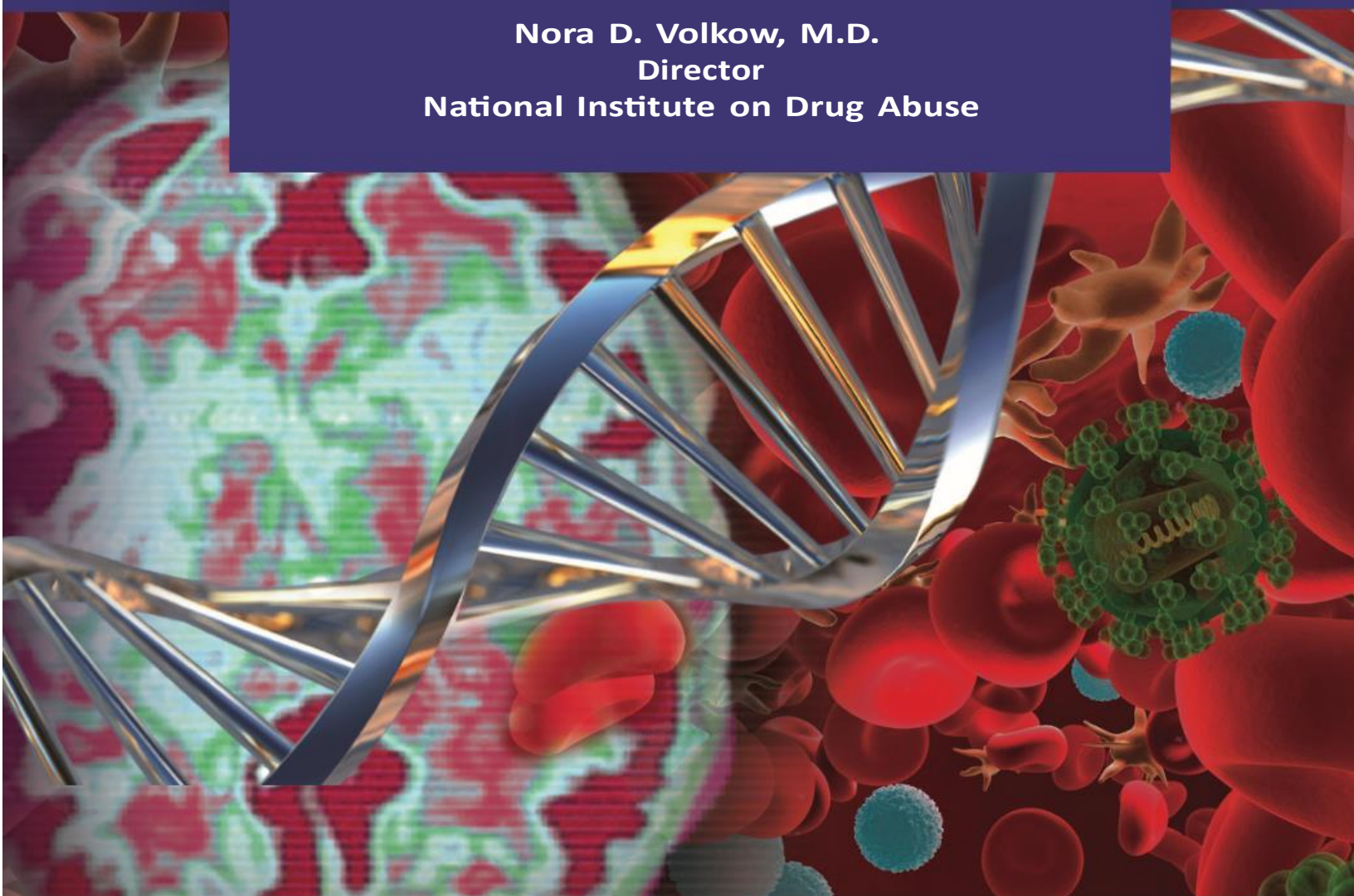
DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

September 9, 2025

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



RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

A Dual-Pathway Architecture For Stress To Disrupt Agency And Promote Habit.
Giovanniello JR, Paredes N, Wiener A, Ramírez-Armenta K, Oragwam C, Uwadia HO, Yu AL, Lim K, Pimenta JS, Vilchez GE, Nnamdi G, Wang A, Sehgal M, Reis FM, Sias AC, Silva AJ, Adhikari A, Malvaez M, Wassum KM. Nature. 2025; 640 (8059): 722-731.
Chronic stress can change how we learn and, thus, how we make decisions. Here we investigated the neuronal circuit mechanisms that enable this. Using a multifaceted systems neuroscience approach in male and female mice, we reveal a dual-pathway, amygdala-striatal neuronal circuit architecture by which a recent history of chronic stress disrupts the action-outcome learning underlying adaptive agency and promotes the formation of inflexible habits. We found that the projection from the basolateral amygdala to the dorsomedial striatum is activated by rewarding events to support the action-outcome learning needed for flexible, goal-directed decision-making. Chronic stress attenuates this to disrupt action-outcome learning and, therefore, agency. Conversely, the projection from the central amygdala to the dorsomedial striatum mediates habit formation. Following stress, this pathway is progressively recruited to learning to promote the premature formation of inflexible habits. Thus, stress exerts opposing effects on two amygdala-striatal pathways to disrupt agency and promote habit. These data provide neuronal circuit insights into how chronic stress shapes learning and decision-making, and help understanding of how stress can lead to the disrupted decision-making and pathological habits that characterize substance use disorders and mental health conditions.

The Polypharmacology Of Psychedelics Reveals Multiple Targets For Potential Therapeutics. Jain MK, Gumpper RH, Slocum ST, Schmitz GP, Madsen JS, Tummino TA, Suomivuori CM, Huang XP, Shub L, DiBerto JF, Kim K, DeLeon C, Krumm BE, Fay JF, Keiser M, Hauser AS, Dror RO, Shoichet B, Gloriam DE, Nichols DE, Roth BL. Neuron. 2025: S0896-6273(25)00470-2.
The classical psychedelics (+)-lysergic acid diethylamide (LSD), psilocybin, and mescaline exert their psychedelic effects via activation of the 5-HT_{2A} serotonin receptor (5-HT_{2A}R). Recent clinical studies have suggested that classical psychedelics may additionally have therapeutic potential for many neuropsychiatric conditions including depression, anxiety, migraine and cluster headaches, drug abuse, and post-traumatic stress disorder. In this study, we investigated the pharmacology of 41 classical psychedelics from the tryptamine, phenethylamine, and lysergamide chemical classes. We profiled these compounds against 318 human G-protein-coupled receptors (GPCRs) to elucidate their target profiles, and in the case of LSD, against more than 450 human kinases. We found that psychedelics have potent and efficacious actions at nearly every serotonin, dopamine, and adrenergic receptor. We quantified their activation for multiple transducers and found that psychedelics stimulate multiple 5-HT_{2A}R transducers, each of which correlates with psychedelic drug-like actions in vivo. Our results suggest that multiple molecular targets likely contribute to the actions of psychedelics.

Molecular Design Of A Therapeutic LSD Analogue With Reduced Hallucinogenic Potential. Tuck JR, Dunlap LE, Khatib YA, Hatzipantelis CJ, Weiser Novak S, Rahn RM, Davis AR, Mosswood A, Vernier AMM, Fenton EM, Aarrestad IK, Tombari RJ, Carter SJ, Deane Z, Wang Y, Sheridan A, Gonzalez MA, Avanes AA, Powell NA, Chytil M, Engel S, Fettinger JC, Jenkins AR, Carlezon WA Jr, Nord AS, Kangas BD, Rasmussen K, Liston C, Manor U, Olson DE. Proc Natl Acad Sci U S A. 2025; 122(16): e2416106122.
Decreased dendritic spine density in the cortex is a key pathological feature of neuropsychiatric diseases including depression, addiction, and schizophrenia (SCZ). Psychedelics possess a remarkable ability to promote cortical neuron growth and increase spine density; however, these compounds are contraindicated for patients with SCZ or a family history of psychosis. Here, we report the molecular design and de novo total synthesis of (+)-JRT, a structural analogue of lysergic acid diethylamide (LSD) with lower hallucinogenic potential and potent neuroplasticity-promoting properties. In addition to promoting spinogenesis in the cortex, (+)-JRT produces therapeutic effects in behavioral assays relevant to depression and cognition without exacerbating behavioral and gene expression signatures relevant to psychosis. This work underscores the potential of nonhallucinogenic psychoplastogens for treating diseases where the use of psychedelics presents significant safety concerns.

