



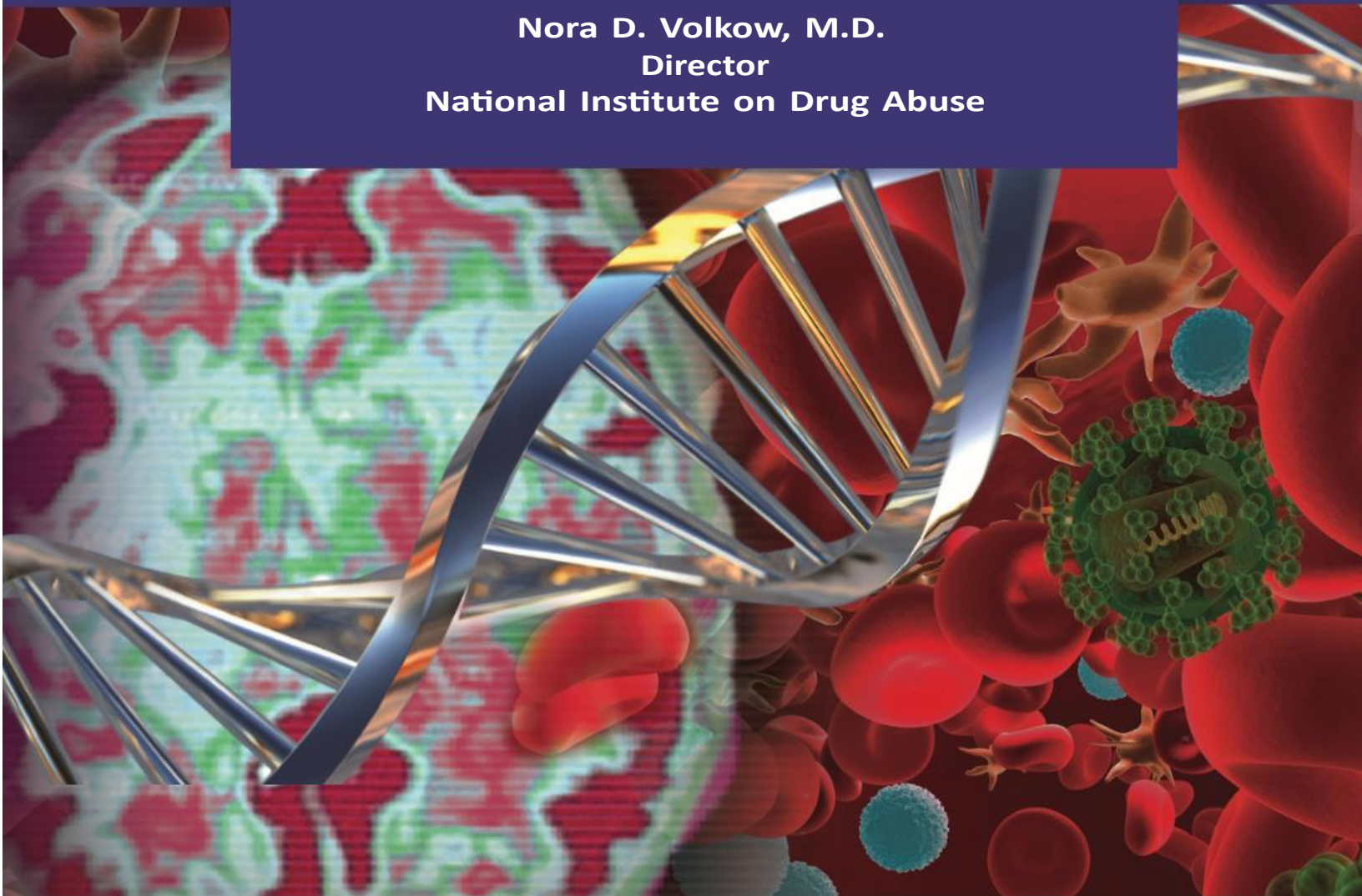
# DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

May 5 2026

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**Director**  
**National Institute on Drug Abuse**



# RESEARCH HIGHLIGHTS

## BASIC AND BEHAVIORAL RESEARCH

**Cholinergic Modulation Of Dopamine Release Drives Effortful Behaviour** Touponse GC, Pomrenze MB, Yassine T, Denomme N, Wang M, Mehta V, Zhang Z, Malenka RC, Eshel N. *Nature*. 2026; 651(8107): 1020-1029.

Effort is costly: given a choice, we tend to avoid it<sup>1</sup>. However, in many cases, effort adds value to the ensuing rewards<sup>2</sup>. From ants<sup>3</sup> to humans<sup>4</sup>, individuals prefer rewards that had been harder to achieve. This counterintuitive process may promote reward seeking even in resource-poor environments, thus enhancing evolutionary fitness<sup>5</sup>. Despite its ubiquity, the neural mechanisms supporting this behavioural effect are poorly understood. Here we show that effort amplifies the dopamine response to an otherwise identical reward, and this amplification depends on local modulation of dopamine axons by acetylcholine. High-effort rewards evoke rapid acetylcholine release from local interneurons in the nucleus accumbens. Acetylcholine then binds to nicotinic receptors on dopamine axon terminals to augment dopamine release when reward is delivered. Blocking the cholinergic modulation blunts dopamine release selectively in high-effort contexts, impairing effortful behaviour while leaving low-effort reward consumption intact. These results reconcile *in vitro* studies, which have long demonstrated that acetylcholine can trigger dopamine release directly through dopamine axons<sup>6,7,8,9,10,11</sup>, with *in vivo* studies that failed to observe such modulation<sup>12,13,14</sup>, but did not examine high-effort contexts. Our findings uncover a mechanism that drives effortful behaviour through context-dependent local interactions between acetylcholine and dopamine axons. K99DA056573, T32DA035165

**Mimicking Opioid Analgesia In Cortical Pain Circuits** Oswell CS, Rogers SA, James JG, McCall NM, Hsu AI, Salimando GJ, Mahmood M, Wooldridge LM, Wachira M, Jo AY, Sandoval Ortega RA, Wojcik JA, Beattie K, Farinas SA, Chehimi SN, Rodrigues A, Wu JWK, Ejoh LL, Kimmey BA, Lo E, Azouz G, Vasquez JJ, Banghart MR, Beier KT, Creasy KT, Crist RC, Ramakrishnan C, Reiner BC, Deisseroth K, Yttri EA, Corder G. *Nature*. 2026; 649(8098): 938-947.

The anterior cingulate cortex is a key brain region involved in the affective and motivational dimensions of pain, but how opioid analgesics modulate this cortical circuit remains unclear<sup>1</sup>. Uncovering how opioids alter nociceptive neural dynamics to produce pain relief is essential for developing safer and more targeted treatments for chronic pain. Here we show that a population of cingulate neurons encodes spontaneous pain-related behaviours and is selectively modulated by morphine. Using deep learning behavioural analyses combined with longitudinal neural recordings in mice, we identified a persistent shift in cortical activity patterns following nerve injury that reflects the emergence of an unpleasant, affective chronic pain state. Morphine reversed these neuropathic neural dynamics and reduced affective-motivational behaviours without altering sensory detection or reflexive responses, mirroring how opioids alleviate pain unpleasantness in humans. Leveraging these findings, we built a biologically inspired chemogenetic gene therapy that targets opioid-sensitive neurons in the cingulate using a synthetic  $\mu$ -opioid receptor promoter to drive inhibition<sup>2</sup>. This opioid-mimetic chemogenetic gene therapy recapitulated the analgesic effects of morphine during chronic neuropathic pain,

thereby offering a new strategy for precision pain management that targets a key nociceptive cortical opioid circuit with safe, on-demand analgesia. R21DA055846, F32DA055458, R00DA043609

**Fentanyl, Methamphetamine And Polysubstance Use Differentially Affect Locomotor Sensitisation And Social Behaviour In Rats: Psychedelic Treatment Reverses Social Deficits**

Salinsky LM, Diaz KC, Fox JL, Panh SM, Ferguson SM. *Addict Biol.* 2026; 31(3): e70132.

Polysubstance use of opioids and stimulants is increasingly common among individuals with a substance use disorder, yet most researchers examine these substances in isolation. This gap limits our understanding of the effects of polysubstance use and how these differ from single substance use. Here, we examined the impact of single versus polysubstance exposure of fentanyl and methamphetamine on locomotor sensitisation and social behaviour in male and female rats. In addition, as recent evidence has suggested the potential for psychedelic compounds to decrease facets of both opioid and stimulant use disorders, we tested whether the psychedelic R-(-)-2,5-dimethoxy-4-iodoamphetamine (DOI) can reverse drug withdrawal-induced social deficits. Baseline sociability was assessed in male and female Sprague-Dawley rats using DeepLabCut and Simple Behavioral Analysis (SimBA). Rats then received injections of saline, methamphetamine (1 mg/kg) and/or fentanyl (20 µg/kg) for 14 days, and locomotion was measured. All rats then underwent 10 days of withdrawal followed by a reassessment of sociability. The following day, all subjects received DOI (0.3 mg/kg; 30 min) and were reassessed for sociability. Our results indicate that the development of locomotor sensitisation and drug withdrawal-induced social deficits vary as a function of drug class, drug history and sex. In addition, acute DOI treatment is sufficient to reverse social deficits as well as enhance social interactions in females. The findings from these experiments suggest a potential therapeutic role of psychedelics in mitigating the social deficits that are associated with withdrawal from polysubstance use of opioids and stimulants. P30DA048736, R01DA058930, T32DA007278, R25DA057786

**Impulsivity And Neuroticism Share Distinct Functional Connectivity Signatures With Alcohol-Use Risk In Youth**

Cheng A, Lichenstein S, Chaarani B, Liang Q, Babaeianjelodar M, Riley SJ, Luo W, Horien C, Greene AS, Banaschewski T, Bokde ALW, Desrivieres S, Flor H, Grigis A, Gowland P, Heinz A, Brühl R, Martinot JL, Martinot MP, Artiges E, Nees F, Papadopoulos Orfanos D, Poustka L, Hohmann S, Holz N, Baeuchl C, Smolka MN, Vaidya N, Walter H, Whelan R, Schumann G, Constable RT, Pearlson G, Garavan H, Yip SW. *Mol Psychiatry.* 2026; 31(2): 953-962.

