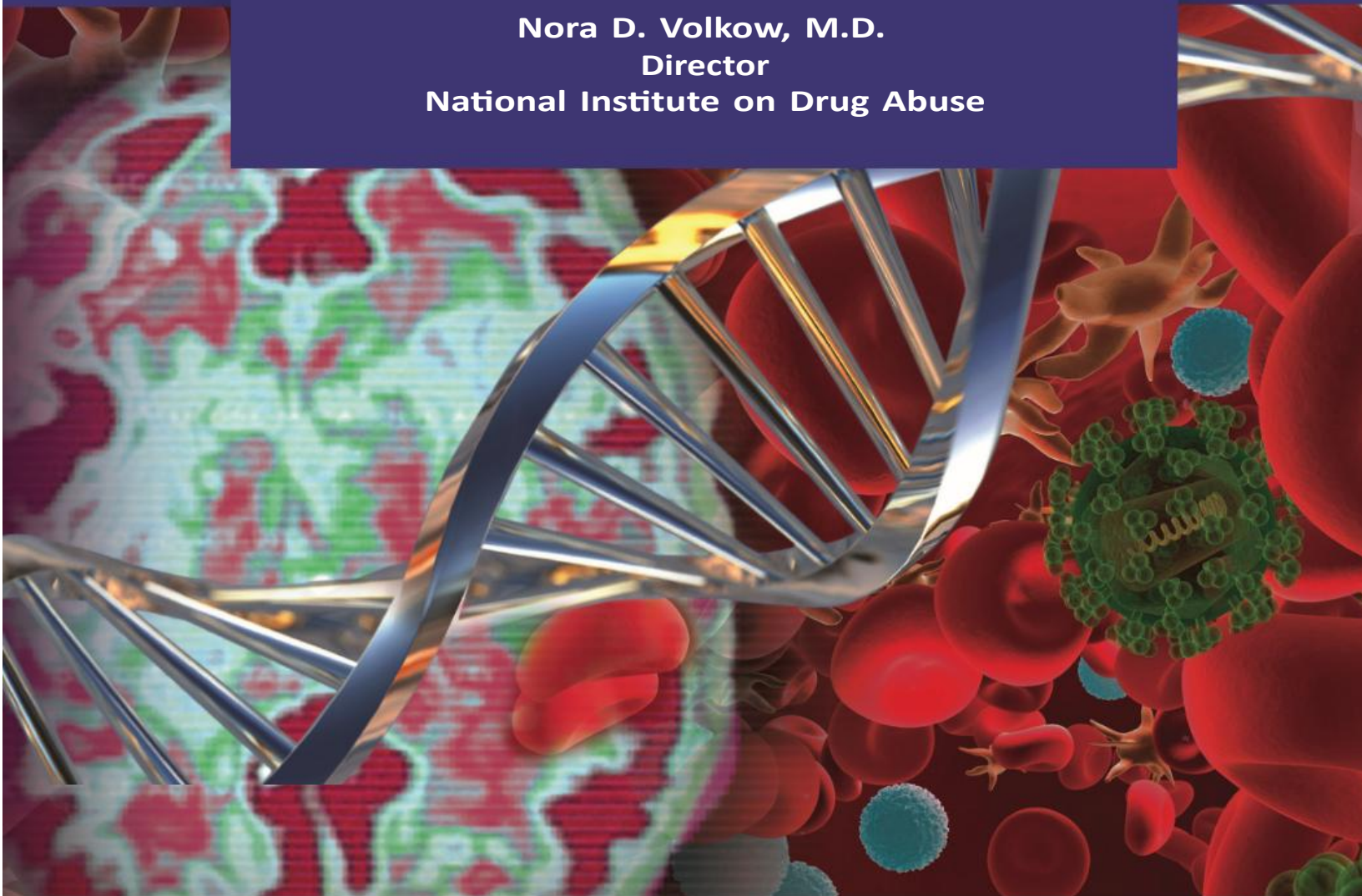
# DIRECTOR'S REPORT

\_\_\_\_\_ to the \_\_\_\_\_

National Advisory Council on Drug Abuse

\_\_\_\_\_ September 8, 2026 \_\_\_\_\_

**Nora D. Volkow, M.D.**  
**Director**  
**National Institute on Drug Abuse**



# RESEARCH HIGHLIGHTS

## BASIC AND BEHAVIORAL RESEARCH

[Searching For Agency In Animal Models Of Addiction: Choice Between Choices](#) Rego FP, Kearns DN. Drug Alcohol Depend. 2026; 283: 113136.

**Purpose:** This study was motivated by Ahmed's (2024) observation that subjects in animal models of addiction lack agency. Animals have been given increasing control over drug-taking in addiction models, but not the opportunity to change their circumstances in ways that favor drug self-administration vs. abstinence. The present study aimed to develop a model wherein rats could intervene to change the choice contingencies available to them.

**Methods:** Rats were trained to choose between self-administered heroin or sucrose pellets in two choice conditions. In one condition, heroin was cheap and sucrose was expensive. In the other condition, the relative prices of these reinforcers were reversed. Then, rats were allowed to choose between these choice conditions.

**Main findings:** Rats frequently switched between the conditions when the cost of switching was low, and obtained many of the cheap reinforcers available in each condition. As the cost of switching increased, rats switched less often and increased consumption of the cheap reinforcer available in their current condition. When rats could only make one choice between conditions per session, large individual differences were observed, with some rats preferring the cheap heroin condition and others preferring the cheap sucrose condition.

**Conclusions:** This study found that when rats are given the ability to choose between choices they will take advantage of this additional level of control. The initial environmental contingencies were, however, an important determinant of heroin-taking behavior. This finding is a step towards refining animal models of addiction towards a stronger analogy to human behavior. NIDA Grant Support: DA055572

[Dorsal Raphe Nucleus Enkephalin Peptide Modulates Behavioral Preference](#) Braden K, Trinagel A, Acevedo E, Massó-Quñones LN, Bernstein AE, Arguello M, Evans-Strong A, Dunn SS, Castro DC. Neuropsychopharmacology. 2026; :10.1038/s41386-026-02456-5.

The endogenous opioid system is a powerful modulator of motivation and affect. The dorsal raphe nucleus (DRN) in the midbrain has been established as an important site of opioid action and is an integral hub in behavioral modulation. To investigate the functional significance of DRN opioid signaling in aversive and appetitive behaviors we disrupted preproenkephalin (Penk) in DRN using CRISPR-Cas9 technology in Penk-Cre mice. We found that CRISPR mediated knockdown of enkephalin peptide in the DRN (DRNPenk) enhanced inflammation-induced mechanical sensitivity and odor avoidance. Additionally, loss of DRNPenk diminished sucrose preference and engagement with a novel social stimulus. To further characterize the opioid system within the DRN, we performed Hiplex in situ hybridization of 12 genes in the same tissue. This revealed that DRNPenk is largely separate from DRN serotonin cells and is instead distributed on glutamatergic and GABAergic cells. However, subtype-specific

knockdown of DRNPenk from glutamatergic and GABAergic cells was insufficient to replicate the behavioral effects of general DRNPenk knockdown. This suggests that these neurons represent a novel population that mediate motivated behaviors distinctly from canonical DRN mechanisms. NIDA Grant Support: DA062455

**Non-Equilibrium Snapshots Of Ligand Efficacy At The  $\mu$ -Opioid Receptor** Robertson MJ, Modak A, Papasergi-Scott MM, Hu M, Peroto MC, Varga BR, Majumdar S, Kalathur R, Blanchard SC, Skiniotis G. *Nature*. 2026; 652(8110): 794-802.