Psilocybin Reduces Heroin Seeking Behavior And Modulates Inflammatory Gene Expression In The Nucleus Accumbens And Prefrontal Cortex Of Male Rats. Floris G, Dabrowski KR, Zanda MT, Daws SE. Mol Psychiatry. 2025; 30(5): 1801-1816.
Preclinical and human studies indicate psilocybin may reduce perseverant maladaptive behaviors, including nicotine and alcohol seeking. Such studies in the opioid field are lacking, though opioids are involved in >50% of overdose deaths. Psilocybin is an agonist at the serotonin 2A receptor (5-HT2AR), a well-documented target for modulation of drug seeking, and evidence suggests 5-HT2AR agonists may dampen motivation for opioids. We sought to investigate the therapeutic efficacy of psilocybin in mediating cessation of opioid use and maintenance of long-lasting abstinence from opioid seeking behavior in a rat model of heroin self-administration (SA). Psilocybin or 5-HT2AR antagonists ketanserin and volinanserin were administered systemically to rats prior to SA of 0.075 mg/kg/infusion of heroin, or relapse following forced abstinence. Psilocybin did not alter heroin taking, but a single exposure to 3.0 mg/kg psilocybin 4-24 h prior to a relapse test blunted cue-induced heroin seeking. Conversely, 5-HT2AR antagonists exacerbated heroin relapse. To begin to elucidate mechanisms of psilocybin, drug-naïve rats received psilocybin and/or ketanserin, and tissue was collected from the prefrontal cortex (PFC), a region critical for drug seeking and responsive to psilocybin, 24 h later for RNA-sequencing. 3.0 mg/kg psilocybin regulated ~2-fold more genes in the PFC than 1.0 mg/kg, including genes involved in the cytoskeleton and cytokine signaling. Ketanserin blocked >90% of psilocybin-regulated genes, including the IL-17a cytokine receptor, Il17ra. Psychedelic compounds have reported anti-inflammatory properties, and therefore we performed a gene expression array to measure chemokine/cytokine molecules in the PFC of animals that displayed psilocybin-mediated inhibition of heroin seeking. Psilocybin regulated 4 genes, including Il17a, and a subset of genes correlated with relapse behavior. Selective inhibition of PFC IL-17a was sufficient to reduce heroin relapse. We conclude that psilocybin reduces heroin relapse and highlight IL-17a signaling as a potential downstream pathway of psilocybin that also reduces heroin seeking.

Leptin Activates Dopamine And GABA Neurons In The Substantia Nigra Via A Local Pars Compacta-Pars Reticulata Circuit. Mancini M, Hikima T, Witkovsky P, Patel JC, Stone DW, Affinati AH, Rice ME. J Neurosci. 2025; 45(21): e1539242025.
Adipose-derived leptin contributes to energy homeostasis by balancing food intake and motor output, but how leptin acts in brain motor centers remains poorly understood. We investigated the influence of leptin on neuronal activity in two basal ganglia nuclei involved in motor control: the substantia nigra pars compacta (SNc) and pars reticulata (SNr). Using a mouse reporter line to identify cells expressing leptin receptors (LepRs), we found that in both sexes, a majority of SNc dopamine neurons express a high level of LepR. Whole-cell recording in ex vivo midbrain slices from male wild-type mice showed that leptin activates SNc dopamine neurons directly and increases somatodendritic dopamine release. Although LepR expression in SNr GABA output neurons was low, leptin also activated these cells. Additional experiments showed that the influence of leptin on SNr neurons is indirect and involves D1 dopamine receptors and TRPC3 channels. Administration of leptin to male mice increased locomotor activity, consistent with activation of dopamine neurons in the SNc coupled to previously reported amplification of axonal dopamine release by leptin in striatal slices. These findings indicate that in addition to managing energy homeostasis through its actions as a satiety hormone, leptin also promotes axonal and somatodendritic dopamine release that can influence motor output.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Medicaid Managed Care Restrictions On Medications For The Treatment Of Opioid Use Disorder. Stewart MT, Andrews CM, Feltus SR, Hodgkin D, Horgan CM, Thomas CP, Nong T. Health Serv Res. 2025; 60 Suppl 2(Suppl 2): e14394.
To examine whether Medicaid managed care plan (MCP) utilization management policies for buprenorphine-naloxone and injectable naltrexone are related to key state Medicaid program policy decisions. We abstracted data on state Medicaid regulatory and policy information from publicly available sources and publicly available insurance benefit documentation from all 241 Medicaid MCPs operating in 2021. In this cross-sectional study, we used bivariate and multivariate analyses to examine whether Medicaid MCP prior authorization and quantity limits on receipt of buprenorphine and injectable naltrexone were associated with key state Medicaid choices to leverage federal funds to expand coverage and eligibility (Medicaid expansion, 1115 waivers) and to regulate Medicaid MCPs (uniform preferred drug lists, medical loss ratio remittance). Models were adjusted for MCP characteristics, including profit status, behavioral health contracting arrangement, National Committee for Quality Assurance accreditation, size, market share, and state opioid overdose death rates. Average marginal effects (AME) were reported. Utilization management was common among MCPs, and restrictions were more commonly applied to buprenorphine than injectable naltrexone, despite its higher cost. States that required MCPs to comply with utilization management policies stipulated in a uniform preferred drug list were more likely to require prior authorization for buprenorphine (AME: 0.29, 95% CI: 0.15-0.42) and injectable naltrexone (AME: 0.25, 95% CI: 0.12-0.38). MCPs in states that required plans to pay back earnings above a certain threshold were less likely to require prior authorization for buprenorphine (AME: -0.30, 95% CI: -0.43 to -0.18). Restrictions on medications for opioid use disorder are widespread among MCPs and vary by medication. State Medicaid regulatory and policy characteristics were strongly linked to MCPs' utilization

management approaches. State Medicaid policy and contracting approaches may be levers to eliminate utilization management restrictions on medications for opioid use disorder.

Outcomes Following Two Models Of Treatment Linkage Facilitation For Women With A History Of OUD Following Jail Release. Staton M, Tillson M, Terrill D, Oser C, Leukefeld C, Fanucchi L, McCollister K, Dickson MF, Winston E, Annett J, Webster JM. J Subst Use Addict Treat. 2025; 174: 209702.
The Kentucky hub of the NIDA-funded Justice Community Opioid Innovation Network (JCOIN) examined implementation of a PreTreatment Telehealth model of assessment, both alone and in combination with Peer Navigation, to increase utilization of SUD treatment (including MOUD) among women with a history of OUD during community re-entry. Participants included women (N = 900) randomly selected, screened for OUD, consented, and randomized to two levels of intervention, as well as a comparison group of women in jail-based treatment. About 90 % of women who were released from jail were followed in the community 3 months post-release to assess treatment outcomes. Findings indicated that almost half (44.2 %) of women entered SUD treatment during the 3 months post-release, and about one-fifth (22 %) entered MOUD treatment. In addition, days of substance use, including opioid use specifically, were significantly reduced among women who engaged with their Peer Navigator regularly in the community after jail release. Study findings support the need for future research on treatment linkage facilitation for women that is not only tailored to their unique needs at re-entry, but also considers the systemic facilitating factors and barriers that may be associated with treatment utilization (including the limited use of MOUD during incarceration).

