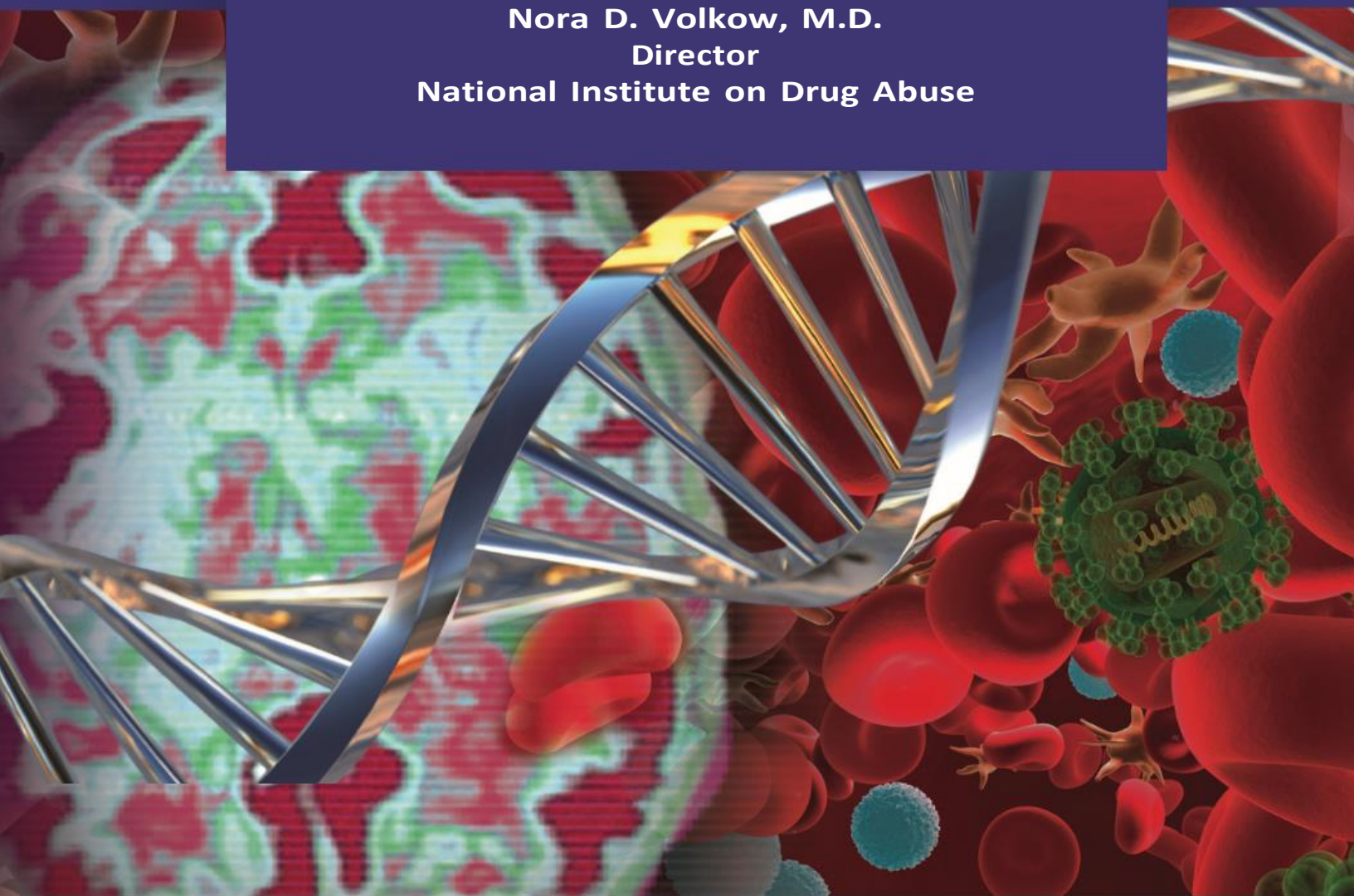
DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