Distinct ligands for the same G-protein-coupled receptor (GPCR) activate intracellular signalling partners to varying extents, but the molecular mechanisms that drive these differences remain elusive. Here, hypothesizing that such differences in signalling efficacy might be captured structurally in intermediate states under non-equilibrium conditions, we use a time-resolved cryo-electron-microscopy approach to visualize the GTP-induced activation of the  $G\alpha i\beta\gamma$  heterotrimer by the  $\mu$ -opioid receptor bound to three ligands that show partial, full or super agonism on the receptor<sup>1</sup>. We resolve ensembles of conformational states along the G-protein activation pathway, including an intermediate state that enables us to visualize receptor dynamics as a function of bound ligand. The results reveal ligand-dependent differences in state occupancy and conformational stability, with higher ligand efficacy correlating with increased dynamics of the receptor's transmembrane helices 5 and 6. Furthermore, we identify key differences between  $G_i$  and  $G_s$  in the mechanism of GTP-induced activation, which are likely to underlie the distinct activation kinetics of these G-protein types. Corroborated by molecular-dynamics simulations and single-molecule fluorescence assays, our findings provide a dynamic structural landscape of GPCR-G-protein interactions for ligands of various efficacies, and suggest that partial agonists produce a 'kinetic trap' during G-protein activation. NIDA Grant Support: DA059978

**Large-Scale Behavioral Characterization Of Oxycodone Self-Administration In Heterogeneous Stock Rats Reveals Initial Analgesic Effects Are Associated With Addiction-Like Behaviors** Kallupi M, de Guglielmo G, Carrette LLG, Simpson S, Kononoff J, Kimbrough A, Smith LC, Shankar K, Avelar A, Conlisk D, Brennan M, Tieu L, Sedighim S, Boomhower B, Maturin L, Fannon MJ, Martinez A, Crook C, Dirik S, Velarde N, Schweitzer P, Bonnet-Zahedi S, Sneddon E, Plasil S, Morgan AA, Othman DN, Sichel B, Peng B, Chitre AS, Polesskaya O, Lau J, Vang A, Solberg Woods LC, Palmer AA, George O. *Neuropsychopharmacology*. 2026; 51(6): 1074-1083.

Family and twin studies indicate that 20-60% of the vulnerability to opioid use disorder (OUD) is influenced by genetic factors, but the specific genes driving addiction-like behaviors, including sensitivity to opioid analgesia, tolerance, dependence, and escalation of oxycodone self-administration, remain unidentified, limiting precision medicine approaches. To address this, we phenotyped over 500 heterogeneous stock (HS) rats, an outbred population with high genetic diversity, to characterize traits associated with OUD vulnerability and resilience. Rats self-administered oxycodone (150  $\mu$ g/kg/infusion) in short-access (2 h/day, 4 days) followed by long-access (12 h/day, 14 days) sessions. We assessed motivation for oxycodone using progressive ratio testing, withdrawal-induced hyperalgesia with von Frey tests, and tolerance to oxycodone's analgesic effects via tail immersion tests. Large cohorts ( $n = 46-60$ ) and Z-score normalization minimized cohort-specific effects. An Addiction Index, derived from averaging Z-scores of escalation, motivation, tolerance, and hyperalgesia, revealed significant individual variability. Rats with severe addiction-like behaviors displayed higher initial analgesia, greater escalation,

and more pronounced tolerance compared to resilient rats. Females showed increased escalation and motivation compared to males, but similar tolerance and hyperalgesia. Principal component analysis confirmed the Addiction Index's validity, accounting for 40% of behavioral variance. This high-throughput phenotyping in HS rats, leveraging their genetic diversity, provides a robust framework for genome-wide association studies to identify gene variants linked to OUD vulnerability, offering translational potential for discovering novel therapeutic targets and advancing pharmacogenetic strategies for OUD treatment. NIDA Grant Support: DA060810, DA062049, DA044451

**Single Cell Multiomic Analysis Of The Impact Of Delta-9-Tetrahydrocannabinol On HIV Infected CD4 T Cells** Ashokkumar M, Ge RY, Cooper-Volkheimer A, Margolis DM, Li Q, Jiang Y, Murdoch DM, Browne EP. J Cannabis Res. 2026; 8(1): 52.

Cannabis use is prevalent among individuals living with HIV in the United States, but the impact of cannabis exposure on the reservoir of latently infected cells that persists during antiretroviral therapy (ART) remains unclear. To address this gap, we analyzed the effect of  $\Delta$ -9-tetrahydrocannabinol (THC) on primary CD4 T cells that were latently infected with HIV. We found that THC did not have a strong effect on baseline or latency reversing agent (LRA) stimulated HIV expression, or on expression of an activation marker (CD38). However, using an integrated multiomic single-cell analysis of genome-wide chromatin accessibility and gene expression, we observed altered expression of several hundred genes in HIV infected CD4 T cells after THC exposure, including transcriptional downregulation of genes involved in protein translation and antiviral pathways, indicating that THC suppresses innate immune activation in infected cells. Additionally, chromatin accessibility analysis demonstrated upregulated chromatin binding activity for the transcriptional regulator CTCF, and reduced activity for members of the ETS transcription factor family in infected cells after THC exposure. These findings provide insights into the mechanisms by which cannabis use could influence the persistence of HIV within cellular reservoirs and the molecular phenotype of latently infected cells. Further elucidation of the underlying mechanisms involved in THC-mediated changes to HIV infected cells, will lead to an improved understanding of the impact of cannabis use on the HIV reservoir. NIDA Grant Support: DA053599, DA059918

**Sigma-1 Receptor Regulates HIV-1 And Methamphetamine-Induced Endothelial/Pericyte Barrier Impairment Via Strain-Specific Inflammatory Responses And Mitochondrial Dysregulation** Fattakhov N, Torices S, Becker S, Joseph JA, Schmidlin S, Ngo A, Okoro A, Naranjo O, Toborek M. J Neuroinflammation. 2026; 23(1): 121.

**Background:** Methamphetamine (METH) use disorder (MUD) is a frequent comorbidity among people with HIV-1 (PWH). While both METH and HIV-1 independently disrupt the brain microvascular system and promote neuroinflammation, the molecular mechanisms underlying their synergistic neurotoxicity remain unclear. The sigma-1 receptor (Sigma-1R) signaling pathway has been suggested as a potential target in METH misuse; however, its involvement in the impact of METH and/or HIV-1 infection on brain pericytes remains unknown.

**Methods:** Transwell co-cultures of human brain microvascular endothelial cells (HBMECs) and human brain vascular pericytes (HBVPs) were employed to assess the impact of combined METH exposure and infection with HIV-1 on barrier integrity. Moreover, mitochondrial functions, inflammatory mediators, oxidative stress markers, and the expression of interferon-stimulated genes were analyzed.

**Results:** HBVP infection with the CXCR4-tropic HIV-1 strain NL4-3, but not the CCR5-tropic JR-CSF strain, disrupted endothelial/pericyte barrier permeability, reduced transendothelial electrical resistance (TEER), and lowered claudin-5 expression, effects alleviated by pretreatment with Sigma-1R antagonist S1RA (10  $\mu$ M). S1RA suppressed interleukin-6 (IL-6) release without affecting increased ROS levels and mitigated HIV-1 NL4-3 and METH co-induced proton leak and mitochondrial network fragmentation in a DRP1 phosphorylation-dependent manner. Importantly, METH enhanced replication of HIV-1 NL4-3, a process modulated by the CXCR4/CCL2 signaling pathway rather than Sigma-1R.

**Conclusions:** The obtained results identify Sigma-1R antagonism as a potential therapeutic strategy to protect microvascular integrity in the context of HIV-1 infection and METH misuse. In addition, they reveal distinct mechanisms that may underly microvascular dysfunction in PWH who experience MUD. NIDA Grant Support: DA050528, DA044579, DA059849

## **EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH**

### **Prevention Research Branch**

**Mobile Telemedicine For Treating Chronic Hepatitis C Among Rural People Who Inject Drugs: A Randomized Clinical Trial** Friedmann PD, Wilson D, de Gijzel D, Nolte K, DeJace J, Hoskinson R Jr, Del Toro-Mejias L, Bianchet E, Dowd P, Soares WE 3rd, Stopka TJ. JAMA Netw Open. 2026; 9(1): e2555125.

Persons who inject drugs in rural areas of the United States have high rates of chronic hepatitis C virus (HCV) infection and poor access to HCV testing, direct-acting antiviral (DAA) treatment, and syringe services, creating a need for effective testing and treatment approaches to achieve national HCV elimination goals. The researchers conducted an open-label, randomized, parallel-group clinical trial to test whether a mobile telemedicine-based HCV treatment intervention increases treatment initiation and viral clearance and decreases sharing of injection equipment among rural persons who inject drugs, comparing mobile telemedicine care (MTC) with enhanced usual care (EUC), both integrated with van-based syringe services, among participants aged 18 or older with a history of drug injection and chronic HCV infection from three rural counties in New Hampshire and Vermont between April 2022 and September 2024. MTC consisted of DAA treatment via telemedicine along with on-demand syringe services on a mobile van, while EUC consisted of treatment referral by van staff with care navigation to a local or regional clinician. Of 503 prescreened individuals, 169 were eligible and 150 were randomized to MTC (n = 75) or EUC (n = 75); participants had a mean age of 38.1 years, 68.7% were male, 70.0% experienced homelessness, and 64.7% reported drug injection in the past 30 days. MTC participants were more likely than EUC participants to initiate DAA treatment (57.3% vs 26.7%; relative risk, 2.15) and to achieve viral clearance (37.3% vs 18.7%; relative risk, 2.00), though no effect was detected on abstinence from sharing syringes or other injection equipment at follow-up. The findings indicate that telemedicine for chronic HCV treatment integrated with syringe services on a mobile van was associated with improved access to HCV treatment initiation and cure for people with a history of drug injection in rural communities where HCV treatment services are scarce, suggesting that optimal strategies in rural areas should include convenient, low-threshold telemedicine treatment.