Community Coalition Functioning, Collaborative Structure, And Coalition Models: Enhancing Support For Evidence-Based Practice Implementation. Im Y, Brown LD, Wells R, Gaddy MY, Chilenski SM. Prev Sci. 2025; 26(3): 426-437.
Coalition initiatives that use evidence-based practices (EBPs) have been shown to reduce youth substance use. Despite the importance of promoting community coalitions' EBP use, there is little empirical evidence about how to do so. This study aimed to identify distinct coalition profiles that foster EBP use by examining clusters of coalitions characteristics and the type of coalition model followed. We analyzed data from 67 coalitions participating in the Coalition Check-Up, a cluster randomized trial designed to increase community anti-drug coalition capacity. Using k-means clustering approach, we identified subgroups of coalitions based on two domains of coalition capacity-functioning and collaborative structure, each also considering coalition model type. We then examined, using analysis of variance (ANOVA), the degree to which each subgroup of coalitions used EBPs. We found that (a) coalitions with higher levels of functioning characterized by sustainability, science-based approaches to prevention, community knowledge, and efficiency, using explicit theory-based models were associated with higher use of EBPs, (b) coalitions with lower levels of collaborative structure defined by formalized procedures, decentralization, sectoral diversity, and intersectoral communication, using explicit theory-based models were associated with higher EBP use, and (c) low functioning coalitions using no model were associated with the lowest level of EBP use. Characterizing coalitions' functioning, collaborative structure, and models used may help coalition leaders and technical assistance providers enhance coalition capacity that enables the use of EBPs. Findings also indicated the importance of using explicit theory-based models to increase coalition impact.

Trends In Medical And Nonmedical Use Of Prescription Stimulants Among US Adolescents. McCabe SE, Wilens TE, Pasman E, McCabe VV, Schepis TS, Jardine J, Veliz P. JAMA. 2025: e2511260.
Among US adolescents, current medical use of prescription stimulants for ADHD increased between 2005 and 2023, while nonmedical use decreased. Lifetime nonmedical use was more prevalent than medical use in early cohorts but shifted to being less prevalent in recent cohorts. These findings are consistent with declines in peer-to-peer diversion among adolescents following COVID-related school closures4 and findings from adult studies. Study limitations include the cross-sectional design, lack of information on medication type and dose, and lack of representation of certain adolescent subpopulations (e.g., homeschooled, truant). Data from 2020 should be interpreted cautiously due to COVID-related disruptions. Despite concerns about increased stimulant prescribing, findings indicate no associated increase in nonmedical prescription stimulant use at this time, although longitudinal research and continued monitoring is necessary. These findings enable clinicians and policymakers to consider population-level trends in medical and nonmedical use patterns when weighing the risks and benefits of prescription stimulants.

Decline In US Drug Overdose Deaths By Region, Substance, And Demographics. Post LA, Ciccarone D, Unick GJ, et al. Decline in US Drug Overdose Deaths by Region, Substance, and Demographics. JAMA Netw Open. 2025; 8(6): e2514997.
Importance: Drug overdose deaths (DODs) surged with the advent of fentanyl. Recent US reports indicated a decline, but standard surveillance systems do not account for monthly variability or seasonality and require monthly population data to calculate DOD rates. Objective: To identify when US DOD rates began to decelerate and to examine patterns by census region, drug type, and demographics. Design, Setting, and Participants: This repeated cross-sectional study of DOD rates was conducted from January 2015 to October 2024, using data from the National Center for Health Statistics and US Census Bureau. Decedents included those whose drug poisoning death was classified as unintentional, intentional (suicide or homicide), or undetermined intent, identified by *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* codes for external overdose causes and T codes for opioids, cocaine, and psychostimulants (eg, methamphetamine). Main Outcomes and Measures: The main outcome was change in monthly DOD rates nationally and by drug type (opioids, cocaine, or methamphetamine), census region, and demographics. Joinpoint regression evaluated significant shifts in DOD rates applying the weighted bayesian information criterion and 2-sided *z* tests ($\alpha = .05$). Results: A total of 800 645 US residents (68.3% male; median age, 42 years [IQR, 33-54 years]) died of drug overdose between January 2015 and October 2024. The national DOD rate increased from 14.54 (95% CI, 14.52-14.55) per 100 000 population in January 2015 to 33.24 (95% CI, 33.15 to 33.33) per 100 000 population in August 2023. From August 2023 to February 2024, the monthly DOD rate declined by −0.36 (95% CI, −0.46 to −0.27) per 100 000 population, accelerating to −0.84 (95% CI, −0.77 to −0.92) per 100 000 population through October 2024 and reaching 24.29 (95% CI, 24.21-24.37) per 100 000 population. Opioid-related DOD rates declined faster than stimulant-related DOD rates (−0.80 [95% CI, −0.74 to −0.87] vs −0.25 [95% CI, −0.23 to −0.27] per 100 000 population). While the national DOD rate peaked in August 2023, rates peaked in the Northeast, Midwest, and South census regions in October 2022 and the West peaked a year later. By late 2023, death rates continued to accelerate among adults aged 55 years or older (0.07 per 100 000 population)

and American Indian or Alaska Native (0.02 per 100 000 population), Black or African American (1.70 per 100 000 population), Hispanic or Latino (0.20 per 100 000 population), and multiracial (0.28 per 100 000 population) populations, though the pace of increase was slowing, suggesting a potential inflection point. Conclusions and Relevance: In this cross-sectional study, US DOD rates entered a new wave of sustained deceleration in 2023 after 2 decades of increase. This shift may reflect changes in drug markets, treatment access, harm reduction efforts, and population-level risk. Although the decline is encouraging, persistent disparities highlight the need for targeted interventions and improved understanding of the underlying drivers. Over time, differences in use across cumulative disabilities persisted or worsened, especially among those with 3 or more disabilities. Targeted prevention, screening, and cessation efforts inclusive of multiple products are needed.

TREATMENT RESEARCH

Synthetic Cannabinoid Receptor Agonists Exacerbate Fentanyl-elicited Respiratory Depression And Confer Resistance To Naloxone Rescue In Mice. James JC, Thrush JR, Yusufali TM, Shaw HE, Avram M, Moran JH, Fantegrossi WE. Drug Alcohol Depend. 2025; 272: 112672.
Concurrent use of fentanyl with other drugs may contribute to the growing phenomenon of naloxone-resistant overdose. Synthetic cannabinoid receptor agonists (SCRAs) bind to CB1 receptors with high affinity and efficacy, eliciting psychoactive and abuse-related effects. Fentanyl is a common adulterant in SCRA products, and SCRAs are frequently detected as adulterants in street opioids, suggesting that these drugs are coadministered. Here we compared respiratory depressant effects of fentanyl to those of two structurally-distinct SCRAs: the naphthyl indole JWH-018 and the indazole carboxamide 5F-ADB-PINACA, following acute and chronic administration, using whole body plethysmography in mice. Fentanyl and the SCRAs were also co-administered, and antagonist rescue studies were conducted using large doses of naloxone, rimonabant, or a combination of both antagonists. In separate groups of mice, fentanyl and the SCRAs were administered alone or in binary combinations, and a single blood sample was drawn at a time of maximal respiratory depression to provide a pharmacokinetic snapshot of blood concentrations of drugs at this overdose-relevant timepoint. Fentanyl decreased respiratory rate, no tolerance to this effect was observed, and naloxone (but not rimonabant) attenuated respiratory depression. Both of the SCRAs similarly decreased respiratory rate, tolerance to this effect was observed with JWH-018 but not with 5F-ADB-PINACA, and rimonabant (but not naloxone) attenuated respiratory depression. Co-administration of fentanyl and the SCRAs exacerbated respiratory depression and confered resistance to naloxone rescue, most likely via pharmacodynamic interactions between μ-opioid and CB1 cannabinoid receptors, but we also suggest that some SCRAs will also instigate pharmacokinetic drug-drug interactions with fentanyl. UM1TR004909,T32DA022981,UL1TR003107