September 11, 2024

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



RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Myelin Plasticity In The Ventral Tegmental Area Is Required For Opioid Reward Yalçın B, Pomrenze MB, Malacon K, Drexler R, Rogers AE, Shamardani K, Chau IJ, Taylor KR, Ni L, Contreras-Esquivel D, Malenka RC, Monje M. Nature. 2024; 630(8017): 677–685.
All drugs of abuse induce long-lasting changes in synaptic transmission and neural circuit function that underlie substance-use disorders. Another recently appreciated mechanism of neural circuit plasticity is mediated through activity-regulated changes in myelin that can tune circuit function and influence cognitive behaviour. Here we explore the role of myelin plasticity in dopaminergic circuitry and reward learning. We demonstrate that dopaminergic neuronal activity-regulated myelin plasticity is a key modulator of dopaminergic circuit function and opioid reward. Oligodendroglial lineage cells respond to dopaminergic neuronal activity evoked by optogenetic stimulation of dopaminergic neurons, optogenetic inhibition of GABAergic neurons, or administration of morphine. These oligodendroglial changes are evident selectively within the ventral tegmental area but not along the axonal projections in the medial forebrain bundle nor within the target nucleus accumbens. Genetic blockade of oligodendrogenesis dampens dopamine release dynamics in nucleus accumbens and impairs behavioural conditioning to morphine. Taken together, these findings underscore a critical role for oligodendrogenesis in reward learning and modification that is required for opioid reward.

A Master Regulator Of Opioid Reward In The Ventral Prefrontal Cortex Smith ACW, Ghoshal S, Centanni SW, Heyer MP, Corona A, Wills L, Andraka E, Lei Y, O'Connor RM, Caligiuri SPB, Khan S, Beaumont K, Sebra RP, Kieffer BL, Winder DG, Ishikawa M, Kenny PJ. Science. 2024; 384(6700): eadn0886.
In addition to their intrinsic rewarding properties, opioids can also evoke aversive reactions that protect against misuse. Cellular mechanisms that govern the interplay between opioid reward and aversion are poorly understood. We used whole-brain activity mapping in mice to show that neurons in the dorsal peduncular nucleus (DPn) are highly responsive to the opioid oxycodone. Connectomic profiling revealed that DPn neurons innervate the parabrachial nucleus (PBn). Spatial and single-nuclei transcriptomics resolved a population of PBn-projecting pyramidal neurons in the DPn that express m-opioid receptors (mORs). Disrupting mOR signaling in the DPn switched oxycodone from rewarding to aversive and exacerbated the severity of opioid withdrawal. These findings identify the DPn as a key substrate for the abuse liability of opioids.

The Cerebellum Directly Modulates The Substantia Nigra Dopaminergic Activity Washburn S, Oñate M, Yoshida J, Vera J, Bhuvanasundaram R, Khatami L, Nadim F, Khodakhah K. Nature Neuroscience. 2024; 27(3): 497–513.
Evidence of direct reciprocal connections between the cerebellum and basal ganglia has challenged the long-held notion that these structures function independently. While anatomical studies have suggested the presence of cerebellar projections to the substantia nigra pars compacta (SNc), the nature and function of these connections (Cb-SNc) is unknown. Here we show, in mice, that Cb-SNc projections form monosynaptic glutamatergic synapses with dopaminergic and non-dopaminergic neurons in the SNc. Optogenetic activation of Cb-SNc axons in the SNc is associated with increased SNc activity, elevated striatal dopamine levels and increased locomotion. During

behavior, Cb-SNc projections are bilaterally activated before ambulation and unilateral lever manipulation. Cb-SNc projections show prominent activation for water reward and higher activation for sweet water, suggesting that the pathway also encodes reward value. Thus, the cerebellum directly, rapidly and effectively modulates basal ganglia dopamine levels and conveys information related to movement initiation, vigor and reward processing.

A μ-Opioid Receptor Modulator That Works Cooperatively With Naloxone O'Brien ES, Rangari VA, El Daibani A, Eans SO, Hammond HR, White E, Wang H, Shiimura Y, Krishna Kumar K, Jiang Q, Appourchaux K, Huang W, Zhang C, Kennedy BJ, Mathiesen JM, Che T, McLaughlin JP, Majumdar S, Kobilka BK. Nature. 2024; 631(8021): 686–693.
The μ-opioid receptor (μOR) is a well-established target for analgesia, yet conventional opioid receptor agonists cause serious adverse effects, notably addiction and respiratory depression. These factors have contributed to the current opioid overdose epidemic driven by fentanyl, a highly potent synthetic opioid. μOR negative allosteric modulators (NAMs) may serve as useful tools in preventing opioid overdose deaths, but promising chemical scaffolds remain elusive. Here we screened a large DNA-encoded chemical library against inactive μOR, counter-screening with active, G-protein and agonist-bound receptor to 'steer' hits towards conformationally selective modulators. We discovered a NAM compound with high and selective enrichment to inactive μOR that enhances the affinity of the key opioid overdose reversal molecule, naloxone. The NAM works cooperatively with naloxone to potently block opioid agonist signaling. Using cryogenic electron microscopy, we demonstrate that the NAM accomplishes this effect by binding a site on the extracellular vestibule in direct contact with naloxone while stabilizing a distinct inactive conformation of the extracellular portions of the second and seventh transmembrane helices. The NAM alters orthosteric ligand kinetics in therapeutically desirable ways and works cooperatively with low doses of naloxone to effectively inhibit various morphine-induced and fentanyl-induced behavioural effects in vivo while minimizing withdrawal behaviours. Our results provide detailed structural insights into the mechanism of negative allosteric modulation of the μOR and demonstrate how this can be exploited in vivo.