Increases in impulsivity and negative affect (e.g., neuroticism) are common during adolescence and are both associated with risk for alcohol-use initiation and other risk behaviors. Whole-brain functional connectivity approaches—when coupled with appropriate cross-validation—enable identification of complex neural networks subserving individual differences in dimensional traits (hereafter referred to as ‘neural signatures’). Here, we analyzed functional connectivity data acquired at age 19 from individuals enrolled in a multisite European study of adolescent development (N ~ 1100) using connectome-based predictive modeling. Network anatomies of these dimensional phenotypes were compared with one another and with a previously identified alcohol-use risk network to identify shared and unique neural mechanisms. Models accurately predicted both impulsivity and neuroticism ( $r$ 's ~ 0.17-0.19,  $p$ 's < 0.05), and successfully

generalized to an external sample. The impulsivity network was predominantly characterized by motor/sensory-related connections. By contrast, the neural signature of neuroticism was relatively more distributed across multiple canonical networks, including motor/sensory, default mode, subcortical, frontoparietal and cerebellar networks. Very few connections were common to both impulsivity and neuroticism networks. Moreover, while ~10-20% of the connections from each trait overlapped with the alcohol-use risk network, these connections were distinct between the two traits. This study for the first time identifies functional connectivity signatures of two common risk factors for alcohol-use in youth—impulsivity and neuroticism. Consistent with current equifinality-based conceptions of development, few connections predicted both impulsivity and neuroticism, indicating that the neural signatures of these two traits are relatively distinct despite both being implicated in alcohol-use risk and a wide array of behaviors.

R01DA053301

[\*\*The Genetics Of Cannabis Lifetime Use\*\*](#) Bright U, Beck S, Galimberti M, Gupta P, Chen Y, Dao C, Nunez YZ, Kranzler HR, Zhou Y, Zhang Y, Choi KW, Levey DF, Gelernter J. *Neuropsychopharmacology*. 2026; 51(3): 554-564.

Cannabis is one of the most commonly used drugs in the world, and use is trending alarmingly higher. We aimed to examine the genetic basis of cannabis lifetime use (CanLU) and its genetic relationships with a variety of psychiatric- and physical health-related phenotypes. We conducted a multi-ancestral genome-wide association study (GWAS) of CanLU using data from All of Us in five genetic populations. We meta-analyzed the results of EUR participants with previously published CanLU data (total effective sample size: 258,823), and conducted a set of post-GWAS analyses, including genetic correlation analysis using LDSC, local genetic correlation analysis with LAVA, Mendelian randomization (MR) to assess causality, and phenomewide association analysis. We found 11 independent variants significantly associated with CanLU, most prominently CADM2\*rs7609594 ( $p = 7.4 \times 10^{-20}$ ). CanLU was genetically correlated with traits related to openness to experience and risk taking, including substance use and sexual behaviors. MR demonstrated that most of these traits had a bidirectional causal relationship with CanLU, and six were locally genetically correlated with CanLU in a region that maps to CADM2. Genetic correlations sometimes differed from those previously observed for cannabis use disorder. Our results highlight the distinct genetic architecture of CanLU, and support the genetic, and biological, differentiation between CanLU and cannabis use disorder. Genetic correlations between CanLU and other risk taking- and substance use-related traits indicate a broad mutual genetic mechanism underlying these traits, and suggest involvement of CADM2. These findings provide potential targets for future prevention and intervention strategies for substance use and risk-taking behaviors. R01DA058862, R01DA054869

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

### **Cannabis Dispensary Exposure And Smoked, Vaped And Edible Cannabis Use Among Young Adults: Comparison Of Web-Scraped And Government-Maintained Registries**

Harlow AF, Williams MP, Pacula RL, Leventhal AM, Pedersen ER, Cockburn MG, Thompson LK, Cho J, Barrington-Trimis JL, Haley DF. *Addiction*. 2026 [Online ahead of print, February 18].

**Background and aims:** The impact of exposure to cannabis dispensaries on young adult cannabis use may depend on how exposures and outcomes are defined. We estimated associations of dispensary exposure with young adult cannabis use across: (a) a government-maintained licensed dispensaries registry versus a web-scraped list of licensed and unlicensed dispensaries; and (b) varying modes of cannabis modes (i.e. smoked, edible, vaped).

**Methods:** This study used three waves of data (2021-2023) from a prospective cohort of n = 2277 young adults (mean baseline age = 22 years) from California, USA. Generalized linear models estimated the contemporaneous association of number of dispensaries within 1 mile of participants' homes with repeated measures of past 6-month, past 30-day frequency and past 30-day daily/near-daily ( $\geq 20$  days/month) smoked, edible and vaped cannabis use (separate models for each product type). We compared associations for dispensary exposure derived from a government-maintained registry versus a validated web-scraped dispensary list.

**Results:** For each additional dispensary located within 1 mile of home, young adults had 5-6% increased risk of past 6-month use of smoked, edible and vaped cannabis use using registry data and 3-4% increased risk using web-scraped dispensary data. Dispensary exposure was positively associated with past 30-day frequency of smoked [incidence rate ratio (IRR)(registry list) = 1.08, 95% confidence interval (CI) = 1.01-1.15; IRR(web-scraped) = 1.04, 95% CI = 1.00-1.08] and edible [IRR(registry list) = 1.07, 95% CI = 0.99-1.15; IRR(web-scraped) = 1.04, 95% CI = 0.99-1.08] cannabis use, but was not consistently associated with cannabis vaping frequency or daily/near-daily use of any product. Magnitude of associations was generally smaller when using dispensary data derived through web-scraping than the government-maintained registry of dispensary licenses, though conclusions were mostly similar between the two lists and confidence intervals consistently overlapped.

**Conclusions:** Living near a greater number of cannabis dispensaries within 1 mile of home appears to be associated with an increased risk of cannabis use. Web-scraped dispensary sources and United States government-maintained registry lists produce similar conclusions regarding the association of living near a greater number of dispensaries with young adult cannabis use.

**Buprenorphine Treatment Duration And Adherence Among Youth And Subsequent Health Outcomes** Hadland SE, Kimmel SD, Yan S, Bettano AL, Lo-Ciganic WH, Bagley SM, Calihan JB, Hsu HE, Laroche MR. *Pediatrics*. 2025; 156(6): e2025071147.

**Objectives:** It is unclear how long youth with opioid use disorder (OUD) should continue taking buprenorphine, and what adherence they should achieve. We identified patterns of duration/adherence and assessed associations with subsequent overdose, emergency department (ED) use, and hospitalization.

**Methods:** This retrospective cohort analysis used 2014-2022 data from the Massachusetts Public Health Data Warehouse. We identified youth aged 13 to 26 years initiating buprenorphine and used group-based trajectory modeling to categorize youth into duration/adherence trajectories over 12 months. Using multivariable Cox regression, we examined associations between trajectories and time to fatal/nonfatal opioid overdose, all-cause ED use, and all-cause hospitalization during the subsequent 12-month period.

**Results:** Among 11 649 Massachusetts youth initiating buprenorphine, most were aged 21 years or older (89.0%), male (60.3%), white non-Hispanic (85.9%), and enrolled in Medicaid (55.4%). We identified 4 patterns of medication use: (1) high adherence for 12 months (23.7%); (2) low adherence for 12 months (27.5%); (3) discontinuation in 3 to 9 months (16.4%); and (4) discontinuation in less than 3 months (32.5%). Trajectories included 580 (5.0%) and 774 (6.6%) youth switching to methadone and naltrexone, respectively. Compared with high adherence for 12 months, overdose risk was higher with low adherence for 12 months (adjusted hazard ratio [aHR], 1.46; 95% CI, 1.24-1.73), discontinuation in 3 to 9 months (aHR, 1.82; 95% CI, 1.52-2.17), and discontinuation in less than 3 months (aHR, 1.76; 95% CI 1.50-2.06). Compared with high adherence, low adherence and discontinuation in less than 3 months had higher risk of ED use, and all other trajectories had higher risk of hospitalization.

**Conclusions:** Medication adherence may prevent overdose, ED use, and hospitalization. Strategies to increase treatment duration/adherence likely avert harm.

**[Characterizing The Substance Use Prevention Funding Landscape In The United States: A Cross-Sectional Study Of National Prevention Network Representatives And Practitioners](#)**

Liu SS, Elek E, Blackburn N, Wondimagegnehu F, Ballard PJ, Graham PW. Prev Sci. 2026 [Online ahead of print, March 10].