## Treatment and Recovery Services Research Branch (TRSRB)

### Toxicant Exposures After Switching From Cigarettes To A Pod-Based Electronic Cigarette: A Randomized Clinical Trial

Yingst JM, Krebs NM, Dahal S, Allen SI, Livelsberger C, Peters V, Salkin A, Bordner C, Mazhar L, Reinhart L, Trushin N, Zimmerman C, Hassan K, Bitzer Z, Sciamanna C, Zhu J, Foulds J. JAMA Netw Open. 2026; 9(5): e2613292.

**Importance:** Electronic cigarettes (EC) have been shown to expose users to fewer tobacco-related toxicants compared with combustible cigarettes. The current generation of ECs has rapidly shifted toward pod-based nicotine salt formulation ECs, and more research is needed to understand the impacts of using these EC products among those who smoke.

**Objective:** To determine the short-term effects of switching from cigarettes to a pod-based 5% nicotine EC, compared with a 0% nicotine EC.

**Design, setting, and participants:** This double-blind, parallel-arm, randomized, placebo-controlled trial with follow-up at 6 weeks (randomized phase) and 10 weeks (postrandomized phase) was conducted at a single-site academic medical center in Pennsylvania from April 22, 2022, to December 12, 2023. Participants included adults who smoked more than 4 cigarettes per day (CPD) and expressed interest in switching completely to an EC. Data were analyzed from August 23, 2024, to December 1, 2025.

**Interventions:** Participants were allocated 1:1 to the standardized research EC (SREC) with 5% nicotine or 0% nicotine for 6 weeks.

**Main outcomes and measures:** The primary outcome was concentration of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in urine corrected for creatinine level at 6 weeks. Secondary outcomes included exhaled carbon monoxide (CO), cotinine level, CPD, CO-verified cigarette abstinence, and levels of volatile organic compounds.

**Results:** A total of 104 participants (52 per group) were randomized, of whom 68 (65.4%) were female, with a mean (SD) age of 50.9 (10.0) years. At 6 weeks, the 5% SREC group did not have significantly lower NNAL levels (mean difference [MD], -116.6 [95% CI, -245.4 to 12.2] pg/mg;  $P = .08$ ). However, a greater proportion of participants in the 5% SREC group were abstinent from cigarettes (19 of 52 [36.5%] vs 6 of 52 [11.5%];  $P = .005$ ), compared with the 0% SREC group. The 5% SREC group had greater cotinine levels (MD, 2367.8 [95% CI, 407.5-4328.2] ng/mg;  $P = .02$ ); however, there were no differences in CPD (MD, -0.9 [95% CI, -3.9 to 2.1] CPD;  $P = .55$ ) or exhaled CO levels (MD, -5.1 [95% CI, -12.9 to 2.6] ppm;  $P = .19$ ) between groups. Levels of cyanoethyl mercapturic acid (CYMA) (MD, -49.0 [95% CI, -90.4 to -7.6] ng/mg;  $P = .02$ ) and 3-hydroxypropyl mercapturic acid (3HPMA) (MD, -290.8 [95% CI, -514.0 to -67.6] ng/mg;  $P = .01$ ), biomarkers of acrylonitrile (a carcinogen) and acrolein (a cardiac toxicant) exposure (both of which are respiratory toxicants), were lower in the 5% SREC group compared with the 0% SREC group.

**Conclusions and relevance:** In this randomized clinical trial of adults who smoke, switching from cigarettes to a 5% SREC vs a 0% SREC resulted in reduced exposure to some toxicants delivered by cigarette smoking and an increased rate of smoking cessation. ECs that deliver nicotine like a cigarette may have an important role in reducing the harmful toxicant exposure caused by cigarette smoking.

### Long-term Opioid Therapy Tapering And Risk Of Substance Use Disorder And Overdose: Differences By Opioid Dose And Duration

Quinn PD, Meraz R, Mazurenko O, Chang Z,

Sjölander A, Medlin AR, Hirsh AT, Pujol TA, Kroenke K, D'Onofrio BM. J Gen Intern Med. 2026 Jun 24. J Gen Intern Med. 2026 [Online ahead of print, June 24].

**Background:** Tapering from long-term opioid therapy (LTOT) for chronic pain is increasingly common. However, there is inadequate evidence regarding the possibility of adverse effects, particularly across heterogeneous LTOT courses.

**Objective:** To estimate associations of tapering from various LTOT doses and durations with risk of substance use disorder (SUD) and overdose.

**Design:** Within-individual cohort study.

**Participants:** US adults tapering from at least 3 months of stable LTOT, obtained from Optum's de-identified Clinformatics® Data Mart Database for 2010-2021.

**Main measures:** Dose tapering was defined as 2 consecutive months of  $\geq 15\%$  lower dose within 6 months of LTOT baseline without abrupt discontinuation. Outcomes were assessed from emergency department or inpatient events with recorded SUD or overdose diagnoses. We compared risk of SUD/overdose across up to 1 year following tapering onset with risk during stable LTOT using conditional logistic regression with time-varying covariates.

**Key results:** Of 732,038 adults who experienced an LTOT taper, 7.6% had at least 1 SUD/overdose event during LTOT baseline or up to 1 subsequent year. Relative to LTOT baseline, odds of SUD/overdose were comparably greater in the month before taper onset (odds ratio [OR], 1.36; 95% CI, 1.32, 1.40) and the first month of tapering (OR, 1.38; 95% CI, 1.34, 1.43). Odds decreased partially across the subsequent year (e.g., month 12: OR, 1.11; 95% CI, 1.07, 1.15). This pattern was consistently observed across groups defined by baseline LTOT dose and duration, although odds returned to baseline levels within approximately 6 months of taper onset for those tapering from higher dose ( $\geq 90$  MME/day) and/or longer duration ( $\geq 12$  months) LTOT.

**Conclusions:** This within-individual study found that LTOT recipients who experienced a dose taper had greater risk of SUD or overdose around the onset of the taper. Much of that risk escalation may precede -rather than result from- changes in monthly dose.

## Epidemiology Research Branch

**Charting The Decline Of The Fourth Wave: US Overdose Deaths By Race, Ethnicity, And Substance Involvement** Friedman JR, Palamar JJ, Ciccarone D, Gaines TL, Borquez A, Shover CL, Strathdee SA. Addiction. 2026 [Online ahead of print, June 2].

**Aims:** To characterize decreases in overdose death rates in the United States between 2023 and 2024 by race/ethnicity, and substance involvement.

**Design:** Population-based study of national death records accessed via the Centers for Disease Control and Prevention (CDC) Wide-ranging ONline Data for Epidemiologic Research (WONDER) platform using an underlying cause of death approach.

**Setting:** United States (US).

**Participants/cases:** All individuals who died from drug overdose between January 1999 and December 2024.

**Measurements:** Annual overdose deaths per 100,000 population. Year of occurrence of overdose death; substance involvement; race/ethnicity of decedents.

**Findings:** After many years of increases, the US overdose death rate dropped 24.4% between 2023 and 2024. Decreases reflected declining illicit fentanyl-involved deaths (with and without stimulant involvement). The fourth wave of the US overdose crisis-defined by deaths involving

fentanyl together with stimulants-declined for the first time in 2024. Despite overall decreases, deaths involving stimulants without fentanyl, and xylazine, continued to represent a growing fraction of overdose fatalities. Non-Hispanic Black and African Americans had the largest decrease in death rates in 2023-2024-falling 29.3%, but remained elevated at 36.0 per 100,000, 1.51 times higher than the national average of 23.7 per 100,000. Non-Hispanic American Indian and Alaska Native individuals had the highest overdose death rates rate in 2024, at 50.8 per 100,000, representing 2.15 times the national average rate, and experienced a below-average relative decrease of 20.1%.

**Conclusions:** All four previously defined waves of the US overdose crisis are in decline, as deaths involving illicit fentanyl, with and without stimulants, are dropping sharply. Concurrently, the fraction of overdose deaths involving stimulants without fentanyl and those involving xylazine, continued to increase. While racial disparities in drug overdose death rates narrowed slightly during this period, significant gaps remain, with the highest rates among American Indian, Alaska Native, and Black individuals.