Speak And You Shall Predict: Evidence That Speech At Initial Cocaine Abstinence Is A Biomarker Of Long-Term Drug Use Behavior. Agurto C, Cecchi GA, King S, Eyigoz EK, Parvaz MA, Alia-Klein N, Goldstein RZ. Biol Psychiatry. 2025; 98(1): 65-75.
BACKGROUND: Valid scalable biomarkers for predicting longitudinal clinical outcomes in psychiatric research are crucial for optimizing intervention and prevention efforts. Here, we

recorded spontaneous speech from initially abstinent individuals with cocaine use disorder (iCUDs) for use in predicting drug use outcomes. METHODS: At baseline, 88 iCUDs provided 5-minute speech samples describing the positive consequences of quitting drug use and negative consequences of using drugs. Outcomes, including withdrawal, craving, abstinence days, and recent cocaine use, were assessed at 3-month intervals for up to 1 year (57 iCUDs were included in the analyses). Predictive modeling compared natural language processing (NLP) techniques, specifically sentence embeddings with established inventories as targets, with models utilizing standard demographic and baseline psychometric variables. RESULTS: At short time intervals, maximal predictive power was obtained with non-NLP models that also incorporated the same drug use measures (as the outcomes) obtained at baseline, potentially reflecting their slow rate of change, which could be estimated by linear functions. However, for longer-term predictions, speech samples alone demonstrated statistically significant results, with Spearman $r \geq 0.46$ and 80% accuracy for predicting abstinence. Therefore, speech samples may capture nonlinear dynamics over extended intervals more effectively than traditional measures. These results need to be replicated in larger and independent samples. CONCLUSIONS: Compared with the common outcome measures used in clinical trials, speech-based measures could be leveraged as better predictors of longitudinal drug use outcomes in initially abstinent iCUDs, as potentially generalizable to other subgroups with cocaine addiction, and to additional substance use disorders and related comorbidity.
R01DA041528,R01DA049547

In Vitro And In Vivo Pharmacokinetic Characterization Of 7-Hydroxymitragynine, An Active Metabolite Of Mitragynine, In Sprague-Dawley Rats. Chiang YH, Kanumuri SRR, Kuntz MA, Senetra AS, Berthold EC, Kamble SH, Mukhopadhyay S, Hampson AJ, McCurdy CR, Sharma A. Eur J Drug Metab Pharmacokinet. 2025; 50(3): 205-218.
BACKGROUND AND OBJECTIVES: Kratom, a Southeast Asian tree, has been researched for its potential as a therapeutic for substance use disorders. The most abundant alkaloid in kratom, mitragynine, is being investigated individually for opioid use disorder. However, the active metabolite of mitragynine,7-hydroxymitragynine (7-HMG) has raised concerns because of its high binding affinity to μ-opioid receptors and abuse potential. This study examines various pharmacokinetic parameters of 7-HMG in both in vitro and in vivo models. METHODS: In vitro pharmacokinetic properties were investigated using human colorectal adenocarcinoma cell monolayers (Caco-2 cells), rat plasma, rat liver microsomes, and rat hepatocytes to determine the permeability, plasma protein binding, and microsomal and hepatocyte stability of 7-HMG, respectively. Oral and intravenous (IV) pharmacokinetic studies of 7-HMG were performed in male Sprague-Dawley rats. RESULTS: 7-HMG exhibits high permeability across Caco-2 cells ($19.7 \pm 1.0 \times 10\text{-}6$ cm/s), with a relatively low plasma protein binding of $73.1 \pm 0.6\%$ to mitragynine. The hepatic extraction ratio was 0.3 and 0.6 in rat liver microsomes and hepatocytes, respectively, indicating that 7-HMG is an intermediate hepatic extraction compound. Oral and IV pharmacokinetic studies were performed in male rats. The volume of distribution was 2.7 ± 0.4 l/kg and the clearance was 4.0 ± 0.3 l/h/kg after IV administration. After oral dosing (5 mg/kg), a Cmax of 28.5 ± 5.0 ng/ml and Tmax of 0.3 ± 0.1 h were observed. However, the oral bioavailability of 7-HMG was only $2.7 \pm 0.3\%$. The results demonstrate 7-HMG is rapidly absorbed but has low oral bioavailability. Mitragynine pseudoindoxyl (MGPI) is a metabolite of 7-HMG that is a more potent μ-opioid agonist than 7-HMG. The parent-to-metabolite ratio for MGPI following IV 7-HMG administration was $0.5 \pm 0.1\%$, indicating very

limited systemic exposure to MGPI. CONCLUSIONS: This study reports the pharmacokinetic parameters of 7-HMG to help with the development of mitragynine, as a therapeutic. R01DA047855,R21DA055908,UH3DA048353

Therapeutic Effects Of Metformin On Cocaine Conditioned Place Preference And Locomotion. Hernandez E, Abdulahi MM, Hunsader P, Alshi A, Ufearo S, Reed A, Spencer S. Behav Neurosci. 2025; 139(3): 122-136.
Lack of Food and Drug Administration-approved treatments for cocaine use disorder contributes to high rates of treatment attrition, relapse, and overdose. Metformin is a Type 2 diabetes drug being investigated for multiple new therapeutic indications. This study set out to determine whether metformin would impact the conditioned rewarding effects of cocaine in an abbreviated or standard two-chamber conditioned place preference (CPP) assay. Adult male (n = 73) and female (n = 82) Sprague Dawley rats were conditioned in a 7-day (abbreviated: 2 × 30 min sessions daily) or a 12-day timeline (standard: 1 × 30 min sessions daily) alternating control and treatment sessions using an unbiased design. Metformin (175 mg/kg) or saline pretreatment occurred 30 min before conditioning with cocaine (20 mg/kg) or vehicle (saline). Data showed sex differences in physiological responses to cocaine and metformin, as well as variant behavioral patterns with different conditioning paradigms. Metformin pretreatment impaired acquisition of cocaine CPP in abbreviated, but not standard conditioning among male rats only. Cocaine-induced locomotor effects are moderated with metformin pretreatment in both female and male rats in different phases of conditioning, suggesting the potential therapeutic value of symptom alleviation when tapering patients off cocaine use with the goal of abstinence. Sex differences observed highlight the importance in better understanding the unique pharmacological profiles of female and male patients. This study provides evidence supporting the potential repurposing of metformin for disrupting rewarding and psychomotor effects of cocaine, paving the way for safe, low-cost, and accessible treatment. (PsycInfo Database Record (c) 2025 APA, all rights reserved). T32GM008244,F30DA059988,R21DA050822

HIV RESEARCH

Medications For Opioid Use Disorder Shape Immune Responses During Chronic HIV Infection. Collora JA, Steinhauser SF, Davenport TC, Lin DC, Eshetu A, Zeidi S, Kim R, Frank C, Kluger Y, Springer SA, Ho YC. Cell Rep Med. 2025; 6(6): 102159.
People living with HIV (PLWHs) have higher risk of opioid use disorder (OUD). Whether medications for opioid use disorder (MOUDs) change immune responses in HIV infection is unknown. We examined the immune profiles in PLWHs before and 3 months after initiation of the μ opioid receptor agonist methadone, partial agonist buprenorphine, and antagonist naltrexone. Using single-cell DOGMA-seq, we profiled 29,462 peripheral blood immune cells in 12 PLWHs. We found that naltrexone treatment increased type I interferon (IFN) responses while buprenorphine increased tumor necrosis factor (TNF) responses in cytotoxic T cell population. We found that HIV+ cells in PLWHs with OUD upregulated PTPN13 and TAF5L, both of which are associated with HIV replication. We found trends suggesting increased HIV RNA expression after methadone and decreased HIV RNA expression after buprenorphine and naltrexone initiation. Overall, PLWHs treated with MOUD had improved immune responses and decreased HIV expression.