Youth and adolescent substance use remains a persistent public health challenge in the United States; the delivery of evidence-based interventions (EBIs) is critical to improving related negative consequences. The Substance Abuse and Mental Health Services Administration funds a large portion of the implemented substance use prevention interventions in the United States by supporting a funding infrastructure that plays an important role in the adoption and scaling of interventions. Prevention intervention developers and researchers need to understand this infrastructure and its influence on local practitioners to increase the adoption of their EBIs. This study sought to identify which agencies in each state and jurisdiction are involved in funding allocation, how they prioritize and distribute funding to intervention implementers, and, subsequently, how they guide the selection of EBIs. This study used a mixed-methods, cross-sectional design to understand the infrastructure of prevention funding that underlies EBI decision-making. In 2023, surveys were conducted with 40 National Prevention Network representatives (NPNs) and 222 community-level practitioners; in early 2024, a subset of 16 NPNs participated in qualitative interviews. NPNs' priorities were shaped by the agencies in which they were housed and the partners with whom they collaborated. Most were located within their state's or jurisdiction's department of health or behavioral health, and many engaged in partnerships with departments of public health or education. Most NPNs reported that they prioritized school and health settings and youth populations for prevention intervention delivery. Almost all NPNs directly distributed funding to intervention implementers (community, regional, or state entities); about half distributed some funds through an intermediary that then subcontracted another entity to implement interventions. More NPNs required or recommended that funded recipients select EBIs from lists or registries (75%) than required or recommended a specific strategy for at least some of their programs (53%). Many practitioners (47%) reported that they selected a recent strategy from a list of interventions provided by their funder, but 27% received no funder guidance on intervention selection. Prevention developers and researchers could increase the adoption of EBIs by focusing them on the priority areas for NPNs, including the health, behavioral health, and education sectors. Developers need to get their EBIs onto

registries or intervention lists and increase the EBIs' wide-scale dissemination. Audiences for information about specific EBIs should include NPNs, regional entities, and their funded community practitioner recipients.

**Youth Initiation Of Cannabis Vaping Is Associated With State Cannabis Policy And E-Cigarette Use** Vuolo M, Orsini MM, Staff J, Maggs JL, Kelly BC. J Adolesc Health. 2026; 78(1): 53-60.

Cannabis vaping has emerged as a growing problem, particularly among youth. It is essential to understand how state policies on medical and recreational cannabis as well as vaping bans may influence initiation into cannabis vaping during adolescence. This study aimed to determine whether changes in state-level cannabis policies, indoor vaping bans, and youths' nicotine use were associated with cannabis vaping initiation in adolescence. Prospective nationally representative cohort data from the Population Assessment of Tobacco and Health study was used for this analysis (19,009 youth across 38,163 observations, ages 13-22). Event history analysis of the role of state-level medical and legal recreational cannabis policies and comprehensive indoor vaping bans on cannabis vaping initiation, net of youth nicotine use and sociodemographics were used for this analysis. Relative to states with illicit cannabis, residing in states where cannabis was legal for recreational use or medical use was associated with 1.449 (95% confidence interval [CI]: 1.285-1.635) and 1.198 (95% CI: 1.006-1.427) higher odds of cannabis vaping initiation, respectively. Though comprehensive indoor vaping bans were not related to cannabis vaping initiation, the associated odds of cannabis vaping initiation were 8.07 times higher (95% CI: 7.170-9.072) for youth reporting e-cigarette use during the past month. Within states that legalized adult use of cannabis, efforts are needed to prevent diversion of novel products, such as vaping devices, from legal marketplaces to adolescents. Prevention efforts for cannabis vaping should focus on youth who already use e-cigarettes.

**Risk Reduction Behaviours Following The Detection Of Unexpected Drugs Through Community Drug Checking: A Cross-Sectional Study** Tobias S, Grant C, Lysyshyn M, Roux P, Wood E, Kerr T, Ti L. Harm Reduct J. 2026 [Online ahead of print, March 5].

**Background:** Community-based drug checking services have scaled up in response to the unregulated drug toxicity crisis across North America. We sought to assess the relationship between the detection of unexpected active drugs in a drug checking sample and subsequent engagement in risk reduction practices.

**Methods:** We used data from a cross-sectional study of people who used community-based drug checking services in British Columbia, Canada (March 2020-July 2024). We constructed multivariable logistic regression models to examine the relationship between the detection of unexpected active drugs (i.e., compounds that have psychoactive properties) in samples brought for analysis (using combination Fourier-transform infrared spectroscopy and immunoassay strips) and engagement in subsequent risk reduction practices (e.g., dose reduction, disposal of the drug).

**Results:** In total, 447 individuals were included: 174 (38.9%) reported detection of unexpected active drugs in their drug checking sample with the most common being benzodiazepines in expected opioid samples. The most common risk reduction behaviours were to dispose of the

drug without using it (n = 24) and taking a smaller dose (n = 11). Through multivariable logistic regression, we found a positive association between detection of unexpected active drugs and engagement in risk reduction practices (adjusted odds ratio = 2.24; 95% confidence interval: 1.30-3.87).

**Conclusion:** Individuals who detected unexpected active drugs in their sample had higher odds of engaging in risk reduction practices. These findings highlight the potential of drug checking services as a harm reduction tool within a suite of services offered to combat the unpredictable and unregulated drug supply.

## **THERAPEUTICS AND MEDICAL CONSEQUENCES RESEARCH**

**[Ketamine-Assisted Mindfulness-Oriented Recovery Enhancement For Opioid Use Disorder: A Randomized Controlled Trial](#)** Garland EL, Lewis BR, Thielking P, Odette M, Pfeffer H, Shen J. *Mental Health*. 2026 [Online ahead of print, March 26].

Here, in this single-blinded clinical trial (NCT04892251), we assessed the safety and preliminary efficacy of ketamine-assisted psychotherapy (KAP) plus Mindfulness-Oriented Recovery Enhancement (MORE) for patients with opioid use disorder (OUD). People receiving buprenorphine for OUD were randomized ( $N = 68$ ) to MORE + KAP or MORE-only. MORE involved 8 weeks of mindfulness, reappraisal and savoring training by telehealth videoconferencing. The MORE + KAP arm received a 0.5 mg kg<sup>-1</sup> intramuscular ketamine dose after week 5 and then 1 week later received a dose up to 1.0 mg kg<sup>-1</sup>. The primary outcome was instances of drug use. Secondary outcomes included craving, distress, affective states and buprenorphine use. No serious ketamine-related adverse events occurred. The MORE + KAP arm reported significantly fewer instances of drug use after treatment and lower cravings at follow-up than the MORE-only arm. No between-groups differences were noted in distress or buprenorphine use. The MORE + KAP arm reported greater increases in mindfulness-related processes. During ketamine administration, 85% of participants reported experiencing a full mystical experience, which predicted reduced opioid craving. Adding intramuscular ketamine to MORE appears safe and may augment OUD treatment outcomes.

**[A Long-Acting Naltrexone Implant \(iSTEP-N\) For Opioid Use Disorder: First-In-Human Phase I Trial](#)** Cohen SM, Benner J, Soni P, Ravis WR, Bertoch T, Ransom J, Berman J. *J Addict Med*. 2026 [Online ahead of print, January 26].

**Objectives:** iSTEP-N is a novel, bioresorbable, subcutaneous implant designed to release naltrexone for 6–12 months after a single procedure and improve adherence. This first-in-human study evaluated the safety and pharmacokinetics of iSTEP-N.

**Methods:** This was a single-center, randomized, double-blind, placebo-controlled, single-ascending-dose trial. Sixteen healthy adults (6 females and 10 males) were assigned to receive either 1 implant (4.8 g naltrexone), 2 implants (9.6 g naltrexone), or placebo implants. Participants were followed for 12 weeks, after which implants were removed per regulatory requirement. Plasma naltrexone concentrations and safety outcomes were assessed throughout. Results: All participants completed the study. The 9.6 g cohort maintained mean plasma naltrexone concentrations above the 2.0 ng/mL opioid blockade threshold from T<sub>max</sub> at 10 hours

through the end of the study at 12 weeks; no mean value fell below 2.8 ng/mL during this time. The 4.8 g cohort maintained therapeutic levels of naltrexone through week 6 but dropped below threshold thereafter. In both cohorts, ~22% of implant drug content was released over 12 weeks, based on plasma exposure and estimated clearance, indicating potential for extended coverage. In the 9.6 g group, seroma formation was observed in 3 of 6 participants (50%) and resolved without intervention. No serious adverse events occurred.

**Conclusions:** At the 9.6 g dose, iSTEP-N provided sustained therapeutic naltrexone exposure for 12 weeks with a favorable safety profile, while releasing less than one-fourth of its drug content. Further studies will evaluate longer-term exposure, safety, and clinical feasibility in individuals with opioid use disorder. UH3DA048338

**Varenicline For Cannabis Use Disorder: A Randomized Controlled Trial** McRae-Clark AL, Gray KM, Baker NL, Sherman BJ, Tolliver B, Burt J, Steplight A, Chapman E, Wagner A. *Addiction*. 2026 [Online ahead of print, January 14].