**Prevalence And Reasons For Microdosing Cannabis, Psilocybin, LSD, and MDMA Among U.S. Adults** Yang KH, Satybaldiyeva N, Kepner W, Friedman J, Ping S, Leas EC. Am J Prev Med. 2026; 71(4): 108381.

**Introduction:** Microdosing involves consuming low doses of psychoactive substances, typically between 1/5th and 1/20th of a recreational dose. Despite increasing public attention to cannabis and psychedelics amid evolving drug policies, epidemiologic data on microdosing remain limited.

**Methods:** A cross-sectional, web-based survey (Characterizing the Epidemiology of Cannabidiol Use Survey) of 1,523 U.S. adults was conducted in October-November 2023 and analyzed in 2024-2025 using the Ipsos KnowledgePanel. Participants reported lifetime microdosing of cannabis, psilocybin, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine (MDMA). Lifetime prevalence, frequency, and reasons for microdosing were assessed, along with associations with demographics, mental health, quality of life, and cannabis and psychedelic policy environments. Survey weights were applied to generate nationally representative estimates.

**Results:** Cannabis was the most commonly microdosed substance (9.4%; 95% CI=8.0, 10.7; 24.1 million adults), followed by psilocybin (5.3%; 95% CI=4.3, 6.3; 13.7 million adults), LSD (4.8%; 95% CI=3.8, 5.9; 12.4 million adults), and MDMA (2.2%; 95% CI=1.5, 2.9; 5.7 million adults). Cannabis (41.2%; 95% CI=33.3, 49.5) was primarily microdosed for medical purposes (e.g., to manage pain), whereas psilocybin (66.6%; 95% CI=56.9, 75.1), LSD (59.2%; 95% CI=46.5, 70.8), and MDMA (86.0%; 95% CI=68.8, 94.5) were more commonly microdosed for recreational purposes (e.g., to get less high). Across all substances, lifetime microdose use was more prevalent among respondents reporting poorer mental health and among those residing in jurisdictions that permitted recreational cannabis use and had decriminalized psychedelic possession.

**Conclusions:** Despite cannabis, psilocybin, LSD, and MDMA remaining illegal at the federal level, a considerable number of U.S. adults reported having microdosed these substances in their lifetime. Microdosing was associated with poorer mental health and was more common among respondents who lived in environments with fewer restrictions on the use of cannabis and psychedelics. As policy reforms continue to expand, the prevalence of microdosing may increase, making ongoing surveillance essential for evidence-based public health responses.

## **THERAPEUTICS AND MEDICAL CONSEQUENCES RESEARCH**

### **DLPFC rTMS Is More Effective Than Sham Or Orbitofrontal Stimulation For Smoking Cessation And Alters Frontal Brain Activity: A Double-Blind, Sham-Controlled Randomized Clinical Trial**

Li X, Caulfield KA, Carpenter MJ, Ramakrishnan V, Herrmann ES, Dancy M, George MS. J Psychiatr Res. 2026; 197: 187-195.

**Objective:** Repetitive transcranial magnetic stimulation (rTMS) shows promise for smoking cessation, but its neural mechanisms remain unclear. It is unknown whether rTMS reduces smoking by enhancing executive control or suppressing reward-related brain activity. This study aimed to address this gap by comparing excitatory and inhibitory rTMS targeting distinct cortical circuits implicated in tobacco use disorder (TUD).

**Methods:** In a double-blind, sham-controlled design, treatment-seeking individuals with TUD were randomized to 15 sessions of personalized, fMRI-guided, E-field-dosed rTMS: (1) sham rTMS, (2) excitatory 10 Hz rTMS over the left dorsolateral prefrontal cortex (L-DLPFC; 3000 pulses/session), or (3) inhibitory 1 Hz rTMS over the left medial orbitofrontal cortex (L-mOFC; 900 pulses/session). fMRI scans were conducted pre- and post- 15 sessions of rTMS. Primary outcomes were reductions in cigarettes per day (CPD) and changes in blood-oxygen-level-dependent (BOLD) activity.

**Results:** Thirty-five of 46 participants completed the study (sham = 9; 10 Hz L-DLPFC = 12; 1 Hz L-mOFC = 14). The 10 Hz L-DLPFC group showed a significantly greater CPD reduction than 1 Hz L-mOFC and sham (-11.14 vs. -4.92 and -6.43, respectively;  $p < 0.0001$ , partial  $\eta^2 = 0.135$ ). rTMS to the L-DLPFC also increased prefrontal activity and decreased orbitofrontal activity ( $p < 0.05$ ), with the degrees of CPD reduction correlating with enhanced activation in L-DLPFC ( $p < 0.05$ ).

**Conclusions:** Enhancing executive control via 10 Hz rTMS over the L-DLPFC was more effective for smoking reduction than suppressing reward circuitry with 1 Hz rTMS over the L-mOFC. Findings suggest that strengthening prefrontal regulation of reward processing is a key mechanism by which rTMS promotes smoking cessation. NIDA Grant Support: UH3DA048507, UG3DA048507

### **Clavulanic Acid Attenuated Cocaine Craving In Individuals With Cocaine Use Disorder**

Morrison MF, Cunningham R, Walters MI, Yu D, Lu X, Maser J, Kampman KM.

Psychopharmacol Bull. 2026; 56(2): 94-107.

This randomized, controlled trial examined the safety of clavulanic acid (CLAV), a GLT-1 (astrocytic glutamate transporter) modulator, in combination with intravenous cocaine to determine whether CLAV can be safely studied in outpatients with cocaine use disorder who may continue to use cocaine. Participants were adults with moderate to severe cocaine use disorder planning to continue regular cocaine use. In a placebo controlled, crossover, inpatient study, the safety of 3 doses of oral CLAV (250 mg/day, 500 mg/day, and added later 750 mg/day) were studied in combination with 40 mg intravenous cocaine on a medical unit with close cardiac monitoring and pharmacokinetic sampling. Ten participants, 8 men and 2 women with cocaine use disorder, were studied with all participants receiving CLAV (250 mg, 500 mg, and placebo) and 5 participants receiving the additional 750 mg dose, in combination with cocaine. There were no clinically significant drug or dose related changes in vital signs, electrocardiogram intervals, pupillary diameters between CLAV and placebo. CLAV 500 mg decreased cocaine craving, using the 10 item Cocaine Craving Questionnaire-Brief, with a large effect size (Cohen's  $d = 1.25$ ). Thirty-two mild to moderate adverse events were recorded, with

most drug related events being gastrointestinal. CLAV, at the doses of 250 mg, 500 mg, and 750 mg was reasonably well tolerated and safe in combination with intravenous cocaine. Associated adverse events were mild to moderate and resolved. CLAV 500 mg was associated with decreased craving for cocaine in people with cocaine use disorder. NIDA Grant Support: U01DA048517, U54DA039002

**Triazole 187 Is A Biased KOR Agonist That Suppresses Itch Without Sedation And Induces Anxiolytic-Like Behaviors In Mice** Volf A, Brust TF, Kobylski RR, Czekner KM, Stahl EL, Cameron MD, Trojaniak AE, Wood AB, Aubé J, Bohn LM. Neuropsychopharmacology. 2026; 51(8): 1485-1496.

Kappa opioid receptor agonists are clinically used to treat pruritus and have therapeutic potential for the treatment of pain and neuropsychiatric disorders. We have previously shown that triazole 1.1 is a G protein signaling-biased KOR agonist, that can suppress itch without producing signs of sedation in mice. This profile was recapitulated in rats and non-human primates; however, triazole 1.1 had limited potency as an antipruritic. Here we describe a more potent, G protein signaling-biased agonist, triazole 187. Triazole 187 is a potent antipruritic agent and does not decrease spontaneous locomotor activity; interestingly, it produces anxiolytic-like behaviors in mice, an effect not observed for triazole 1.1. In addition to curbing sedation, triazole 187 produces only mild diuresis, resulting in 30% of urine output induced by U50,488H at a dose that is more than 100-fold the antipruritic potency dose. Compounds like triazole 187 may present a means to treat anxiety that is independent of or accompanied by persistent chronic itch while avoiding sedation and diuresis accompanied by typical KOR agonists. NIDA Grant Support: R01DA031927, R01DA048490, S10OD030332

**Compacted Solid Implant Formulations For Long-Term Buprenorphine Delivery** Otte A, Park K. J Control Release. 2026; 392: 114722.