The Strategies Timeline And Activities Reporting Tables: Improving HIV Care By Improving The Reporting Of Implementation Strategies. Garner BR, Bouris A, Charlebois ED, Li DH, Dakin A, Moskowitz J, Benbow N, Christopoulos K, Hickey MD, Imbert E. J Acquir Immune Defic Syndr. 2025; 98(5S): e205-e215.
The United States has made significant progress toward achieving the goals of its Ending the HIV Epidemic initiative. However, systematic reviews on HIV implementation research have identified problems regarding strategy specification that limit the research's transparency and replicability, and in turn limit improvements regarding HIV care in real-world practice. The strategies timeline, activities, and resources (STAResources) Table, developed as part of the substance abuse treatment to HIV Care II Project, was completed for it and 3 other HIV implementation research projects funded by the National Institute of Health. Each evaluated it in terms of the extent to which it addressed prior recommendations on strategy specification; issues related to rigor and reproducibility; and the extent to which it seemed pragmatic, simple, adaptable, relevant, helpful, useful, acceptable, appropriate, suitable, applicable, and fitting. Each was rated on a 4-point scale (0 = not at all; 1 = a little; 2 = moderately, and 3 = very much). Overall, the STAResources Table was rated favorably. It received a mean of 3.0 (SD = 0) in terms of being pragmatic, relevant, helpful, acceptable, appropriate, and applicable. The Strategies Timeline, Activities, and Rationale (STARationale) Table emerged during the process and was also rated favorably. To help the Ending the HIV Epidemic initiative achieve its goals, there is a critical need for transparent and replicable implementation research on identifying the most effective strategies for equitably implementing evidence-based practices within real-world settings. Addressing this need, the Strategies Timeline and Activities Reporting (STAReporting)Tables are pragmatic tools for helping improve the transparency and replicability of implementation strategy research.

A Treatment Mobile App For Sexual Minority Men Who Use Methamphetamine Demonstrates Reductions In Methamphetamine Use And HIV Sexual Risk Behaviors: Getting Off. Reback CJ, Lin C, Li MJ, Fletcher JB, Mata RP. AIDS Behav. [Online ahead of print July 18, 2025].
Sexual minority men (SMM) have elevated rates of methamphetamine use, which is deeply integrated into their sexual identities, sexual behaviors, and cultural spaces. Smartphone applications (apps) are often used to procure drugs and sexual partners. This study was a randomized clinical trial that evaluated the efficacy of the adaptation of an evidence-based intervention (Getting Off) into a mobile app format. From May 2021 to May 2023, 226 SMM who self-reported methamphetamine use in the past year were randomized to immediate delivery (ID) of the Getting Off app (n = 113) or a 30-day delayed delivery (DD) of the Getting Off app (n = 113). The average DSM-5 score for MUD was in the severe range (8.9 out of a possible 11). Mixed-effects models showed that at 1-month assessment, participants in the ID condition had significantly fewer days of injection methamphetamine use (estimate = - 0.57; SE = 0.15; p K01DA051329,P30MH058107,R01DA045562

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-Berluche D, Mayes TL, Shoptaw S, Trivedi MH, Potter JS, Schmitz J. Int J Behav Med. [Online ahead of print April 7, 2025].
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.
K01DA047912,R34DA060078

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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.

CLINICAL TRIALS NETWORK RESEARCH

Medications For Opioid Use Disorder: Predictors Of Early Discontinuation And Reduction Of Overdose Risk In US Military Veterans By Medication Type. Hayes CJ, Raciborski RA, Nowak M, Acharya M, Nunes EV Jr, Winhusen TJ. Addiction. 2025; 120(1): 138-151.
Aim: This study: (1) estimated the effect of early discontinuation of medication for opioid use disorder (MOUD) on overdose probability and (2) measured the relationship between patient characteristics and early discontinuation probability for each MOUD type. Design, setting and participants: This was a retrospective cohort using electronic health record data from the US Veterans Healthcare Administration. Participants were veterans initiating MOUD with buprenorphine (BUP), methadone (MET) or extended-release naltrexone (XR-NTX) from fiscal years 2012-19. A total of 39 284 veterans met eligibility with 22 721 (57.8%) initiating BUP, 12 652 (32.2%) initiating MET and 3911 (10.0%) initiating XR-NTX. Measurements: (1) determined whether the veteran experienced an overdose in the 365 days after MOUD initiation (primary) and (2) early discontinuation of MOUD, defined as discontinuation before 180 days (secondary). We assumed that unobserved patient characteristics would jointly influence the probability of discontinuation and overdose. and estimated the joint distribution with a bivariate probit model. Findings: We found that 9.0% of BUP initiators who experienced an overdose above the predicted 3.9% had no veteran-discontinued BUP early; findings for XR-NTX were similar, with 12.2% of initiators overdosing above the predicted 4.5%, but this was statistically inconclusive. We found no relationship between early discontinuation and overdose for MET initiators, probably due to the high risk of both events. The patient characteristics included in our post-estimation exploratory analysis of early discontinuation varied by MOUD type, with between 14 (XR-NTX) and 25 (BUP) tested. The only characteristics with at least one level showing a statistically significant change in probability of early discontinuation for all three MOUD types were geography and prior-year exposure to psychotherapy, although direction and magnitude varied. Conclusion: Early discontinuation of buprenorphine, and probably extended-release naltrexone, appears to be associated with a greater probability of experiencing a fatal or non-fatal overdose among US veterans receiving medication for opioid use disorder (MOUD); methadone does not show the same association. There is no consistent set of characteristics among early

discontinuers by MOUD type. Keywords**:** Geographic disparities; medication treatment for opioid use disorder; opioid use disorder; overdose; racial disparities; veterans.

Mortality Among Veterans With Opioid Use Disorder After Medical Hospitalization. Incze MA, Huebler S, Baylis JD, Stofko A, Kelley AT, Binswanger IA, Gordon AJ. JAMA Intern Med. 2025; 185(6): 734-736.
It is estimated that 1 in 9 hospitalized patients in the US has a substance use disorder (SUD).[1] The high prevalence of SUD among hospitalized patients makes hospitals especially important venues for identifying patients with SUD and offering real-time access to treatment. However, medical hospitalizations also represent periods of destabilization. Sequelae of acute medical illness, SUD-related vulnerability, and unfavorable contextual and environmental factors may synergize, increasing risk of overdose, readmission, and death immediately after hospital discharge. Regional studies have demonstrated an increased risk of death after hospitalization among individuals with SUD, but to date none have characterized the timing of greatest mortality risk. We used a national sample from the Veterans Health Administration (VHA) to estimate the risk of opioid-related and all-cause mortality during prespecified time periods after hospital discharge among patients with opioid use disorder (OUD). Understanding when patients experience the highest risk of harm after hospital discharge can inform the development of tailored interventions and targeted patient support.

Craving, Impulsivity, And Subsequent Methamphetamine Use With Naltrexone-Bupropion Versus Placebo: Findings From A Randomized Clinical Trial. Jha MK, Ghitza UE, Carmody T, Kuruvila S, Shoptaw S, Minhajuddin A, Wakhlu S, Schmitz JM, Coffin PO, Bart G, Nunes EV, Kenny P, Trivedi MH. J Addict Med. [Online ahead of print July 7, 2025].
Objectives: The accelerated development of additive pharmacotherapy treatment (ADAPT-2) for methamphetamine use disorder (MUD) trial demonstrated the efficacy of extended-release injectable naltrexone (NTX) and oral bupropion (BUP). In this secondary analysis, we determined whether craving and impulsivity levels could predict subsequent use of methamphetamine. Methods: Participants (N = 357) of the ADAPT-2 trial with at least one transition point [transition from positive-to-negative urine drug screen (UDS) or vice versa] during stage 1 (baseline through week-6) were included in this secondary analysis. Craving was assessed using the Visual Analog Scale (VAS). Impulsivity was assessed using the 2-item impulsivity factor of the Concise Health Risk Tracking (CHRT) Scale. Results: A significant treatment by craving by time interaction was noted (P = 0.018), where higher craving levels were consistently associated with a lower likelihood positive-to-negative UDS transition at the next visit in both NTX-BUP and placebo groups. However, no such effect was present by week 6 of treatment in the placebo group. CHRT Impulsivity also had a significant effect on the probability of a positive-to-negative UDS transition (P = 0.019) in addition to the 3-way interaction of VAS, week, and treatment group. Individuals with lower craving levels but higher impulsivity exhibited a lower probability of transitioning to negative UDS at the next visit. Higher craving, but not impulsivity, was associated with a higher likelihood of negative-to-positive UDS transition at the next visit in both treatment groups. Conclusions: Further investigations are necessary to optimize NTX-BUP treatment, focusing on the impact of craving and impulsivity on outcomes.