**BACKGROUND AND AIMS:** Although cannabis use is widespread and prevalence of cannabis use disorder (CUD) is increasing, limited advancements have been made in CUD medication development. The objective of this study was to test the efficacy of varenicline with medical management for reducing cannabis use in treatment-seeking individuals with CUD. **DESIGN:** A phase 2, randomized, double-blind, parallel group, placebo-controlled trial was conducted. **SETTING:** Two outpatient research clinics in South Carolina, USA, from February 2020 to February 2023. **PARTICIPANTS:** Eligible participants met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for CUD and used cannabis a minimum of 3 days per week. One hundred and seventy-four participants were randomized to either varenicline (n = 90) or placebo (n = 84) stratified by smoking status and sex. **INTERVENTIONS:** Varenicline (titrated to goal dose of 1 mg twice daily) or matching placebo for 12 weeks. Medical management was provided weekly. **MEASUREMENTS:** Primary outcome measure was reduction in total number of cannabis use sessions at each weekly visit (weeks 6-12). **FINDINGS:** There was no main effect of treatment on reduction of total number of cannabis use sessions per week during weeks 6 through 12 [between group difference ( $\Delta$ ) = 1.7; 95% confidence interval (CI) = -1.0 to 4.7; P = 0.41]; however, a statistically significant treatment by sex interaction was found (F<sub>1,132</sub> = 5.1; P = 0.026), with a statistically significant effect of varenicline on reduction of cannabis use sessions per week observed in men ( $\Delta$  = 4.2; 95% CI = 0.6-7.8; P = 0.04) but not women ( $\Delta$  = -1.4; 95% CI = -5.7 to 3.0; P = 0.18). **CONCLUSIONS:** Varenicline with medical management resulted in decreased cannabis use among men with cannabis use disorder seeking treatment, but not women (no effect was observed on the overall sample of treatment-seeking individuals with cannabis use disorder).

UH3DA043231

**ACT On Vaping: Pilot Randomized Controlled Trial Of A Novel Digital Health App With Text Messaging For Young Adult Vaping Cessation** Heffner JL, Baker K, Georgiou K, Graham AL, Kelly MM, Konstantinou P, Lamprou E, Lele C, Lok KZ, Orzechowski M, Ruiz RA, Serfozo E, Karekla M. *Nicotine Tob Res*. 2025 [Online ahead of print, May 24].

**Background:** There is no published evidence to support the efficacy of any digital vaping cessation program for young adults (YAs) at differing levels of readiness to quit. In this pilot randomized controlled trial, we evaluated the preliminary acceptability and efficacy of a program for vaping cessation based on acceptance and commitment therapy (ACT on Vaping), delivered via a smartphone app and text messaging.

**Methods:** YAs age 18-30 (n=61) were randomized 1:1 to ACT on Vaping (n=31) or incentivized text message control (n=30). Outcome data were collected at 3 months post-randomization. Results were compared against a priori benchmarks for acceptability (satisfaction of  $\geq 3.5$  on 5-point scale) and efficacy relative to control (meeting at least one of three):  $\geq 1$ -point difference in Contemplation Ladder change scores;  $\geq 5$  percentage difference in 24-hour quit attempts,  $\geq 5$  percentage difference in cotinine-confirmed 30-day point prevalence abstinence (PPA) from all non-therapeutic nicotine/tobacco.

**Results:** Satisfaction with ACT on Vaping averaged 3.8, exceeding the acceptability benchmark. A higher proportion of participants in the ACT on Vaping arm reported a 24-hour quit attempt (87.5% vs. 75.9%), exceeding the efficacy benchmark. Both change in quit readiness (+0.96 in ACT on Vaping vs. +0.72 in control) and cotinine-confirmed 30-day PPA (4.2% in ACT on Vaping vs. 0% in control) were descriptively higher for ACT on Vaping but did not reach the benchmark level for efficacy.

**Conclusions:** ACT on Vaping had promising acceptability and preliminary efficacy. A fully-powered trial of ACT on Vaping is warranted to evaluate its efficacy.

**Implications:** Digital interventions are a promising yet under-researched approach for reaching and supporting young adults to quit vaping. This proof-of-concept pilot randomized controlled trial evaluated a novel mobile health application and associated text messaging program (ACT on Vaping) for young adult vaping cessation and found preliminary evidence for acceptability and efficacy relative to an incentivized text message control arm, warranting evaluation in a fully-powered trial as a next step.

**[Transcutaneous Cervical Vagus Nerve Stimulation Modulates Prefrontal Cortex Activity During Opioid Withdrawal In Individuals With Opioid Use Disorder](#)** Rahman FN, Nawar A, Nye JA, Choi J, Lambert TP, Robinson M, Gazi AH, Abbaraju V, Tomic N, Harrison AB, Jaquemet N, Mermin-Bunnell K, Mesfin H, Gray TA, Welsh JW, Dunn KE, Bikson M, Vaccarino V, Shah AJ, Inan OT, Bremner JD. *Neuromodulation*. 2025; 28(8): 1396-1407.

**BACKGROUND:** Opioid use disorder (OUD) is associated with considerable morbidity and mortality with limited treatment approaches. Understanding brain mechanisms in response to treatment could be useful in guiding future developments in treatment approaches. **OBJECTIVE:** The purpose of this study was to assess the effects of transcutaneous cervical vagus nerve stimulation (tcVNS) on brain response to opioid use cues in patients with OUD in opioid withdrawal. **MATERIALS AND METHODS:** Patients with OUD who were in the early stage of recovery and/or on medication underwent brain imaging with positron emission tomography and radiolabeled water in conjunction with stimulation with active tcVNS or sham devices and exposure to opioid-use-related cues. **RESULTS:** tcVNS caused a relative increase in function in the anterior cingulate, dorsal anterior cingulate, and left inferior frontal gyrus during exposure to

opioid cues. There also was a pattern of increased activation in the ventral striatum and orbitofrontal cortex. **CONCLUSION:** tcVNS modulates brain areas implicated in opioid addiction, suggesting a useful role as an adjunctive therapy for OUD. **CLINICAL TRIAL REGISTRATION:** The Clinicaltrials.gov registration number for the study is NCT04556552.

UH3DA048502, R01MH120262, UG3DA048502, T32EB025816

**[Heart Rate Variability Biofeedback For Substance Use Disorder: A Randomized Clinical Trial](#)** Eddie D, Nguyen M, Zeng K, Mei S, Emery N. JAMA Psychiatry. 2025; 82(12): 1177-1185.

**IMPORTANCE:** Preliminary studies suggest heart rate variability biofeedback (HRVB) may reduce craving and negative affect in individuals with substance use disorder (SUD), but few studies have evaluated whether this translates into improved substance use outcomes, and no prior studies have examined second-generation wearable HRVB technology in this context.

**OBJECTIVE:** To evaluate the effects of second-generation HRVB on negative affect, positive affect, craving, and alcohol and other drug (AOD) use in adults with SUD. **DESIGN, SETTING, AND PARTICIPANTS:** This phase 2 randomized clinical trial included 8 weeks of outpatient treatment. Recruitment was conducted virtually across the US from February 2023 to June 2024. Treatment-seeking adults with SUD were randomized to receive HRVB + treatment as usual (TAU) or TAU only. **INTERVENTION:** Eight weeks of HRVB.

**MAIN OUTCOMES AND MEASURES:** The primary outcomes were negative affect, positive affect, craving, and substance use, assessed with ecological momentary assessment. Results: Of 260 individuals assessed for eligibility, 120 were randomized to receive HRVB + TAU or TAU only. Among study participants (69 female participants of 115 [60.0%]; mean [SD] age, 46.18 [11.59] years), HRVB was associated with significant reductions in negative affect (b, -0.01; z, -3.21; P = .001) and craving (b, -0.01; z, -4.60; P < .001) over 8 weeks. In contrast, the control group experienced increases in both negative affect and craving. No differences were observed for positive affect. HRVB was also associated with a significantly lower proportion of AOD use days (odds ratio [OR], 0.36; 95% credible interval [CrI], 0.25-0.54), representing a 64% reduction in AOD use compared to controls. Treatment condition moderated the within-person relationship between craving and later AOD use (OR, 0.84; 95% CrI, 0.73-0.97), such that those receiving HRVB were less likely to use AOD following craving (b, -0.18; 95% CrI, -0.32 to -0.03). **Conclusions and relevance:** In this randomized clinical trial, findings suggest second-generation HRVB can reduce negative affect, craving, and substance use among individuals in early recovery from SUD. HRVB appears to confer benefit in part by disrupting the association between craving and subsequent AOD use; these results support HRVB as a potentially efficacious treatment for SUD and warrant further investigation in phase 3 trials. R21DA056468, K23AA027577

**[Reinforcing Effects Of Fentanyl/Xylazine Mixtures In Monkeys Responding Under A Food-Versus-Drug Choice Procedure](#)** Maguire DR. Behav Pharmacol. 2026; 37(1): 22-30.