Opioid use disorder (OUD) remains a major public health challenge in the United States, and medication-assisted treatment with buprenorphine, a  $\mu$ -opioid receptor partial agonist, is a cornerstone of effective management. Currently marketed long-acting buprenorphine products provide drug release for 1 week or 1 month. Here, we describe the development of new biodegradable PLGA rod formulations capable of sustaining buprenorphine release for  $\geq 3$  months. Poly(lactide-co-glycolide) (PLGA) and buprenorphine free base were thermally compacted into solid rods using a plastometer at 165-180 °C under a compression load of 4-16 kg. A primary objective of this formulation strategy was to minimize the initial burst release characteristic of conventional PLGA systems by reducing interconnected pore formation through compaction. The resulting implants contain 70% w/w buprenorphine and are straightforward to manufacture. In vivo pharmacokinetic evaluations in both rat and dog models demonstrated sustained plasma buprenorphine concentrations for more than 3 months. These long-acting implants may provide extended therapeutic coverage compared with existing products, potentially improving patient adherence and clinical outcomes in OUD treatment. NIDA Grant Support: UG3DA059270, UH3DA048774

**An Opioid-Withholding Human Laboratory Paradigm During Opioid Agonist Treatment For Opioid Use Disorder And Chronic Pain: Phase- And Dose-Dependent Effects Of Cannabidiol** Costa GPA, Sofuoglu M, Compton P, Ranganathan M, Pittman B, De Aquino JP. Neuropsychopharmacology. 2026 [Online ahead of print, May 20].

Even during opioid agonist treatment (OAT) for opioid use disorder (OUD), chronic pain remains common and unrelieved, as opioids impair endogenous pain modulation. Cannabidiol (CBD) may represent a non-opioid adjunct, but its effects among persons with co-occurring OUD and chronic pain receiving OAT are unknown. We conducted a randomized, double-blind, placebo-controlled crossover study evaluating acute oral CBD (400, 800, 1200 mg) effects on pain modulation, craving, and cognition among 23 participants (11 female) with co-occurring OUD and chronic pain receiving methadone (mean dose 85.7; SD: 29.7 mg/day). An opioid withholding model assessed CBD effects during two phases: Pre-OAT (delayed methadone dosing) and Post-OAT (following methadone administration). Primary outcomes included conditioned pain modulation (CPM; descending inhibition) and temporal summation of pain (TSP; ascending facilitation) assessed via quantitative sensory testing. Secondary outcomes included heat pain threshold and tolerance, and exploratory outcomes included cue-induced craving and cognitive performance. Pre-OAT, CBD was associated with a significant linear dose-response for enhanced descending pain inhibition ( $p = 0.034$ ;  $d' = 0.34$  at 800 mg,  $d' = 0.59$  at 1200 mg). Post-OAT, CBD 1200 mg was associated with significant reduction of heat pain threshold relative to placebo ( $d' = -0.63$ ,  $p = 0.017$ ). CBD showed no significant effects on opioid craving. Cognitive performance was preserved across doses and CBD demonstrated a favorable safety profile. Among persons with co-occurring OUD and chronic pain receiving OAT, CBD demonstrated phase-dependent effects on pain modulation-dose-dependent enhanced descending inhibition Pre-OAT but worsened pain sensitivity Post-OAT at higher doses. These findings highlight OAT timing as a critical consideration for CBD-based pain interventions. NIDA Grant Support: R01DA060066, K23DA052682

## **CLINICAL TRIALS NETWORK RESEARCH**

### **The Association Between Sleep Disturbance And Stimulant Use: A Cross-Lagged**

**Examination** Horigian VE, Schmidt RD, Feaster DJ, Duan R, Gonzalez ST, Hefner K, Shmueli-Blumberg D, Vena A, Moran LM, DiCamillo CA, Shafazand S, Tross S, Feinberg J. *Addiction*. 2026; 121(8): 2116-2126.

**Background and aims:** Sleep disruptions increase the risk of substance misuse. Substance use—especially stimulants—can increase acute and chronic sleep dysfunction. This study aimed to estimate the associations between sleep disturbance and stimulant use over time among participants with stimulant use disorder (StUD).

**Design:** In this secondary analysis, a Random Intercept Cross-Lagged Panel Model (RI-CLPM) was used to assess sleep disturbance and stimulant use over 8 weeks among participants with StUD.

**Setting:** United States of America.

**Participants:** The analysis included 793 participants with StUD enrolled across 3 randomized controlled trials in the National Institute on Drug Abuse's Clinical Trials Network (CTN): CTN-0037, CTN-0048 and CTN-0068.

**Measurements:** Self-reported sleep disturbance was harmonized as a binary indicator across trial measures at each week. Stimulant use days per week were captured by Timeline Follow Back. Baseline covariates included age, sex, race/ethnicity, employment status, presence of depressive symptoms, any psychiatric history, treatment arm and trial.

**Findings:** Sleep disturbance was associated with a higher average number of stimulant use days the following week [ $\beta = 0.15$ , 95% confidence interval (CI) = 0.09, 0.22,  $P < 0.001$ ], and greater stimulant use was linked to increased odds of subsequent sleep disturbance (odds ratio = 1.20, 95% CI = 1.14, 1.26,  $P < 0.001$ ).

**Conclusions:** Higher-than-usual stimulant use appears to be associated with increased likelihood of sleep disturbance the following week, and vice versa.

**Keywords:** random-intercept cross-lagged panel model; sleep; sleep disturbance; sleep problems; stimulant use; substance use; substance-related disorders.

### **Comparative Effectiveness Of Social-Contextual Treatments For Improving Substance-Related Problems Among Black Adults: An Individual-Level Data Synthesis**

Espinosa A, Haeny AM, Ruglass LM, McCuistian C, Vena A, Roundtree C, Lopez J, Morgan-López AA, Burlew AK. *Addiction*. 2026; 121(7): 1699-1708.

**Background and aims:** Despite similar substance use levels, Black adults experience greater family, legal, employment and other social-contextual challenges related to recovery than other groups. Substance use treatments that address both substance use and social-contextual factors are uniquely positioned to address these substance-related problems and produce more sustainable improvements in social functioning than treatment as usual (TAU) or behavioral controls (Control). The aim of this study was to evaluate changes in substance-related problems among Black adults, focusing on the comparative effectiveness between social-contextual treatments and TAU/Control.

**Design:** Individual-level data synthesis based on secondary analysis of Black adults enrolled in the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN).

**Setting:** All data were collected in the primary studies between 2001 and 2008 at clinics across the United States.

**Participants:** Black adults who reported cocaine and/or opioid use across nine studies within the NIDA CTN. The sample used herein consisted of individuals from five of these studies who provided data on substance-related problems ( $n = 532$ ; mean age = 39.34; standard deviation = 9.6).

**Measurements:** There were two treatment conditions: Social-contextual (e.g. Motivational Interviewing, Seeking Safety, STAGE 12) and TAU/Control. Moderated nonlinear factor analysis estimated latent scores for substance-related problems, using subscales from the Addiction Severity Index, while accounting for measurement noninvariance across studies, time and covariates. Linear mixed models estimated latent score differences over time between social-contextual treatments and TAU/Control during treatment and from the end of treatment through 12-month follow-up.

**Findings:** Both treatment groups improved across substance-related problem areas from baseline to the end-of-treatment (Cohen's  $d = -0.10$  to  $d = -0.47$ ), with effects maintained at 12-month follow-up. Although social-contextual treatments did not statistically significantly outperform TAU/Control from baseline to end-of-treatment, they showed greater effects from end of treatment to 12-month follow-up in family/social [Cohen's  $d$  difference ( $\Delta d$ ) = -0.47, 95% confidence interval (CI) = -0.57 to -0.38], legal ( $\Delta d = -0.20$ , 95% CI = -0.31 to -0.10) and psychiatric problems ( $\Delta d = 0.29$ , 95% CI = -0.38 to -0.20) than TAU/Control. Sensitivity analyses indicated that Seeking Safety and STAGE 12 predominantly drove post-treatment improvements in family/social problems.

**Conclusions:** Substance use treatment may yield broader, delayed benefits beyond substance use reduction among Black adults in the United States. Compared with treatment-as-usual, social-contextual treatments can yield more sustainable effects in legal, family and psychiatric areas among Black adults, with interventions such as Seeking Safety and STAGE 12 showing particular benefits in addressing family-related challenges.

**Keywords:** individual-level data synthesis; social functioning; social-contextual treatments; substance use; substance-related problems; treatment as usual.

**Collaborative Care Intervention For Risky Opioid Use Among Primary Care Patients: The STOP Randomized Clinical Trial** McNeely J, Subramaniam GA, Stone R, Mazel S, Appleton N, Rostam-Abadi Y, Bunting AM, Shi Y, Lovejoy TI, Gelberg L, Beers D, Kline M, Zhang S, Kim T, Case A, McCormack J, Incze MA, Liebschutz JM; STOP Trial Site Principal Investigators. *Addiction*. 2026 [Online ahead of print, June 22].