Clinical Decision Support System For Primary Care Of Opioid Use Disorder: A Randomized Clinical Trial. Rossom RC, Crain AL, Wright EA, Olson AW, Haller I, Haapala J, Dehmer SP, Hooker SA, Solberg L, O'Connor PJ, Borgert-Spaniol C, Gorodisher J, Miley K, Romagnoli K, Allen C, Tusing L, Ekstrom H, Appana D, Sperl-Hillen JM, Kobylinski M, Huntley K, McCormack J, Chen W, Bart G. JAMA Intern Med. e252535 [Online ahead of print July 14, 2025].

Importance: Nearly 727 000 individuals in the US died of opioid overdoses between 1999 and 2022. The current workforce of addiction medicine specialists is inadequate to address the scale of this crisis, and primary care clinicians (PCCs) do not feel sufficiently supported to treat opioid use disorder (OUD). Objective: To evaluate whether an electronic health record-integrated clinical decision support system (CDSS) increases OUD diagnosis and treatment in primary care. Design, setting, and participants: This pragmatic cluster randomized clinical trial was conducted from April 2021 to December 2023. Primary care clinics in 3 health systems in 4 US states were randomized to receive or not receive an electronic health record-integrated CDSS aimed at improving OUD diagnosis and treatment. Eligible patients were aged 18 to 75 years, visited a randomized clinic, and had an OUD diagnosis in the last 2 years, opioid overdose in the last 6 months, or risk score indicating high risk of OUD or opioid overdose. Data were analyzed from September 2023 to October 2024. Interventions: The OUD CDSS provided personalized treatment recommendations to patients and PCCs in intervention clinics. Main outcomes and measures: Primary outcomes were likelihood to receive (1) an OUD diagnosis (among high-risk patients without a baseline OUD diagnosis), (2) a naloxone prescription, or (3) a prescription of a medication for OUD (MOUD) or specialty referral, all within 30 days of first eligible (index) visit, and (4) days covered by a MOUD prescription in the 90 days after index. Results: Among 10 891 patients meeting eligibility criteria, 5918 (54.3%) were female, and the mean (SD) age was 48.0 (13.9) years. There was no difference in OUD diagnoses within 30 days between groups. Patients in the intervention group had more naloxone orders (80 of 5538 [1.4%] vs 40 of 5353 [0.7%]; odds ratio, 1.76; 95% CI, 1.14-2.72) and orders for MOUDs or treatment referral (775 of 5538 [14.0%] vs 503 of 5353 [9.4%]; odds ratio, 1.48; 95% CI, 1.05-2.08) within 30 days. There were no differences in median (IQR) days covered by MOUD over 90 days postindex between intervention (84 [55-90] days) and usual care (83 [55-90] days; rate ratio, 1.00; 95% CI, 0.93-1.08) or in overdose or death rates during the intervention period. Conclusions and relevance: In this cluster randomized clinical trial, the intervention improved rates of naloxone orders and OUD treatment in primary care but did not affect days covered by a MOUD over 90 days postindex or overdose or death rates. These findings demonstrate an OUD CDSS can help increase access to OUD treatment in primary care. Trial registration: Clinical Trials.gov Identifier: NCT04198428.

Effects Of Randomization To Buprenorphine Or Naltrexone For OUD On Cannabis Use Outcomes: A Secondary Analysis Of The X:BOT Trial. Shulman M, Choo TH, Ohrtman K, Pavlicova M, Rotrosen J, Nunes EV. Drug Alcohol Depend. 2025;; 268: 112550.

Aims: Cannabis use is highly prevalent in patients seeking treatment for opioid use disorder. Studies have shown mixed results on the association between cannabis use and opioid use as well as the impact of MOUD on cannabis use. The current study aims to investigate the effects of buprenorphine versus naltrexone on cannabis use outcomes in treatment seeking individuals with Opioid Use Disorder (OUD). Methods: The current study was based on data from the CTN-0051 X:BOT trial, which compared the time to return to significant opioid use survival outcomes of

two treatment seeking groups, one receiving Extended-Release Naltrexone (XR-naltrexone) (N = 283) versus another receiving Buprenorphine-Naloxone (N = 287) for OUD. A mixed-effects logistic regression model including treatment assignment (buprenorphine-naloxone vs XR-naltrexone), time, and a time by treatment interaction was run on the sample with the odds of cannabis use as the outcome, as well as two cross-lagged mediation models to explore the prospective mediation of cannabis use on opioid use outcomes (and opioid use on cannabis use outcomes) by treatment assignment during the trial. Results: There was a significant effect of buprenorphine treatment on reduced cannabis use. Participants receiving buprenorphine treatment were 39 % less likely to use cannabis than those receiving naltrexone over all the timepoints (p = .0499). No significant mediation was found between treatment assignment and opioid use on cannabis use outcomes or between treatment assignment and cannabis use on opioid use outcomes in this trial. Conclusion: Participants in this trial receiving buprenorphine treatment for OUD used less cannabis than those receiving naltrexone treatment.

INTRAMURAL RESEARCH

Hippocampal Output Suppresses Orbitofrontal Cortex Schema Cell Formation. Zong W, Zhou J, Gardner MPH, Zhang Z, Costa KM, Schoenbaum G.Nat Neurosci. 2025; 28(5): 1048-1060.
Both the orbitofrontal cortex (OFC) and the hippocampus (HC) are implicated in the formation of cognitive maps and their generalization into schemas. However, how these areas interact in supporting this function remains unclear, with some proposals supporting a serial model in which the OFC draws on task representations created by the HC to extract key behavioral features and others suggesting a parallel model in which both regions construct representations that highlight different types of information. In the present study, we tested between these two models by asking how schema correlates in rat OFC would be affected by inactivating the output of the HC, after learning and during transfer across problems. We found that the prevalence and content of schema correlates were unaffected by inactivating one major HC output area, the ventral subiculum, after learning, whereas inactivation during transfer accelerated their formation. These results favor the proposal that the OFC and HC operate in parallel to extract different features defining cognitive maps and schemas.

Brain Reactivity To Nicotine Cues Mediates The Link Between Resting-State Connectivity And Cue-Induced Craving In Individuals Who Smoke Or Vape Nicotine. Murray L, Scavnicky MK, Korponay C, Lukas SE, Frederick BB, Janes AC. Neuropsychopharmacology. 2025; 50(6): 983-990.
Individual differences in brain intrinsic functional connectivity (FC) and reactivity to nicotine cues are linked to variability in clinical outcomes in nicotine dependence. However, the relative contributions and potential interdependencies of these brain imaging-derived phenotypes in the context of craving and nicotine dependence are unclear. Moreover, it is unknown whether these relationships differ in individuals who smoke versus vape nicotine. To investigate these questions, eighty-six individuals who use nicotine daily (n = 67 smoking, n = 19 vaping) completed either a smoking or vaping cue-reactivity task and a resting-state scan during functional magnetic resonance imaging (fMRI). Validating the efficacy of the smoking and vaping tasks, both cohorts displayed robust reactivity to nicotine versus neutral cues in the

default mode network (DMN) and the anterior insula (AI), a primary node of the salience network (SN), which did not habituate over time. In the smoking and vaping groups, lower prefrontal reactivity to nicotine versus neutral cues and greater resting-state FC between nodes of the SN and DMN were associated with higher cue-induced craving. Moreover, we found that the former partially mediated the latter, suggesting a mechanism in which high resting SN-DMN connectivity increases craving susceptibility partly via a constraining effect on regulatory prefrontal reactivity to cues. These relationships were not impacted by group, suggesting that links between brain function and craving are similar regardless of smoking or vaping nicotine.

Locomotor Activity Depends On B-Arrestin Recruitment By The Dopamine D1 Receptor In The Striatal D1-D3 Receptor Heteromer. Evans AH, Ciruela-Jardí M, Rea W, Keegan BM, Levinstein MR, Bonifazi A, Cao J, Jackson SN, Shi L, Casajuana-Martin N, Cai NS, Casadó V, Earley CJ, Newman AH, Michaelides M, Pardo L, Moreno E, Ferré S. Pharmacol Res. 2025; 218: 107826.