Overdose deaths involving opioids and xylazine, a nonopioid adulterant with sedative, analgesic, and muscle-relaxant properties, have increased dramatically over the past decade. Anecdotal

reports suggest xylazine enhances some effects of opioids; however, motivations for their co-use remain unclear. This study examined the reinforcing effects of fentanyl/xylazine mixtures in nonhuman primates responding under a food-versus-drug choice procedure. Rhesus monkeys ( $n = 4$ ) responded under a concurrent schedule where responding on one lever delivered a sucrose pellet while responding on the other lever delivered an intravenous infusion of fentanyl (0.032-1.0  $\mu\text{g}/\text{kg}/\text{infusion}$ ) alone or in combination with xylazine (1.0-100  $\mu\text{g}/\text{kg}/\text{infusion}$ ). Unit dose of drug increased across blocks within each session, and the ratio of xylazine to fentanyl (10 : 1, 32 : 1, 100 : 1, and 320 : 1) varied across conditions. Choice of infusions increased and choice of food decreased with increasing unit dose of fentanyl, whether available alone or in combination with xylazine. Xylazine increased the choice of otherwise ineffective doses of fentanyl, resulting in a shift in the fentanyl dose-effect curve leftward 2- to 6-fold across monkeys. Combining xylazine with relatively small doses of fentanyl increased choice of infusions over food compared with fentanyl alone. These data suggest that xylazine enhanced the potency (and possibly effectiveness) of fentanyl to function as a reinforcer, which might contribute to increased potential for abuse. R01DA046532, R01DA060215

## **HIV RESEARCH**

### **Using Incentivization As A Strategy To Improve Implementation Of A Motivational Interviewing Brief Intervention For Substance Use Disorders In HIV Settings: Results Of A 26-Site Parallel Groups Cluster-Randomized Type-3 Hybrid Trial Using Incentivization**

Garner BR, Tueller SJ, Bradshaw M, Speck KJ, Satre DD, Rash C, Donohoe T, Mungo J, Philbrick S, Ruwala R, Roosa MR, Zehner M, Ford JH 2nd. *Implement Res Pract.* 2025 [Online ahead of print, December 5].

**Background:** To help improve the implementation of evidence-based substance use disorder (SUD) treatment in practice settings, the United States funds a support system called the Addiction Technology Transfer Center (ATTC) network. Prior implementation research in HIV care found the team-focused Implementation and Sustainment Facilitation (ISF) strategy as an effective addition to the ATTC's staff-focused training, feedback, and consultation (TFC) strategy. Using the ISF + TFC strategy as the control, this type-3 hybrid trial tested the effectiveness of adding a staff-focused incentivization (INC) strategy (ISF + TFC + INC vs. ISF + TFC). Staff-focused incentivization was selected because prior implementation research found it to be highly effective and cost-effective for improving SUD treatment implementation.

**Methods:** Twenty-six HIV service organizations (HSOs), their staff participants ( $N = 87$ ), and their client participants ( $N = 341$ ) were cluster-randomized to either the ISF + TFC control condition or ISF + TFC + INC experimental condition. The INC strategy rewarded/reinforced motivational interviewing brief intervention (MIBI) implementation (US\$10 per MIBI delivered) and MIBI implementation at or above a pre-defined level of quality (US\$10 per demonstration). In addition to these outcomes, past 4-week changes/reductions in client participant's days of primary substance use and anxiety symptoms were examined.

**Results:** The addition of the INC strategy had a large and significant ( $p < .05$ ) effect on the number of MIBIs implemented ( $d = 1.30$ ) and reduction in anxiety ( $d = -1.54$ ). There was no significant impact on days of substance use.

**Conclusions:** The addition a staff-focused INC strategy improved implementation of an evidence-based brief intervention for adults with comorbid HIV and SUD, and also reduced anxiety. To help improve the integration of evidence-based SUD services in HSOs across the United States, use of the ISF + TFC + INC strategy by the ATTC network and/or the AIDS Education and Training Center (AETC) network is recommended.

**"PrEP Is Always On The Table": Mixed Methods Study Of Provider Willingness To Refer/Link Clients To PrEP In Community Sexual Health And Drug Use-Related Programs**

Paschen-Wolff MM, Laschober TC, Spector AY, Ertl MM, Nelson CM, Hatch MA, Lancaster C, Wright L, Tross S. J HIV AIDS Soc Serv. 2025 [Online ahead of print, August 22].

Southern U.S. communities experience high HIV incidence and substance use prevalence, yet low PrEP uptake. Providers ( $N = 191$ ) completed a survey about willingness to refer/link clients with HIV risk to PrEP. Through in-depth interviews, 12 directors (5 sexually transmitted infection [STI] clinics; 5 syringe services programs [SSPs]; 2 substance use treatment programs [SUTPs]) described multi-level factors that contextualized provider willingness. Providers were more willing to refer/link clients with unspecified HIV risk and men who have sex with men to PrEP vs. other populations. SUTP (vs. SSP) providers were less willing to refer/link clients with unspecified risk and men who use opioids. Older (vs. younger) providers were less willing, and more (vs. less) experienced providers more willing to refer/link to PrEP. Directors described facilitators (e.g., comprehensive health center partnerships) and barriers (e.g., provider stigma toward people who use drugs) to PrEP implementation. Findings highlight the importance of considering multi-level factors in PrEP implementation.

**Keywords:** HIV pre-exposure prophylaxis; PrEP implementation; mixed methods; people who use drugs.

**CLINICAL TRIALS NETWORK RESEARCH**

**Emergency Department-Initiated Buprenorphine For Opioid Use Disorder: A Randomized Clinical Trial**

D'Onofrio G, Herring AA, Hawk KF, Perrone J, Cowan E, McCormack RP, Dziura J, Matthews AG, Pantaloni MV, Owens P, Martel S, Coupet E Jr, Lofwall MR, Walsh SL, Edelman EJ, Carpenter JE, Strout TD, Baumann MR, Anderson E, Barrett TW, Dorey A, Taillac P, Cochran G, Crandall CS, Wilson J, Manteuffel J, Cole JB, Whiteside LK, Jones C, Samuels E, Huntley K, Fiellin DA; ED INNOVATION Investigators. JAMA. 2026; 335(11): 948-960.

**Importance:** Extended-release injectable buprenorphine may expand the reach of initiating medications for opioid use disorder in high-risk and hard-to-reach individuals who visit the emergency department (ED) and can be administered in low levels of withdrawal.

**Objective:** To compare the effect of ED-initiated 7-day extended-release injectable buprenorphine vs sublingual buprenorphine on treatment engagement at 7 days.

**Design, setting, and participants:** Multicenter randomized clinical trial enrolling adult patients presenting to the ED with untreated opioid use disorder and a Clinical Opiate Withdrawal Scale (COWS) score of 4 or higher across 29 EDs in the US from July 12, 2020, to August 21, 2024. Final follow-up was completed on October 24, 2024.

**Interventions:** Patients were randomized to receive a 24-mg injection of extended-release buprenorphine (equivalent to 16 mg/d) or sublingual buprenorphine, which included either self-administration instructions if the COWS score was less than 8 or administration of 8 mg of sublingual buprenorphine in the ED if the COWS score was 8 or higher. All sublingual buprenorphine group patients received a 7-day prescription for 16 mg/d. Both groups were provided referral for ongoing medication with a scheduled appointment within 7 days.

**Main outcomes and measures:** Engagement in opioid use disorder treatment on day 7 was the primary outcome. Secondary outcomes included engagement at 30 days, precipitated withdrawal and overdose events, craving scores, days of illicit opioid use, and patient satisfaction with treatment.

**Results:** Among 2000 patients randomized, 6 who were enrolled twice were excluded, resulting in 991 in the extended-release group and 1003 in the sublingual group. The median age was 37 (IQR, 30-47) years, 68% were male, 31% had an initial COWS score of 4 to 7, and 76% tested positive for fentanyl. The adjusted proportion of engagement in opioid use disorder treatment at 7 days was 40.5% with extended-release buprenorphine vs 38.5% with sublingual buprenorphine (adjusted difference, 1.6%; 95% CI, -2.8% to 6.0%). Engagement at 30 days was similar, with adjusted proportions of 43.8% with extended-release buprenorphine vs 44.9% with sublingual buprenorphine (adjusted difference, -1.5%; 95% CI, -6.2% to 3.2%). Precipitated withdrawal was rare: 6 (0.6%) with extended-release buprenorphine and 8 (0.8%) with sublingual buprenorphine. Overdose events within 30 days occurred in 18 participants (2.3%) in each group. Patients receiving extended-release buprenorphine reported lower mean craving scores at 7 days vs those receiving sublingual buprenorphine (scale, 0-100; mean score, 26.5 vs 30.2, respectively; adjusted mean difference, -3.85; 95% CI, -7.08 to -0.63), fewer days of illicit opioid use in the past 7 days (adjusted ratio of means, 0.77; 95% CI, 0.68-0.95), and better treatment satisfaction scores (scale, 1-5; adjusted mean difference, 0.13; 95% CI, 0.01-0.25).

**Conclusions and relevance:** No difference was detected in opioid use disorder treatment engagement on day 7 between the 7-day extended-release and sublingual buprenorphine groups. Both buprenorphine formulations were well tolerated; precipitated withdrawal was rare despite a high prevalence of fentanyl.

**Trial registration:** ClinicalTrials.gov Identifier: [NCT04225598](https://clinicaltrials.gov/ct2/show/study/NCT04225598).

**Barriers To Buprenorphine Initiation In Patients Using Fentanyl** Kawasaki SS, Liebschutz JM, Murray-Krezan C, Switzer GE, Nash S, Jeong K, Winstanley EL. JAMA Netw Open. 2026; 9(1): e2552136.

**Importance:** Anecdotal accounts suggest an increase in problems initiating buprenorphine (BUP) treatment among individuals using illicitly manufactured fentanyl. Limited empirical data illuminate these challenges.

**Objective:** To determine the prevalence of clinician-reported problems initiating BUP treatment among patients using fentanyl and describe clinical strategies used to overcome engagement challenges.