**Background and aims:** Individuals who engage in illicit or nonmedical opioid use may have elevated risk of health and social consequences, including progression to opioid use disorder (OUD). Preventive interventions to reduce this risk are lacking. This trial tested the impact of a primary care-integrated collaborative care approach for reducing risky opioid use, defined as nonmedical use of prescription opioids or any use of illicit opioids.

**Design:** Cluster-randomized controlled trial randomized primary care providers (PCPs) and their patients into the Subthreshold Opioid Use Disorder Prevention (STOP) intervention or enhanced usual care (EUC).

**Setting:** Primary care clinics at 5 U.S. sites.

**Participants:** PCPs and their patients were recruited January 2021-May 2023. A total of 119 PCP clusters (STOP = 48, EUC = 51) and 202 patients (STOP = 88, EUC = 114) enrolled. Eligible patients were adults ( $\geq 18$  years) having current risky opioid use, without moderate-severe OUD. Patient participants were majority female (63.4%), white (70.8%) and non-Hispanic (96.5%), with a mean age of 55.7 [standard deviation (SD) = 12.7] years. At baseline, 63.4% of participants had moderate-severe pain (Brief Pain Inventory) and below average physical (79.2%) and mental (62.4%) health (SF-12).

**Interventions:** The STOP collaborative care intervention consisted of brief advice from the PCP about reducing risky opioid use, meetings with a clinic-embedded nurse care manager over 12 months and remote health coaching (2-6 sessions). Both groups received primary care treatment as usual and overdose risk reduction materials.

**Measurements:** The primary outcome was total days of risky opioid use, recorded from 6 monthly electronic surveys. A key secondary outcome was moderate-severe OUD at 6 and 12 months.

**Findings:** A total of 77 (87.5%) STOP and 107 (93.9%) EUC participants completed the 6-month assessment period. The primary outcome analysis used the Intention-to-Treat sample with multiple imputations of missing data. Mean days of risky opioid use at 180 days were lower in STOP than EUC [12.2 (SD = 27.73) vs. 15.5 (SD = 32.64)]; the difference between groups adjusted for baseline risky opioid use was not statistically significant (rate ratio 0.95, 95% confidence interval = 0.52-1.74). One STOP participant (1.1%) and 13 EUC participants (11.4%) developed moderate-severe OUD at 6 months, and 3 (3.4%) STOP and 6 (5.3%) EUC participants had moderate-severe OUD at 12 months ( $P < 0.001$ ).

**Conclusions:** This cluster-randomized controlled trial did not find evidence that the STOP intervention for reducing risky opioid use produced greater reductions over 6 months compared

with enhanced usual care, though fewer intervention participants progressed to moderate-severe opioid use disorder. Patients had a high burden of pain and comorbidities that may present challenges to reducing opioid use.

**Keywords:** collaborative care; opioid misuse; opioid-related disorders; pain; prevention; primary care; substance use disorder.

**Burden Of All-Cause And Cause-Specific Mortality Among Individuals With Medications For Treatment Of Opioid Use Disorder: A Matched Cohort Study From 4 US Health Systems, 2012-2021** Nguyen AP, Narwaney KJ, Glanz JM, Goodrich G, Campbell CI, Xu S, Loree AM, Christine PJ, Binswanger IA. J Subst Use Addict Treat. 2026 [Online ahead of print, April 15].

**Objectives:** To estimate all-cause and cause-specific mortality burden in patients who received medication treatment for opioid use disorder (OUD).

**Methods:** We conducted a cohort study of 27,230 patients who received medications for opioid use disorder (MOUD), buprenorphine or naltrexone, matched 1:1 to individuals without MOUD from 4 US health systems in California, Colorado, and Michigan between 2012 and 2021. We calculated standardized mortality ratios (SMRs) with bootstrapped 95% CI to assess mortality burden.

**Results:** Patients who received treatment for OUD were 4 times more likely to die from any cause (SMR 4.37, 95% CI 3.80-4.64) and 37 times more likely to die from drug overdose (SMR 37.58, 95% CI 29.33-55.09; 41.6% of all deaths) compared to demographically similar individuals. Deaths from non-overdose causes showed modest but significant burden (SMR 2.68, 95% CI 2.31-2.86; 58.4% of deaths). The top contributors to non-overdose deaths were circulatory system diseases (SMR 3.06, 95% CI 1.73-3.63; 13.9% of deaths), other external causes (SMR 4.50, 95% CI 3.64-5.62; 11.3% of deaths), and cancers (SMR 1.59, 95% CI 1.30-1.86; 9.4% of deaths), which all showed elevated mortality.

**Conclusions:** Continued efforts are needed to prevent high burden of mortality from both overdose and non-overdose causes among patients with MOUD treatment.

**Keywords:** Comorbidities; Excess mortality; Opioid use disorder.

**External Validation Of Epic's Risk Of Opioid Abuse And Overdose Model Among Primary Care Patients In Three Health Systems** Hooker SA, Rossom RC, Haapala J, Crain AL, Miley K, Olson AW, Kane S, Christensen K, O'Connor PJ, Bart G, Wright EA. J Gen Intern Med. 2026 [Online ahead of print, February 17].

**Background:** Most people with opioid use disorder (OUD) do not receive evidence-based treatment. To increase treatment rates, primary care clinics may choose to implement risk prediction tools available in the electronic health record (EHR) to identify patients with a high risk of OUD or overdose.

**Objective:** To externally validate Epic's cognitive computing model to predict the Risk of Opioid Abuse or Overdose (referred to as the Opioid Risk Score; ORS) in three large integrated health systems.

**Design:** Prospective cohort study secondary to an ongoing clinical trial.

**Participants:** Patients (N = 704,764) aged 18-75 who had a primary care encounter during the study period (April 2021-December 2022) and did not have an OUD diagnosis at index.

**Main measures:** Data were extracted from the EHR. The index date was defined as the first date within the study period where the patient met eligibility criteria and had an ORS calculated by

the EHR. The binary outcome variable was whether the patient was diagnosed with OUD or experienced an opioid overdose within 12 months of the index date.

**Key results:** Most patients were classified as low risk on ORS (99.6%). Few patients experienced an OUD diagnosis or overdose in the 12-month follow-up period (0.3%). The model correctly classified 185 of 2362 patients who experienced an event (sensitivity 0.0783, 95% CI 0.0675, 0.0892) and 699,926 of 702,406 patients who did not experience an event (specificity 0.9965, 95% CI 0.9963, 0.9966). Few patients with high ORS experienced the event (PPV 0.0694, 95% CI 0.0598, 0.0791). The model had excellent discrimination (c-statistic = 0.815) but was poorly calibrated, underestimating risk for patients who experienced the outcomes.

**Conclusions:** Epic's ORS demonstrated excellent discrimination but very low sensitivity across three large integrated health systems. Health systems should exercise caution before implementing vendor risk prediction models without validating their use in their patient populations.

**Clinical trial number:** Not applicable.

**Keywords:** electronic health record; healthcare delivery; opioid use disorder; overdose; prediction; risk estimation.

## **HIV/AIDS**

**The Association Between Receiving Medications For Opioid Use Disorder And Human Immunodeficiency Virus Testing: Findings From The Rural Opioid Initiative.** Zinsli KA, Mixson LS, Delaney JA, Feinberg J, Stopka TJ, Seal DW, Smith GS, Pho MT, Wu EL, Jenkins W, Cooper HLF, Young AM, Khoury D, Friedmann PD, Miller WC, Go VF, Korthuis PT, Spencer H, Westergaard RP, Tsui JJ. J Addict Med. 2026 [Online ahead of print, March 24].

**Objectives:** Injection drug use is associated with increased risk of blood-borne infectious disease transmission. People with opioid use disorder (OUD) may be less likely to receive health care services, including human immunodeficiency virus (HIV screening), especially in rural areas. Addiction treatment settings may provide additional opportunities to screen for HIV in this population.

**Methods:** The rural opioid initiative (ROI) conducted a survey of people who use drugs (PWUD) on substance use, health care access, and utilization. From January 2018 to March 2020, PWUD were enrolled across 65 rural counties in 10 US states. Eligible participants either used opioids or reported injecting any drug "to get high" in the past 30 days. We evaluated the association between reporting past 30-day medication for OUD (MOUD) receipt and past-year HIV testing using relative risk regression.