Several dopaminergic compounds, including the clinically used pramipexole, are labelled as preferential dopamine D_3 receptor (D_3R) agonists based on their moderately higher affinity for the D_3R versus other D_2-like receptor subtypes. In rodents, these compounds typically produce locomotor depression with low doses and locomotor activation with higher doses, which has been assumed to be mediated by presynaptic D_3Rs and postsynaptic striatal D_2Rs, respectively. However, studies with selective pharmacological and genetic blockade of each dopamine receptor subtype suggest opposite roles. We address this apparent conundrum by performing a comprehensive *in vitro*, *in vivo* and *ex vivo* pharmacological comparison of several preferential D_3R agonists. Their differential properties reveal that their locomotor activating effects in mice are dependent on the striatal postsynaptic D_3Rs forming heteromers with D_1Rs, via their ability to potentiate β-arrestin recruitment by the D_1R in the D_1R-D_3R heteromer. The results also indicate that the locomotor depressant effects are largely dependent on their ability to activate presynaptic D_2Rs. More broadly, it is demonstrated that locomotor activity in mice depends on β-arrestin recruitment by the D_1R in the striatal D_1R-D_3R heteromer. These results can have implications for the treatment of L-dopa-induced dyskinesia and Restless Legs Syndrome.

Serotonin 1A Receptors Modulate Serotonin 2A Receptor-Mediated Behavioral Effects Of 5-Methoxy-N,N-dimethyltryptamine Analogs In Mice. Glatfelter GC, Clark AA, Cavalco NG, Landavazo A, Partilla JS, Naeem M, Golen JA, Chadeayne AR, Manke DR, Blough BE, McCorvy JD, Baumann MH.ACS Chem Neurosci. 2024; 15(24): 4458-4477.

5-methoxy-*N*,*N*-dimethyltrytpamine (5-MeO-DMT) analogs are used as recreational drugs, but they are also being developed as potential medicines, warranting further investigation into their pharmacology. Here, we investigated the neuropharmacology of 5-MeO-DMT and several of its *N*-alkyl, *N*-allyl, and 2-methyl analogs, with three major aims: 1) to determine in vitro receptor profiles for the compounds, 2) to characterize in vitro functional activities at serotonin (5-HT) 2A receptors ($5\text{-}HT_{2A}$) and 1A receptors ($5\text{-}HT_{1A}$), and 3) to examine the influence of $5\text{-}HT_{1A}$ on $5\text{-}HT_{2A}$-mediated psychedelic-like effects in the mouse head twitch response (HTR) model. In vitro receptor binding and functional assays showed that all 5-MeO-DMT analogs bind with high affinity and activate multiple targets (e.g., 5-HT receptor subtypes, alpha adrenergic receptors), including potent effects at $5\text{-}HT_{2A}$ and $5\text{-}HT_{1A}$. In C57Bl/6J mice, subcutaneous injection of the analogs induced HTRs with varying potencies (ED_{50} range = 0.2–1.8 mg/kg) and maximal effects (E_{max} range = 20–60 HTRs/30 min), while inducing hypothermia and

hypolocomotion at higher doses (ED_{50} range = 3.2–20.6 mg/kg). 5-HT_{2A} antagonist pretreatment blocked drug-induced HTRs, whereas 5-HT_{1A} antagonist pretreatment enhanced HTRs. In general, *N*,*N*-dialkyl and *N*-isopropyl derivatives displayed HTR activity, while the *N*-methyl, *N*-ethyl, and 2-methyl analogs did not. Importantly, blockade of 5-HT_{1A} unmasked latent HTR activity for the *N*-ethyl analog and markedly increased maximal responses for other HTR-active compounds (40–90 HTRs/30 min), supporting the notion that 5-HT_{1A} agonist activity can dampen 5-HT_{2A}-mediated HTRs. Suppression of 5-HT_{2A}-mediated HTRs by 5-HT_{1A} only occurred after high 5-MeO-DMT doses, suggesting involvement of other receptors in modulating psychedelic-like effects. Overall, our findings provide key information about the receptor target profiles for 5-MeO-DMT analogs, the structure–activity relationships for inducing psychedelic-like effects, and the critical role of 5-HT_{1A} agonism in modulating acute psychoactive effects of 5-HT_{2A} agonists.

RDS-04-010: A Novel Atypical DAT Inhibitor That Inhibits Cocaine Taking And Seeking And Itself Has Low Abuse Potential In Experimental Animals. Soler-Cedeno O, Galaj E, Klein B, Cao J, Bi GH, Newman AH, Xi ZX.Transl Psychiatry. 2025; 15(1): 182.
Cocaine use disorder (CUD) is a severe public health problem, and currently, there is no FDA-approved medication for its treatment. Atypical dopamine (DA) transporter (DAT) inhibitors display low addictive liability by themselves and may have therapeutic potential for treatment of psychostimulant use disorders. Here, we report that RDS-04-010, a novel atypical DAT inhibitor that binds to an inward-facing conformation of DAT due to its sulfoxide moiety, displayed distinct pharmacological profiles in animal models of addiction from its sulfide analog, RDS-03-094, a DAT inhibitor that binds to a more outward-facing conformation. Systemic administration of RDS-04-010 dose-dependently inhibited cocaine self-administration, shifted the cocaine self-administration dose-response curve downward, decreased motivation for cocaine seeking under progressive-ratio reinforcement conditions, and inhibited cocaine-primed reinstatement of drug-seeking behavior. RDS-04-010 alone neither altered optical brain-stimulation reward nor evoked reinstatement of drug-seeking behavior. RDS-04-010 substitution for cocaine was not able to maintain self-administration in rats trained to self-administer cocaine. In contrast, RDS-03-094 displayed more cocaine-like reinforcing effects. Its pretreatment upward-shifted both the cocaine self-administration dose-response and optical brain-stimulation reward curves. RDS-03-094 alone was able to reinstate extinguished cocaine-seeking behavior and sustain self-administration during a substitution test. Collectively, these findings suggest that RDS-04-010 is a novel atypical DAT inhibitor with favorable therapeutic potential in reducing cocaine-taking and -seeking behavior with low addictive liability. Moreover, this extensive behavioral evaluation further confirms the role that DAT binding conformation plays in the distinctive profiles of atypical DAT inhibitors that prefer the inward facing conformation.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

Longer Scans Boost Prediction And Cut Costs In Brain-Wide Association Studies. Ooi LQR, Orban C, Zhang S, Nichols TE, Tan TWK, Kong R, Marek S, Dosenbach NUF, Laumann TO, Gordon EM, Yap KH, Ji F, Chong JSX, Chen C, An L, Franzmeier N, Roemer-Cassiano SN, Hu Q, Ren J, Liu H, Chopra S, Cocuzza CV, Baker JT, Zhou JH,

Bzdok D, Eickhoff SB, Holmes AJ, Yeo BTT; Alzheimer's Disease Neuroimaging Initiative. Nature. [Online ahead of print July 16, 2025].
A pervasive dilemma in brain-wide association studies1 (BWAS) is whether to prioritize functional magnetic resonance imaging (fMRI) scan time or sample size. We derive a theoretical model showing that individual-level phenotypic prediction accuracy increases with sample size and total scan duration (sample size × scan time per participant). The model explains empirical prediction accuracies well across 76 phenotypes from nine resting-fMRI and task-fMRI datasets ($R2 = 0.89$), spanning diverse scanners, acquisitions, racial groups, disorders and ages. For scans of ≤20 min, accuracy increases linearly with the logarithm of the total scan duration, suggesting that sample size and scan time are initially interchangeable. However, sample size is ultimately more important. Nevertheless, when accounting for the overhead costs of each participant (such as recruitment), longer scans can be substantially cheaper than larger sample size for improving prediction performance. To achieve high prediction performance, 10 min scans are cost inefficient. In most scenarios, the optimal scan time is at least 20 min. On average, 30 min scans are the most cost-effective, yielding 22% savings over 10 min scans. Overshooting the optimal scan time is cheaper than undershooting it, so we recommend a scan time of at least 30 min. Compared with resting-state whole-brain BWAS, the most cost-effective scan time is shorter for task-fMRI and longer for subcortical-to-whole-brain BWAS. In contrast to standard power calculations, our results suggest that jointly optimizing sample size and scan time can boost prediction accuracy while cutting costs. Our empirical reference is available online for future study design (https://thomasyeolab.github.io/OptimalScanTimeCalculator/index.html).