**Design, setting, and participants:** For this survey study, an online survey was pilot tested and refined with a convenience sample of physicians. The final survey included 96 items and took less than 15 minutes to complete. The survey queried patients' use of fentanyl, BUP induction problems (precipitated or prolonged withdrawal), strategies to overcome induction problems, clinician characteristics, and practice characteristics. Eligible clinicians initiated BUP for at least 10 patients with opioid use disorder in the past year and at least 1 patient in the past 90 days. The survey was live from June 2, 2023, to March 18, 2024.

**Main outcome and measures:** The main outcome of interest was precipitated and/or prolonged opioid withdrawal. Descriptive statistics are reported, and logistic regression was used to identify factors associated with BUP initiation problems.

**Results:** A random sample of physicians and advanced practice clinicians in the US Drug Enforcement Administration (DEA) registrant dataset from October 2022 (n = 3141) were invited to participate; of 2485 eligible for inclusion, 649 (26.1%) completed the prescreen survey. Of 421 (64.9%) eligible to complete the survey, the final sample included 396 (94.1%) clinicians who completed at least 50% of the survey items. Of 390 participants, 284 (72.8%) reported problems when initiating BUP in patients using fentanyl, with 242 of 394 (61.4%) reporting patients' experiencing precipitated withdrawal. A total of 264 or 392 participants (67.3%) reported modifying their standard induction procedures, changing how they counsel patients, or changing both medication and counseling protocols. In multivariable modeling, clinicians were more likely to report problems initiating BUP in patients if they had a DEA waiver to treat more than 100 patients (OR, 1.92; 95% CI, 1.08-3.40), vs those waived to treat fewer patients; if they reported at least 75% of their patients using fentanyl (OR, 6.31; 95% CI, 2.59-15.35), vs no patients; or if they inducted patients in noninpatient settings (OR, 2.79; 95% CI, 1.39-5.61), vs inpatient settings.

**Conclusions and relevance:** In this survey study of clinician-reported problems initiating BUP treatment, clinicians working in high-volume noninpatient settings reported more problems initiating BUP in patients using fentanyl, and many reported changing their clinical practices in response to these problems. Further research is warranted to match alternate BUP induction strategies by clinical settings.

**[A Community-Driven Approach To Address Substance Use And Create A Great Plains American Indian Addiction And Recovery Research Agenda](#)** Luger B, Kihlström A, Sivaramakrishnan B, Kelliher A, Kropp F, Rosa C, Winhusen TJ, Warne D; CTN0129 participating Tribal communities. *Am J Community Psychol.* 2025 [Online ahead of print, December 26].

Substance use, specifically opioid and methamphetamine use, is of increasing concern among American Indian (AI) populations in the Great Plains. This community-driven participatory study investigated the impacts of substance use and community-defined needs in treating addiction. It determined the priorities for future research on behavioral health and substance misuse in the Great Plains region. Behavioral health and social services professionals and community stakeholders were identified from eight Great Plains communities and invited to attend eight focus groups (N = 47). Conversations were audio-recorded, transcribed, and coded by the research team. The qualitative data analysis identified four themes: (1) Challenges with

Treatment and Recovery, (2) Impact of Substance Use, (3) Reasons for Substance Use, (4) Solutions and Research Priorities. The findings highlight barriers to substance use disorder (SUD) treatment ranging from policy issues to lack of funding. The most significant finding centered on integrating cultural strengths into treatment and recovery programs, including Ceremony Assisted Treatment (CAT). Data reports for each participating organization were provided to disseminate outcomes in their respective communities. Other key findings suggest that addressing the root causes of substance use disorder, along with early intervention and comprehensive counseling services, are essential for long-term success.

**Health Plan Disenrollment And Mortality After Initiation Of Medications For Opioid Use Disorder** Nguyen AP, Binswanger IA, Narwaney KJ, Goodrich G, Christine PJ, Campbell CI, Xu S, Loree AM, Glanz JM. JAMA Psychiatry. 2026 [Online ahead of print, March 4].

**Importance:** Health plan disenrollment may interrupt treatment for opioid use disorder (OUD) and overall care, increasing risk for serious outcomes, including overdose and death. There is limited evidence on the association of disenrollment with all-cause and overdose mortality after initiating medications for OUD (MOUD) treatment.

**Objective:** To assess the association of health plan disenrollment with all-cause and overdose mortality in patients treated with MOUD.

**Design, setting, and participants:** This cohort study included privately and publicly insured patients aged 16 years or older who initiated buprenorphine or naltrexone for OUD treatment between January 1, 2012, and December 31, 2021, at 3 integrated health insurance and care delivery systems in 2 US states. Patients were followed up to 2 years until December 31, 2022. Data were analyzed July 2024 to November 2025.

**Exposure:** Health plan disenrollment following MOUD initiation.

**Main outcomes and measures:** All-cause mortality and drug-related and alcohol-related overdose mortality within 2 years of MOUD initiation ascertained from the National Death Index. Survival analyses were adjusted for patient sociodemographic and clinical characteristics.

**Results:** Among 20 011 patients (mean [SD] age 38.7 [15.1] years; 12 299 males [61.5%]) who were treated for OUD, 6948 (34.7%) experienced disenrollment and 586 (2.9%) died during follow-up. The crude rate was 15.3 (95% CI, 14.1-16.6) per 1000 person-years for all-cause mortality and 6.2 (95% CI, 5.4-7.0) per 1000 person-years for overdose mortality. Ever experiencing disenrollment showed elevated all-cause mortality (17.6 [95% CI, 14.9-20.8] vs 14.7 [95% CI, 13.4-16.1] per 1000 person-years) and overdose mortality (8.9 [95% CI, 7.1-11.3] vs 5.4 [95% CI, 4.7-6.3] per 1000 person-years) relative to remaining enrolled. In adjusted analyses, ever experiencing disenrollment was associated with increased hazards of all-cause (hazard ratio [HR], 1.51; 95% CI, 1.23-1.84) and overdose mortality (HR, 1.56; 95% CI, 1.17-2.09). Compared with remaining enrolled and receiving MOUD treatment, being disenrolled (HR, 4.34; 95% CI, 3.19-5.89) and being enrolled and not receiving MOUD treatment (HR, 4.19; 95% CI, 3.24-5.43) were associated with overall mortality.

**Conclusions and relevance:** In this cohort study of patients who initiated MOUD, experiencing health plan disenrollment was associated with increased mortality risk compared with remaining

enrolled. Strategies are needed to improve continuity of health coverage and mitigate the elevated mortality risk during insurance transitions for patients receiving medications for OUD.

**Extended-Release Vs Sublingual Buprenorphine In Pregnancy Through 12 Months Post Partum: A Randomized Clinical Trial** Winhusen TJ, Lofwall MR, Kropp F, Lewis D, Smid MC, Young JL, Hodgkins C, Krans EE, Hansen Z, Wachman EM, Schiff DM, Guille C, Rudolf V, Chowdhury T, Leeman L, Lewis M, Matthews AG, Cochran G, King J, Wilder C, Rosa C. JAMA Intern Med. 2026 [Online ahead of print, March 16].

**Importance:** Treating opioid use disorder (OUD) in pregnancy with sublingual buprenorphine is an evidence-based practice, but it has disadvantages that could be addressed with an extended-release formulation.

**Objective:** To evaluate the effectiveness and safety of extended-release buprenorphine vs sublingual buprenorphine for OUD in pregnancy through 12 months post partum.

**Design, setting, and participants:** This 2-group, open-label, noninferiority, randomized clinical trial was conducted between July 2, 2020, and October 30, 2024, among adults with OUD and a singleton pregnancy of 6 to 30 weeks' gestational age at 13 outpatient cross-disciplinary peripartum OUD treatment sites.

**Interventions:** Randomization to sublingual or extended-release buprenorphine (weekly formulation during pregnancy, monthly formulation optional post partum if not breastfeeding).

**Main outcomes and measures:** The primary and key secondary outcomes were illicit opioid abstinence during pregnancy and the postpartum period, respectively, defined as the proportion of weekly collected urine samples negative for illicit opioids. If noninferiority was demonstrated at a margin of 0.15, testing for superiority was planned. Key secondary infant outcomes from medical records were opioid treatment for neonatal opioid withdrawal syndrome (NOWS; yes or no) and number of opioid treatment days for NOWS.

**Results:** Among 140 randomized participants, the mean (SD) age was 31.2 (4.6) years. There were 10 Black participants (7.1%), 10 Hispanic participants (7.1%), 116 (82.9%) White participants, and 14 participants (10.0%) who belonged to additional groups. All but 2 were already prescribed sublingual buprenorphine. Study completion was 98% through pregnancy (137 participants) and 81% through 12 months post partum (114 participants). Illicit opioid abstinence was higher during pregnancy for participants receiving extended-release vs sublingual buprenorphine (82.5% vs 72.6%; mean difference, 9.84 [95% CI, 1.72 to 17.95] percentage points;  $P = .009$ ). Postpartum abstinence rates declined and were similar in both groups (60.2% vs 59.5%; mean difference, 0.65 [98% CI, -12.72 to 14.02] percentage points;  $P = .45$ ). Those receiving extended-release buprenorphine experienced fewer serious adverse events during pregnancy (8.7% vs 26.8%;  $P = .007$ ) and post partum (6.0% vs 18.6%;  $P = .04$ ). Nonserious adverse events rates did not differ between groups, but more were deemed medication-related for extended-release participants during pregnancy (26.1% vs 7.0%;  $P = .003$ ). Infants exposed to extended-release vs sublingual buprenorphine did not differ in need for opioid treatment (30.2% vs 26.5%; relative risk, 1.14 [98% CI, 0.54 to 1.99];  $P = .64$ ) or mean (SE) treatment days (10.9 [2.2] vs 14.8 [3.0] days; relative risk, 0.73 [98% CI, 0.36 to 1.51];  $P = .28$ ). At birth, extended-

release-exposed neonates had larger mean (SE) head circumferences than those exposed to sublingual buprenorphine (34.0 [0.2] vs 33.4 [0.2] cm; mean difference, 0.63 [95% CI, -0.00 to 1.26] cm; P = .049).