Unlocking Opioid Neuropeptide Dynamics With Genetically Encoded Biosensors Dong C, Gowrishankar R, Jin Y, He XJ, Gupta A, Wang H, Sayar-Atasoy N, Flores RJ, Mahe K, Tjahjono N, Liang R, Marley A, Or Mizuno G, Lo DK, Sun Q, Whistler JL, Li B, Gomes I, Von Zastrow M, Tejeda HA, Atasoy D, Devi LA, Bruchas MR, Banghart MR, Tian L. Nature Neuroscience. 2024. [Online ahead of print].
Neuropeptides are ubiquitous in the nervous system. Research into neuropeptides has been limited by a lack of experimental tools that allow for the precise dissection of their complex and diverse dynamics in a circuit-specific manner. Opioid peptides modulate pain, reward and aversion and as such have high clinical relevance. To illuminate the spatiotemporal dynamics of endogenous opioid signaling in the brain, we developed a class of genetically encoded fluorescence sensors based on kappa, delta and mu opioid receptors: κLight, δLight and μLight, respectively. We characterized the pharmacological profiles of these sensors in mammalian cells and in dissociated neurons. We used κLight to identify electrical stimulation parameters that trigger endogenous opioid release and the spatiotemporal scale of dynorphin volume transmission in brain slices. Using in vivo fiber photometry in mice, we demonstrated the utility of these sensors in detecting optogenetically driven opioid release and observed differential opioid release dynamics in response to fearful and rewarding conditions.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Leveraging Pooled Medical Examiner Records To Surveil Complex And Emerging Patterns Of Polysubstance Use In The United States Shover CL, Friedman JR, Romero R, Jimenez S, Beltran J, Garcia C, Goodman-Meza D. The International Journal on Drug Policy. 2024; 9: 104397. [Online ahead of print].

Background: The United States (US) is an extreme global outlier for drug-related death rates. However, data describing drug-related deaths are generally available only on an 8-13-month lag. Furthermore, granular details about substance-involvement are often not available, which particularly stymies efforts to track fatal polysubstance and novel psychoactive substance use. Detailed medical examiner records provide a powerful source of information for drug-related death surveillance, but have been underutilized. **Methods:** We pooled medical examiner data from five US states and 14 counties that together comprise 18% of the US population to examine demographic, geographic, and drug-specific trends in polysubstance drug-related deaths. We employed mixed effects logistic regression to identify demographic factors associated with polysubstance rather than single substance drug-related deaths. We assessed the correlations between drug classes and described geographic variation in the prevalence of specific drugs and the presence of novel and emerging psychoactive substances. **Results:** Our sample included 73,077 drug-related deaths from 2012 through early 2022. Nearly two-thirds of drug-related deaths were polysubstance-involved, with the number and percentage growing annually. High percentages of polysubstance drug-related deaths were observed in both urban and rural jurisdictions. After adjusting for year and jurisdiction, female, American Indian and Alaska Native, and White individuals had the most elevated odds of polysubstance drug-related deaths. Drug-related deaths involving benzodiazepines or opioids, whether pharmaceutical or illicit, and other pharmaceutical drugs were most likely to have polysubstance involvement, while methamphetamine-involved deaths were least likely to involve multiple substances. Strong correlations were observed between prescription opioids and prescription benzodiazepines, fentanyl and xylazine, and designer benzodiazepines and novel synthetic opioids. **Conclusions:** Analysis of detailed medical examiner records reveals the breadth and complexity of polysubstance drug-related deaths in the US. Future efforts to use this unique resource can improve population-based surveillance of drug-related deaths to better tailor interventions and solutions to this critical health crisis.

Adolescent-Onset Cannabis Use And Parenting Young Children: An Investigation Of Differential Effectiveness Of A Digital Parenting Intervention Hails KA, McWhirter AC, Sileci ACB, Stormshak EA. Frontiers in Child and Adolescent Psychiatry. 2024; 3: 1392541.