Social Media Use And Depressive Symptoms During Early Adolescence. Nagata JM, Otmar CD, Shim J, Balasubramanian P, Cheng CM, Li EJ, Al-Shoaibi AAA, Shao IY, Ganson KT, Testa A, Kiss O, He J, Baker FC. JAMA Netw Open. 2025; 8(5): e2511704.
Importance: In 2023, the US Surgeon General issued the Advisory on Social Media and Youth Mental Health, identifying critical research gaps that preclude evidence-based guidance given that most studies of social media and mental health have been cross-sectional rather than longitudinal and have focused on young adults or older adolescents rather than on younger adolescents. Objective: To evaluate longitudinal associations between social media use (time spent on social media) and depressive symptoms across 4 annual waves spanning a 3-year follow-up period from late childhood to early adolescence. Design, setting, and participants: In this prospective cohort study using data from the Adolescent Brain Cognitive Development Study across 21 study sites from October 2016 to October 2018, children aged 9 to 10 years at baseline were assessed across 4 waves (baseline, year 1, year 2, and year 3), with year-3 follow-up through 2022. Sample sizes varied across waves and measures due to attrition and missing data. Analyses retained all available data at each wave. Data were analyzed from January 2024 to March 2025. Exposures: Self-reported time spent on social media at baseline to 3-year follow-up. Main outcomes and measures: Reciprocal associations between social media use and depressive symptoms (Child Behavior Checklist) at baseline and at 1, 2, and 3 years of follow-up were assessed using longitudinal, cross-lagged structural equation panel models. Covariates included sex, race and ethnicity, household income, and parental educational level. Results: At baseline, the sample included 11 876 participants (mean [SD] age, 9.9 [0.6] years), of whom 6196 (52.2%) were male. After adjusting for stable between-person differences and covariates, within-person increases in social media use above the person-level mean were associated with elevated depressive symptoms from year 1 to year 2 (β, 0.07; 95% CI, 0.01-0.12; P = .01) and

from year 2 to year 3 (β, 0.09; 95% CI, 0.04-0.14; P < .001), whereas depressive symptoms were not associated with subsequent social media use at any interval. The final random-intercept cross-lagged panel model demonstrated a good fit (comparative fit index, 0.977; Tucker-Lewis index, 0.968; root mean square error of approximation, 0.031 [90% CI, 0.029-0.033]). Between-person differences in social media use were not associated with depressive symptoms (β, -0.01; 95% CI, -0.04 to 0.02; P = .46) after accounting for demographic and family-level factors. Conclusions and relevance: In this cohort study of 11 876 children and adolescents, reporting higher than person-level mean social media use in years 1 and 2 after baseline was associated with greater depressive symptoms in the subsequent year. The findings suggest that clinicians should provide anticipatory guidance regarding social media use for young adolescents and their parents.

Human Lifespan Changes In The Brain's Functional Connectome. Sun L, Zhao T, Liang X, Xia M, Li Q, Liao X, Gong G, Wang Q, Pang C, Yu Q, Bi Y, Chen P, Chen R, Chen Y, Chen T, Cheng J, Cheng Y, Cui Z, Dai Z, Deng Y, Ding Y, Dong Q, Duan D, Gao JH, Gong Q, Han Y, Han Z, Huang CC, Huang R, Huo R, Li L, Lin CP, Lin Q, Liu B, Liu C, Liu N, Liu Y, Liu Y, Lu J, Ma L, Men W, Qin S, Qiu J, Qiu S, Si T, Tan S, Tang Y, Tao S, Wang D, Wang F, Wang J, Wang P, Wang X, Wang Y, Wei D, Wu Y, Xie P, Xu X, Xu Y, Xu Z, Yang L, Yuan H, Zeng Z, Zhang H, Zhang X, Zhao G, Zheng Y, Zhong S; Alzheimer's Disease Neuroimaging Initiative; DIDA-MDD Working Group; MCADI; He Y. Nat Neurosci. 2025; 28(4): 891-901.
Functional connectivity of the human brain changes through life. Here, we assemble task-free functional and structural magnetic resonance imaging data from 33,250 individuals at 32 weeks of postmenstrual age to 80 years from 132 global sites. We report critical inflection points in the nonlinear growth curves of the global mean and variance of the connectome, peaking in the late fourth and late third decades of life, respectively. After constructing a fine-grained, lifespan-wide suite of system-level brain atlases, we show distinct maturation timelines for functional segregation within different systems. Lifespan growth of regional connectivity is organized along a spatiotemporal cortical axis, transitioning from primary sensorimotor regions to higher-order association regions. These findings elucidate the lifespan evolution of the functional connectome and can serve as a normative reference for quantifying individual variation in development, aging and neuropsychiatric disorders.

Genetic Risk-Dependent Brain Markers Of Resilience To Childhood Trauma. Lu H, Rolls ET, Liu H, Stein DJ, Sahakian BJ, Elliott R, Jia T, Xie C, Xiang S, Wang N, Banaschewski T, Bokde ALW, Desrivières S, Flor H, Grigis A, Garavan H, Heinz A, Brühl R, Martinot JL, Martinot MP, Artiges E, Nees F, Orfanos DP, Lemaitre H, Poustka L, Hohmann S, Holz N, Fröhner JH, Smolka MN, Vaidya N, Walter H, Whelan R, Schumann G, Feng J, Luo Q; IMAGEN Consortium. Nat Commun. 2025; 16(1): 6219.
Resilience to developing emotional disorders is critical for adolescent mental health, especially following childhood trauma. Yet, brain markers of resilience remain poorly understood. By analyzing brain responses to angry faces in a large-scale longitudinal adolescent cohort (IMAGEN), we identified two functional networks located in the orbitofrontal and occipital regions. In girls with high genetic risks for depression, higher orbitofrontal-related network activation was associated with a reduced impact of childhood trauma on emotional symptoms at age 19, whereas in those with low genetic risks, lower occipital-related network activation had a similar association. These findings reveal genetic risk-dependent brain markers of resilience

(GRBMR). Longitudinally, the orbitofrontal-related GRBMR predicted subsequent emotional disorders in late adolescence, which were generalizable to an independent prospective cohort (ABCD). These findings demonstrate that high polygenic depression risk relates to activations in the orbitofrontal network and to resilience, with implications for biomarkers and treatment.

A Pattern-Learning Algorithm Associates Copy Number Variations With Brain Structure And Behavioural Variables In An Adolescent Population Cohort. Kopal J, Huguet G, Marotta J, Aggarwal S, Osayande N, Kumar K, Saci Z, Jean-Louis M, Chai XJ, Ge T, Yeo BTT, Thompson PM, Bearden CE, Andreassen OA, Jacquemont S, Bzdok D. Nat Biomed Eng. [Online ahead of print July 18, 2025].

Our genetic makeup, together with environmental and social influences, shape our brain's development. Yet, the imaging-genetics field has struggled to integrate all these modalities to investigate the interplay between genetic blueprint, brain architecture, environment, human health and daily living skills. Here we interrogate the Adolescent Brain Cognitive Development (ABCD) cohort to outline the effects of rare high-effect genetic variants on brain architecture and their corresponding implications on cognitive, behavioural, psychosocial and socioeconomic traits. We design a holistic pattern-learning framework that quantitatively dissects the impacts of copy number variations (CNVs) on brain structure and 938 behavioural variables spanning 20 categories in 7,338 adolescents. Our results reveal associations between genetic alterations, higher-order brain networks and specific parameters of the family wellbeing, including increased parental and child stress, anxiety and depression, or neighborhood dynamics such as decreased safety. We thus find effects extending beyond the impairment of cognitive ability or language capacity which have been previously reported. Our investigation spotlights the interplay between genetic variation and subjective life quality in adolescents and their families.