**Results:** Participants (N = 2649, mean age = 36 y) were predominantly male (57%), reporting White race (85%) and non-Hispanic ethnicity (96%). Among participants receiving MOUD (methadone or buprenorphine) in the past year, 42% (179/431) were HIV-tested in the past year compared with 29% (636/2,218) among those not receiving MOUD. The prevalence of HIV testing in the past year was 1.42 times greater when comparing those who received MOUD in the past 30 days compared with those who did not (95% CI: 1.25-1.62).

**Conclusions:** Recent HIV testing prevalence among this rural population of PWUD was low, given testing guidelines. Future research should explore ways to increase testing in rural drug treatment settings and whether there are differences by treatment setting type. NIDA Grant Support: UH3DA044798, UG3DA044831, T32DA057920, UG3DA044829, UH3DA044826, UH3DA044830, UH3DA044831, P30AI027757, UG3DA044798, U24DA044801,

UH3DA044823, UG3DA044822, UH3DA044829, UG3DA044826, UG3DA044830, U24DA048538, UG3DA044823, UG3DA044825, UH3DA044822

**Exploring The Impact Of Reduction In Methamphetamine Use On Sexual Risk Behaviors Among Men Who Have Sex With Men And Women: Findings From The ADAPT- 2 Trial**

Okafor CN, Yoon JH, Jean-Berluce D, Mayes TL, Shoptaw S, Trivedi MH, Potter JS, Schmitz J. Int J Behav Med. 2026; 33(3): 487-493.

**Background:** Methamphetamine (MA) use has been linked to engaging in sexual risk behaviors (SRBs) that are associated with HIV/STIs, particularly among men who have sex with men (MSM) and men who have sex with men and women (MSMW; hereafter MSM/W). The objectives of this analysis were to determine whether reduced MA is associated with decreases in SRBs in a sample of MSM/W.

**Method:** Data came from the ADAPT- 2 trial, a randomized, double-blind, two-stage sequential parallel design trial evaluating extended-release injectable naltrexone (NTX) and oral bupropion (BUP) vs. placebo for MA use disorder. In the first 6 weeks of the trial (stage 1), participants were randomized to receive NTX-BUP or placebo. In the second 6 weeks, participants in the placebo group who did not have a treatment response were rerandomized (stage 2). For this secondary analysis, the independent variable was the number of MA-negative urine drug screens (UDS). The dependent variables included three different types of SRBs. Regression models of the independent and dependent variables were adjusted for age, race/ethnicity status, marital status, treatment assignment, and baseline SRBs.

**Results:** Of the 151 participants, median age was 40 years and majority were non-Hispanic white (52%) and completed more than high school education (82%). Each additional MA-negative UDS was associated with a 7% (adjusted rate ratio (aRR) = 0.93; 95% CI, 0.87, 0.99) reduction in total number of sex partners in stage 2 only. Each additional MA-negative UDS was associated with a 13% (aRR = 0.87 95%; confidence interval (CI), (0.76, 0.98)) and 9% (aRR = 0.91; 95% CI, 0.84, 0.99) reduction in number of condomless sexual encounters in stage 1 and stage 2, respectively. Lastly, each additional MA-negative UDS was associated with a 16% (aRR = 0.84; 95% (CI), 0.75, 0.94)) and 27% (aRR = 0.73; 95% CI, 0.64, 0.84) reduction in number of sexual encounters when high on MA.

**Conclusion:** Our analysis showed that reductions in MA use was associated with reductions in several sexual risk behaviors associated with HIV/STI. These findings provide further support for exploring reductions in sexual risk behaviors as a clinical endpoint in future treatment interventions for MA use.

## **INTRAMURAL RESEARCH**

**A  $\mu$ -Opioid Receptor Superagonist Analgesic With Minimal Adverse Effects** Gomez JL, Ventriglia EN, Frangos ZJ, Sulima A, Robertson MJ, Sacco MD, Budinich RC, Giosan IM, Xie T, Solis O, Tischler AE, Bossert JM, Caldwell KE, Bonbrest H, Essmann A, Garçon-Poca ZM, Choi S, Noya MR, Limiac F, Arce A, Glatfelter GC, Robinson M, et al. *Nature*. 2026; 652(8112): 1393-1404. Erratum in: *Nature*. 2026; 653(8114).

Developing safe and effective pain medications is an ongoing challenge for human health. Agonists for the  $\mu$ -opioid receptor (MOR) are essential pain medications, but their high intrinsic efficacy also induces adverse side effects, including respiratory depression, constipation, tolerance, dependence, withdrawal and addiction. Strategies to limit adverse effects traditionally include developing MOR agonists that have low intrinsic efficacy or that preferentially activate G-protein signalling over  $\beta$ -arrestin signalling<sup>8</sup>. Here we identify a novel MOR agonist with supramaximal intrinsic efficacy and a unique pharmacological profile that produced effective analgesia in rodents with minimal adverse effects. N-desethyl-fluornitrazene (DFNZ) was derived from a class of synthetic benzimidazole opioids called nitazenes. DFNZ has impaired brain penetrance, a unique spatiotemporal MOR cellular signalling profile, and diminished efficacy at the MOR-galanin 1 receptor (GAL1) heteromer. DFNZ does not induce respiratory depression, tolerance or MOR downregulation after repeated exposure. Compared with other MOR agonists, DFNZ has limited effects on dopamine neurotransmission in nucleus accumbens and weaker reinforcing effects in the drug self-administration procedure. These results provide novel insights about MOR and nitazene pharmacology, have important implications for pain and addiction treatment, and challenge the prevailing dogma that high-efficacy MOR agonists cannot constitute safe and effective therapeutic agents.

## **Deviation In Development Of Dorsal Association Tracts During Preadolescence Links To Concurrent And Future Cognitive Performance And Transdiagnostic Psychopathology**

Wang D, Hammond CJ, Salmeron BJ, Xiao X, Murray L, Gu H, Zhai T, Quam A, Hill J, Nguyen H, Lu H, Janes A, Ross TJ, Yang Y. *Nat Commun*. 2026; 17(1): 2943.

Many psychiatric disorders begin during adolescence, coinciding with the rapid development of brain white matter (WM). However, it remains unclear whether deviations from normal WM development during this period contribute to psychopathology. In this study, we developed normative models of brain age based on specific WM tracts using three large-scale developmental datasets (~ 10,000 subjects). We found that tract-specific deviations in WM development of association and limbic/subcortical systems were linked to concurrent and future cognition and psychopathology. The spatial pattern of the association system aligned closely with high-order brain networks and mitochondrial maps. Importantly, delayed brain-age especially in dorsal association tracts predicted psychiatric disorders across diagnoses and disorder onset over a 2-year follow-up. By identifying tract-specific WM development during preadolescence as a predictor of cognitive capacity and psychiatric risks, this study provides a framework for tracking individualized brain development and understanding the neurobiological underpinnings of cognition and transdiagnostic psychopathology.

### Persistent Vulnerability To Heroin Relapse After More Than One Year Of Abstinence In Rats

Madangopal R, Drake OR, Pham DQ, Lennon VA, Weber SJ, Lee J, Sobukunola A, Holmes AR, Nurudeen O, Shaham Y, Hope BT. *Neuropsychopharmacology*. 2026; 51(8): 1519-1523.

Relapse to opioid use during abstinence is often triggered by drug-associated cues but the persistence of this effect during prolonged abstinence is unknown. Using a rat model, we found that relapse provoked by heroin-predictive discriminative stimuli persisted for over one year of abstinence, suggesting enduring, potentially lifelong opioid relapse vulnerability.

### Physiological arousal as a predominant source of individual differences in functional brain networks

Hill JA, Zhai T, Korponay C, Welsh JC, Salmeron BJ, Ross TJ, Yang Y, Frederick BD, Janes AC. *Commun Biol*. 2026 [Online ahead of print, July 10].

Characterizing individual variation in brain network organization is essential for developing fMRI-based biomarkers in precision psychiatry. We show that arousal, assessed by systemic low-frequency oscillation (sLFO) amplitude in the fMRI signal, is strongly associated with interindividual variability in functional brain network properties (e.g.,  $R = 0.70$  for default mode network (DMN)-dorsal attention network (DAN) connectivity;  $R = -0.63$  for DMN dynamics), with replication across independent sessions and samples. These relationships persist after regressing the sLFO out of the BOLD signal and are replicated using established physiological arousal indices, indicating that arousal-related physiology significantly contributes to variability in brain network measures. Pharmacological manipulation shows that increased arousal under catecholaminergic agonism is associated with enhanced network differentiation, whereas antagonism produces the opposite effect. These findings highlight arousal-related physiological processes as a major contributor to individual differences in functional brain network properties as estimated with fMRI and indicate that catecholaminergic modulation is associated with these effects via arousal-related processes.