**Conclusions and relevance:** The findings of this randomized clinical trial support weekly extended-release buprenorphine for OUD treatment during pregnancy.

**Trial registration:** ClinicalTrials.gov Identifier: [NCT03918850](https://clinicaltrials.gov/ct2/show/study/NCT03918850).

## **INTRAMURAL RESEARCH**

**Predicting Individual Incubation Of Opioid Craving By Whole-Brain Functional Connectivity** Duan Y, Tsai PJ, Ma Z, Fredriksson I, Wang D, Lu H, Shaham Y, Yang Y. Proc Natl Acad Sci U S A. 2026; 123(11): e2531921123.

A high risk of relapse triggered by craving during abstinence remains a main challenge in opioid addiction treatment. Multiple brain regions have been implicated in opioid craving, but the brain-wide neural mechanisms underlying this process remain poorly understood. Using resting-state fMRI and connectome-based predictive modeling, we identified a whole-brain connectome that predicted the time-dependent increases (incubation) in oxycodone craving in individual rats after voluntary abstinence induced by exposure to an electric barrier. Incubation of oxycodone craving was operationally defined as the increase in nonreinforced lever pressing during relapse tests from early (day 1) to late (day 15) abstinence (incubation score). We found that changes in whole-brain functional connectivity during abstinence, but not during oxycodone self-administration, predicted the incubation score. Greater decreases in functional connectivity were associated with higher incubation scores. The predictive connectome involved complex interactions across multiple brain systems, including frontal-striatal, frontal-insula, insula-striatal, and hippocampal and sensorimotor circuits. To test causality of the predictive connectome, we examined the effect of pharmacological inactivation of dorsomedial striatum (DMS), which significantly decreased oxycodone seeking after electric barrier-induced abstinence. DMS inactivation increased connectivity strength within the predictive connectome, supporting a causal role of this connectome in incubation of oxycodone craving. The predictive connectome did not predict food-reward seeking after electric barrier-induced abstinence, indicating specificity to oxycodone craving. Our findings identify a brain-wide connectome marker that predicts individual differences in the incubation of opioid craving and provide potential targets for developing personalized interventions and monitoring therapeutic outcomes in opioid addiction treatment.

**Potentiation Of Fentanyl-Induced Respiratory Depression By Alcohol Is Not Fully Reversed By Naloxone** Frye EV, Hastings LE, Matthews AN, Gregory-Flores A, Vendruscolo JC, Kryszak LA, Jackson SN, Hampson AJ, Volkow ND, Vendruscolo LF, Marchette RC, Koob GF. JCI Insight. 2026; 11(6): e198059.

The high frequency of opioid overdose deaths often involves co-use of alcohol, which is reported in approximately 30% of fentanyl fatalities. Both substances depress respiratory function, and their combined effects can be lethal. The present study investigated physiological parameters of respiratory-depressant effects of fentanyl when coadministered with alcohol and their sensitivity

to naloxone reversal using whole-body plethysmography in male and female Long-Evans rats. Administration of a high, sedative-like dose of alcohol alone or fentanyl alone resulted in no mortality, but fentanyl plus alcohol led to mortality rates of 42% and 33% in females and males, respectively. The fentanyl+alcohol combination reduced minute ventilation and increased apneic pauses compared with either drug alone. Lower, binge-like alcohol doses when combined with fentanyl also amplified respiratory depression. Pretreatment with naloxone did not fully restore normal respiration. Naloxone administered after fentanyl+alcohol transiently reversed the decrease in minute ventilation but did not reverse apneic pauses. Fentanyl-dependent rats were partially tolerant to fentanyl- and fentanyl+alcohol-induced respiratory depression, but alcohol-dependent rats exhibited sensitization to alcohol- and fentanyl+alcohol-induced apnea. These findings highlight physiological parameters of severe respiratory risks with fentanyl+alcohol co-use, which are inadequately reversed by naloxone, underscoring the need for targeted strategies to manage opioid+alcohol overdoses.

**[Brain CB2 Receptor: A New Target In Medication Development For Treating Opioid Use Disorder In Rodents](#)** Soler-Cedeño O, Zhang HY, Xiong E, Bi GH, Alton H, Maras M, Liu QR, Bhattacharjee P, Iyer MR, Xi ZX. *Mol Psychiatry*. 2026; 31(4): 2351-2364.

Opioid use disorder (OUD) remains a major public health crisis, underscoring the urgent need for safer and more effective treatments. Cannabinoid CB2 receptor (CB2R) agonists show therapeutic promise for neuropsychiatric disorders and pain, with minimal psychoactive effects by themselves, but their potential in treating OUD is not well defined. Here, we report that MRI-2594, a novel, highly selective CB2R agonist, reduced heroin self-administration and heroin-primed reinstatement of drug-seeking behavior in rats. MRI-2594 produced modest analgesia by itself without impairing oxycodone-induced analgesia, hyperlocomotion, or causing sedation. Local infusion of MRI-2594 into the ventral tegmental area (VTA) or nucleus accumbens (NAc) also inhibited heroin self-administration in rats. Systemically administered MRI-2594 reduced dopamine (DA) release in the NAc, as measured by fiber photometry. In DAT-Cre mice, MRI-2594 attenuated brain-stimulation reward driven by optogenetic activation of VTA DA neurons - an effect blocked by the selective CB2R antagonist MRI-2687. To confirm CB2R mechanism, we generated a new strain of CB2-KO-eGFP mice in which the CB2R coding region was replaced with an eGFP reporter. Immunostaining revealed CB2R-driven GFP expression in tyrosine hydroxylase (TH)-positive VTA DA neurons of CB2-KO-eGFP, but not wild-type, mice. Lastly, MRI-2594 inhibited heroin self-administration in wild-type but not CB2-KO-eGFP mice. These findings demonstrate that brain CB2Rs mediate the anti-addictive effects of MRI-2594 and highlight CB2R as a potential target for OUD therapy.

**[A Ketogenic Diet Reduces Hepatic Alcohol Metabolism And Alcohol Consumption In Rats](#)** Elvig SK, McGinn A, Li X, Vendruscolo JCM, Gomez JL, Pawlosky R, Mackowiak B, Gonzalez L, King MT, Michaelides M, Gao B, Volkow ND, Koob GF, Wiers CE, Vendruscolo LF. *Neuropsychopharmacology*. 2026 [Online ahead of print, March 20].

Previous work showed that rats that were exposed to a high-fat, low-carbohydrate/protein ketogenic diet (KD) exhibited elevated blood alcohol levels following alcohol exposure compared with rats fed regular chow. Additionally, the administration of a KD prior to alcohol exposure (i.e., a history of KD) reduced alcohol consumption in alcohol-dependent rats that were no longer on the diet. In the present study, we investigated the mechanisms by which a KD alters

alcohol metabolism and tested whether ongoing KD exposure reduces alcohol consumption in rats. We hypothesized that chronic KD exposure alters hepatic alcohol-metabolizing enzymes, slows alcohol metabolism, and reduces alcohol self-administration in alcohol-dependent rats. We found that male and female rats maintained on a KD had higher blood alcohol levels, lower hepatic alcohol dehydrogenase 1 protein levels, and a higher nicotinamide adenine dinucleotide [NAD<sup>+</sup>]/[NADH] ratio in the liver cytoplasm compared with chow-fed control rats. Furthermore, KD-fed rats demonstrated lower brain glucose uptake relative to chow-fed control rats. In a model of alcohol dependence, the KD reduced alcohol consumption in male, but not female, rats compared with chow-fed rats. These findings suggest that a KD alters brain energetics and alcohol metabolism, which may contribute to reduced alcohol consumption in male rats.

**[Persistent Representation Of A Prior Schema In The Orbitofrontal Cortex Facilitates Learning Of A Conflicting Schema](#)** Maor I, Atwell J, Ascher I, Zhao Y, Takahashi YK, Hart E, Pereira F, Schoenbaum G. Nat Commun. 2026; 17(1): 2610.

Schemas allow efficient behavior in new situations, but reliance on them can impair flexibility when new demands conflict. Evidence implicates the orbitofrontal cortex (OFC) in deploying schemas in new situations. But how does this role affect learning of a conflicting schema? Here we addressed this question by recording or transiently inactivating OFC neurons in rats learning odor problems with identical external information but orthogonal rules governing reward. OFC representations adapted to track the underlying rules, and both performance and encoding were faster on subsequent than initial problems. Surprisingly, when the rule changed, persistent representation of the prior schema predicted faster acquisition of the new, and disrupting OFC activity during initial schema learning, later impaired acquisition of the second schema. Thus, rather than interfering with new learning, OFC neural activity was linked to improved acquisition by preserving accurate representations of the prior schema alongside the new one.