### Experimenter-Free Pain Assessment In Mice Using A Thermal Gradient Ring And Functional Linear Models

Garcia A, Siemian JN, Loewinger G, Yadav PM, Sarsfield S, Pereira F, Aponte Y. *Pain Rep*. 2026; 11(4): e1469.

**Introduction:** Traditional preclinical laboratory animal tests of pain can be suboptimal for many reasons, such as experimenter bias, interference of motor effects, and a lack of emotional or motivational pain process engagement. These shortcomings may also impede the search for novel pain therapies. Recently, thermal preference or gradient tests have gained popularity, and several apparatuses are either commercially available or can be self-made. The thermal gradient ring (TGR) offers a high-resolution thermal preference assessment and removes spatial confounds that may arise in two-chamber or linear designs.

**Objectives:** The aim of this study was to determine the effectiveness of the TGR as a tool to assess pharmacotherapies and develop an appropriate statistical framework for data analysis.

**Methods:** We examined the effects of 17 treatment conditions, including pronociceptive and antinociceptive compounds, in male and female mice. Behavioral data were analyzed using functional linear models (FLM), enabling hypothesis testing of temperature preference and motor activity at each timepoint of the TGR session.

**Results:** Functional linear models captured the temporal dynamics and magnitudes of treatment effects and identified locomotor side effects that were obscured by traditional session-averaged

analyses. Minute-by-minute comparisons revealed distinct temporal progressions of treatment effects and locomotor side effects.

**Conclusion:** Our findings demonstrate that the TGR-FLM combination is a robust framework and a valuable tool for screening novel pain therapies.

## **ADOLESCENT BRAIN COGNITIVE DEVELOPMENT (ABCD) AND HEALTHY BRAIN CHILD DEVELOPMENT (HBCD) STUDIES**

**Prenatal Cannabis And Opioid Exposure Are Associated With Smaller Birth Size In The HEALthy Brain And Child Development (HBCD) Study** Bandoli G, Psaras C, Bakhireva LN, Burris HH, et al. HBCD Consortium. *Pediatrics*. 2026; 157(6): e2025076404

Prenatal substance exposure has been associated with adverse birth outcomes, but prior studies have produced inconsistent findings due to methodological limitations, including small sample sizes, reliance on self-report, and inadequate characterization of substance use. Using data from the first public release of the HEALthy Brain and Child Development (HBCD) Study, the authors examined associations between more than minimal prenatal exposure to nicotine, alcohol, cannabis, and opioids and birth outcomes among 660 mother-infant dyads. After accounting for maternal and other confounding factors, prenatal cannabis and opioid exposures were each associated with lower birthweight and lower birthweight-for-gestational age, whereas associations with nicotine and alcohol were not statistically significant, and no significant relationships were observed with gestational age at delivery. These findings provide prospective evidence supporting current recommendations to avoid cannabis use during pregnancy, highlight the importance of considering prenatal opioid exposure when counseling expectant parents, and demonstrate the value of the HBCD Study's comprehensive assessment of prenatal substance exposure for understanding its effects on child health and development.

**Characterizing Infant Leg Movements Using 72-Hour Wearable Sensor Data: Descriptive Analysis From A Large, Heterogeneous Sample Of Infants 0–2 Months Of Age From The HEALthy Brain And Child Development Study** Oh J, Pini N, Nebeker C, Smith BA, Novel Technology/Wearable Sensors Working Group. *Infant Behavior and Development*. 2026; 84: 102199

Spontaneous limb movements during early infancy provide the foundation for later motor development, yet existing knowledge has been limited by small, homogeneous study samples and brief laboratory observations. Leveraging data from the HEALthy Brain and Child Development (HBCD) Study, the authors analyzed 72-hour wearable sensor recordings from 421 infants 0–2 months of age to provide the first large-scale characterization of infant leg movements in naturalistic settings. The study established reference distributions for multiple measures of infant motor behavior, including movement frequency, acceleration, duration, movement variability, and physical activity intensity. These findings substantially extend previous research by providing ecologically valid benchmarks for early motor development, establishing a foundation for future studies linking infant movement patterns with brain development, environmental exposures, and later neurodevelopmental outcomes.

**Patterns Of Brain-Wide Associations Reflect Socioeconomics** Marek S, Donohue MR, Karcher NR, Hoyniak CP, Chauvin RJ, Meyer AC, Miller J, Van AN, Wang A, Baden NJ, Suljic V, Scheidter KM, Monk J, Whiting FI, Ramirez-Perez NJ, Krimmel SR, Metoki A, Paul SE, Gorelik AJ, Hendrickson TJ, Malone SM, Schwarzlose RF, Cardenas-Iniguez C, Herting MM, Petersen SE, Luby J, Randolph AC, Shanahan MJ, Turkheimer E, Kay BP, Gordon EM, Laumann TO, Barch DM, Fair DA, Tervo-Clemmens B, Dosenbach NUF. Science. 2026; 392(6803): eae6213.

Previous brain-wide association studies (BWAS) have linked specific environmental and behavioral variables to brain variability. In this work, we mapped 649 variables to children's brains and compared the resultant BWAS maps with each other and with neurobiological reference patterns. Socioeconomic status (SES) showed the strongest brain-wide associations. The SES associations were strongest in motor and sensory but not cognitive regions, a pattern shared across many BWAS maps, including intelligence quotient (IQ). A single, common BWAS brain pattern existed across variables that was most reflective of a child's socioeconomics. Adjusting for SES weakened brain-IQ associations, eliminating the BWAS motor and sensory pattern. Brain-with-IQ associations also did not generalize when trained on higher-SES subsamples. Thus, children's brains vary the most with SES, potentially through SES-dependent sleep deprivation and stress.

**ADHD Medications And Preadolescent Brain Structure: Patterns Of Cortical Attenuation From The ABCD Study** Overholtzer LN, Bottenhorn KL, Karalunas SL, Peterson BS, Herting MM. Sci Rep. 2026 [Online ahead of print, June 12].

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in the U.S. Amphetamine (AMP), methylphenidate (MPH), and nonstimulants (NS) used to treat ADHD are among the most prescribed pediatric drugs. Although pharmacotherapy is the most effective treatment, its neurostructural effects remain poorly characterized. Leveraging the ABCD Study, we used a machine learning approach to identify neuroanatomical targets of medications (N = 1306), followed by linear mixed-effects modelling to estimate the effects of ADHD status and medication use (AMP, MPH, NS) on cortical thickness, surface area, and cortical and subcortical volumes (N = 8762). ADHD was not associated with significant differences in brain structure; effects were small and bidirectional. Nevertheless, a consistent pattern emerged in which AMP and MPH effects were opposite in direction to ADHD associations (i.e., "attenuation" toward control phenotype), while NS showed a weaker pattern. AMP and MPH use were both associated with significantly reduced right banks of the superior temporal sulcus and left posterior cingulate surface area. Additionally, AMP was associated with reduced left posterior cingulate volume and MPH with increased right temporal pole volume. Significant stimulant associations suggest partly independent structural effects in the cortex, with effects that extend beyond the ADHD phenotype.

**Linking Temporal Dynamics Of Children's Natural Behavior To Brain Development**

Koepp AE, Nishio M, Mackey AP. Dev Cogn Neurosci. 2026; 80: 101742.

Across the school day, children must continually modulate their behavior to be appropriate to the classroom. Such behavioral regulation is effortful, and children vary in their ability to sustain behavioral regulation over time. We have previously shown that daily increases in activity levels (DIA) across the school day relate to questionnaire measures of self-control, and that children who show shallower DIA in third grade are more likely to graduate from college. Here, we ask

how individual differences in brain development relate to children's ability to sustain behavioral regulation as measured by DIA. We take advantage of neuroimaging and actigraphy data collected in the ABCD study ( $N = 4338$ ,  $M_{\text{age}} = 11.95$ , 15.65 days of actigraphy data per child). We preregistered hypotheses that steeper DIA (lower sustained control) would be associated with thinner cortex, lower surface area, and weaker correlations between the executive control network and somatomotor network. We first replicated typical patterns of DIA, as well as associations between steeper DIA and lower inhibitory control. We then showed that greater DIA is associated with thinner cortex in areas related to executive control ( $\beta\text{s} = -0.04$  to  $-0.06$ ) and motor action ( $\beta\text{s} = -0.04$  to  $-0.05$ ). Greater DIA was also associated with lower connectivity between the executive control and somatomotor networks ( $\beta = -0.07$ ), and greater connectivity within the somatomotor network ( $\beta = 0.12$ ). Our results suggest that DIA is a promising measure of naturalistic self-control that can be used to study between- and within-person variability at scale.