## **ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY**

**[Genetic Susceptibility To Schizophrenia And The Onset Of Brain Developmental Change In Adolescence](#)** Xu B, Dijkzeul A, Zhang Y, Schuurmans IK, Cecil CAM, Lee PH, Muetzel RL, Tiemeier H. Biol Psychiatry. 2026 [Online ahead of print, March 13].

**Background:** Early neurodevelopmental manifestations of genetic vulnerabilities to psychopathology are crucial for understanding disease onset and informing early intervention. However, the timing of when genetic risks begin to manifest in the brain remains unclear.

**Methods:** We leveraged two large neurodevelopmental cohorts: the Adolescent Brain Cognitive Development (ABCD) Study in the US and the Generation R (GenR) Study in the Netherlands. Repeated measures brain imaging data were collected from 6,229 individuals of European descent (mean baseline age 10 years), with an average follow-up of 2 (ABCD) to 4 (GenR) years. Using whole-brain vertex-wise linear mixed models, we investigated how polygenic scores (PGS) for four psychiatric disorders (attention-deficit/hyperactivity disorder (ADHD), autism, schizophrenia, major depression) and educational attainment associate with brain morphological trajectories.

**Results:** Children with low genetic susceptibility to schizophrenia presented expected increases in cortical surface area of the caudal middle and superior frontal regions during early adolescence, whereas those with higher genetic susceptibility showed decreases in these regions, suggesting divergent neurodevelopmental trajectories that may begin during this period. No significant associations were found between other psychiatric PGSs and brain structural changes over time. However, higher PGS for educational attainment were associated with persistently larger surface areas, while higher PGS for ADHD were related to persistently smaller surface areas in frontal and temporal lobes across time.

**Conclusions:** We show that the impact of genetic susceptibility to schizophrenia may begin to manifest in the brain in early adolescence, revealing dynamic neurodevelopmental changes that may serve as potential biomarkers for early detection of schizophrenia.

**Adolescent Pain Reports Share Genetic Overlap With Adult Chronic Pain Conditions: A Polygenic Score Analysis Using The ABCD Study** Rader L, Zorina-Lichtenwalter K, Gustavson DE, Wager TD, Friedman NP. *J Pain*. 2026; 43: 106260.

Adolescent pain complaints may be related to genetic risk for chronic pain across the life course. Identifying whether adolescent pain is genetically linked to chronic pain in adulthood can advance understanding of pain etiology and inform early intervention. Two waves of pain assessments were used from the Adolescent Brain Cognitive Development (ABCD) study, a population-based sample of 11,876 adolescents. The analyses included 6,387 adolescents of European-like ancestry (mean ages = 12.03 and 12.93 at waves 2 and 3; 52% males), with 94.0% retention across waves. Two polygenic scores (PGSs) were constructed using genome-wide association study summary statistics from up to 435,917 adults in the UK Biobank. One PGS captured shared genetic risk across 24 pain conditions (General Chronic Pain), while the second captured additional musculoskeletal-specific genetic risk across 11 conditions after adjusting for general pain (Musculoskeletal-specific Pain). Mixed-effects models were used to examine associations between these PGSs and adolescent self-reported pain presence, intensity, recurrence, and multi-site pain. Across both waves, 36.0%-37.0% adolescents reported pain. The General Pain PGS was associated with pain presence ( $b=0.07$ ,  $OR=1.07$ ,  $95\%CI=1.02-1.13$ ,  $FDR\text{-corrected } p=0.023$ ) and intensity ( $b=0.14$ ,  $95\%CI=0.07-0.21$ ,  $FDR\text{-corrected } p<0.001$ ); but not recurrent pain ( $b=0.08$ ,  $OR=1.08$ ,  $95\%CI=1.01-1.16$ ,  $FDR\text{-corrected } p=0.091$ ) or multi-site pain ( $b=0.01$ ,  $OR=1.00$ ,  $95\%CI=0.94-1.07$ ,  $FDR\text{-corrected } p=0.958$ ). The Musculoskeletal-specific Pain PGS was not significantly associated with the outcomes. Genetic risk for chronic pain in adulthood, as measured by PGSs, is associated with adolescent pain complaints. Adolescent pain signals early vulnerability for chronic pain, highlighting adolescence for early intervention. **PERSPECTIVE:** This study links adolescent pain to polygenic risk for adult chronic pain, suggesting that early pain reflects enduring genetic liability and reflects central pain processes. These results provide mechanistic insight into chronic pain across the lifespan and highlight adolescence as a period for intervention.

**Built Environment In Early Life Is Linked To Heterogeneous Trajectories Of Loneliness From Childhood To Adolescence In The ABCD Study** Liu H, Peng Z, Wong EL, Jim CY, Li L, Hou WK. *Health Place*. 2026; 97: 103568.

**Background:** Little is known about the predictors of loneliness in childhood and adolescence compared with late adulthood. Addressing the methodological limitations of recent studies on environment-loneliness associations, this study investigated the associations between a comprehensive list of built environment attributes in early life and longitudinal trajectories of loneliness from childhood to adolescence, considering together with demographic, personal, and social characteristics.

**Methods:** Built environment attributes at baseline (9-10 years of age) and the subsequent 4-year trajectories of loneliness (i.e., no, transitory, and chronic loneliness) were extracted from the Adolescent Brain Cognitive Development (ABCD) study dataset. Participants resided in the West (34.40 %), South (28.30 %), Midwest (20.40 %), and Northeast (16.90 %) Census Regions in USA. Least absolute shrinkage and selection operator (LASSO) logistic regression examined the associations between the built environment attributes and the three trajectories, weighted by lifetime exposure to the attributes and covariates.

**Findings:** Among 8638 children (mean age = 9.48, 47.46 % female) across the 4-year observations, 70.13 % presented no loneliness, 27.44 % transitory loneliness, and 2.43 % chronic loneliness. Among all built environment attributes and covariates, fewer social services, higher lead risk, higher noise and residential density, more alcohol outlets, and greater distance from major roads differentiated adolescents with transitory loneliness from no loneliness, whereas non-environmental individual attributes of female sex, higher internalizing symptoms, and higher personality trait of behavioral inhibition differentiated those with chronic loneliness from no loneliness.

**Interpretation:** Community support and urban planning should, on top of individualized assessment and interventions, be designed to encourage interactions between social groups within the physical spaces of cities, enhance the living environment, and address the social determinants of health for upholding child and adolescent mental health.

**[Stimulant Medications Affect Arousal And Reward, Not Attention Networks](#)** Kay BP, Wheelock MD, Siegel JS, Raut RV, Chauvin RJ, Metoki A, Rajesh A, Eck A, Pollaro J, Wang A, Suljic V, Adeyemo B, Baden NJ, Scheidter KM, Monk JS, Whiting FI, Ramirez-Perez N, Krimmel SR, Shinohara RT, Tervo-Clemmens B, Hermsillo RJM, Nelson SM, Hendrickson TJ, Madison T, Moore LA, Miranda-Domínguez Ó, Randolph A, Feczko E, Roland JL, Nicol GE, Laumann TO, Marek S, Gordon EM, Raichle ME, Barch DM, Fair DA, Dosenbach NUF. *Cell*. 2025; 188(26): 7529-7546.e20.

Prescription stimulants (e.g., methylphenidate) are thought to improve attention, but evidence from prior fMRI studies is conflicted. We utilized resting-state fMRI data from the Adolescent Brain Cognitive Development Study (n = 11,875; 8-11 years old) and validated the functional connectivity findings in a precision imaging drug trial with highly sampled (n = 5, 165-210 min each) healthy adults (methylphenidate 40 mg). Stimulant-related connectivity differences in sensorimotor regions matched fMRI patterns of daytime arousal, sleeping longer at night, and norepinephrine transporter expression. Taking stimulants reversed the effects of sleep deprivation on connectivity and school grades. Connectivity was also changed in salience and parietal memory networks, which are important for dopamine-mediated, reward-motivated learning, but not the brain's attention systems (e.g., dorsal attention network). The combined noradrenergic

and dopaminergic effects of stimulants may drive brain organization towards a more wakeful and rewarded configuration, improving task effort and persistence without effects on attention networks.

## **HEALTHY BRAIN CHILD DEVELOPMENT STUDY**

**Substance Use Patterns Among Individuals Who Consume Alcohol During Pregnancy: Results From A US Multi-Site Study** Bakhireva LN, Xingya M, Psaras C, Brtek V, Sullivan EL, Bogdan R, Chaiyachati BH, Chambers CD, Bandoli G, Croff JM, HBCD Substance Exposure Working Group. Drug and Alcohol Dependence. 2026; 282: 113101.

Alcohol use during pregnancy often co-occurs with other substance use, yet patterns of polysubstance exposure are not well characterized in large, diverse U.S. samples. In this multi-site study, the authors examine substance use behaviors among pregnant women who report alcohol consumption, focusing on the prevalence, combinations, and correlates of co-use with substances such as tobacco, cannabis, and opioids. They found that polysubstance use is common, with patterns shaped by demographic and psychosocial factors, and that certain subgroups are more likely to engage in concurrent use. Notably, this paper is among the first to use data from the HEALthy Brain and Child Development (HBCD) Study, a large, longitudinal, and diverse cohort examining early life exposures and neurodevelopment. The use of HBCD data strengthens these findings by providing a robust, harmonized framework to better characterize prenatal substance use patterns and their implications for child development. Overall, the results underscore that alcohol use during pregnancy frequently occurs within a broader context of multiple substance exposures, highlighting the need for integrated screening, prevention, and intervention strategies.