There is scant empirical work on associations between current and past cannabis use and parenting skills in parents of young children. As recreational cannabis use is now legal in nearly half of states in the U.S., cannabis use is becoming more ubiquitous. **Methods:** In the current study, parents of toddler and pre-school age children were randomly assigned to participate in an app-based parenting skills program that included telehealth coaching (Family Check-Up Online; FCU-O), with a focus on parenting in the context of substance use. We aimed to test associations between adolescent-onset and current cannabis use and parent mental health and parenting skills, as well as whether effects of the FCU-O on parent mental health outcomes varied as a function of past cannabis use. Participants were 356 parents of children ages 1.5–5 participating in a randomized controlled trial of the FCU-O. Parents screened into the study if they reported current or past substance misuse or current depressive symptoms. After completing a baseline assessment, parents were randomly assigned to the FCU-O or control group and completed a follow-up assessment 3 months later.

Parents retrospectively reported on the age when they initially used substances, as well as their current use. **Results:** After accounting for current cannabis use, adolescent-onset cannabis use was significantly associated with higher symptoms of anxiety and depression, but not with parenting skills. Adolescent-onset cannabis use was found to significantly moderate the effect of the FCU-O on parents' anxiety symptoms. Specifically, the FCU-O was particularly effective in reducing anxiety symptoms for parents with adolescent-onset regular cannabis use, after accounting for current cannabis use. **Discussion:** Adolescent-onset regular cannabis use may be a risk factor for later mental health challenges in parents of children under 5. An app-based parenting intervention may be particularly helpful in reducing symptoms of anxiety for parents who used cannabis regularly as adolescents. The findings have significant implications for the prevention of multigenerational risk for substance use and mental health challenges.

A Content Analysis Of Cannabis Edibles Package Marketing In The United States Reboussin BA, Lazard AJ, Ross JC, Sutfin EL, Romero-Sandoval EA, Suerken CK, Lake S, Horton OE, Zizzi AR, Wagoner E, Janicek A, Boucher M, Wagoner KG. The International Journal on Drug Policy. 2024; 130: 104526. [Online ahead of print].
Background: With states legalizing cannabis at a rapid pace, and the increasing popularity of edibles, it is important to document marketing practices to better understand how they might be appealing and misleading to consumers to guide state policymakers. **Methods:** A descriptive content analysis of 1229 cannabis edible packages advertised on a publicly available website between June and November 2022 and available for sale in licensed dispensaries was performed. **Results:** Healthy ingredient descriptors were the most common type of descriptor with 31 % of packages including words like "vegan", "gluten free" and "natural". Quality descriptors like "handcrafted" were on 28 % of packages. Other descriptors were focused on the consumer experience including expected effects (e.g., "relax") (27 %), taste or flavor (e.g., "sour") (21 %) and pharmacokinetics (e.g., "fast-acting") (19 %). Images of non-cannabis plants and outdoor nature settings were on half of packages. Images of the cannabis plant were on 33 % of packages. Flavor imagery including images of food were common (43 %). Other marketing appeals included images of people (15 %), animals (12 %) and space (10 %). **Conclusions:** Package marketing used by other commercial industries was common on cannabis edible packages. Edibles marketing is distinct from other cannabis products in its ability to focus on the food ingredients which could mislead consumers into thinking the cannabis, rather than the food, is healthy or less harmful. Research examining the impact of cannabis edibles marketing strategies on appeal and harm perceptions is critically needed to guide policymakers as they establish packaging regulations to optimize public health and safety.

Addiction Consultation Services For Opioid Use Disorder Treatment Initiation And Engagement: A Randomized Clinical Trial McNeely J, Wang SS, Rostam Abadi Y, Barron C, Billings J, Tarpey T, Fernando J, Appleton N, Fawole A, Mazumdar M, Weinstein ZM, Kalyanaraman Marcello R, Dolle J, Cooke C, Siddiqui S, King C. JAMA Internal Medicine. 2024: e243422. [Online ahead of print].
Importance: Medications for opioid use disorder (MOUD) are highly effective, but only 22% of individuals in the US with opioid use disorder receive them. Hospitalization potentially provides an opportunity to initiate MOUD and link patients to ongoing treatment. **Objective**: To study the effectiveness of interprofessional hospital addiction consultation services in increasing MOUD treatment initiation and engagement. **Design, Setting, and Participants:** This pragmatic stepped-wedge cluster randomized implementation and effectiveness (hybrid type 1) trial was conducted in

6 public hospitals in New York, New York, and included 2315 adults with hospitalizations identified in Medicaid claims data between October 2017 and January 2021. Data analysis was conducted in December 2023. Hospitals were randomized to an intervention start date, and outcomes were compared during treatment as usual (TAU) and intervention conditions. Bayesian analysis accounted for the clustering of patients within hospitals and open cohort nature of the study. The addiction consultation service intervention was compared with TAU using posterior probabilities of model parameters from hierarchical logistic regression models that were adjusted for age, sex, and study period. Eligible participants had an admission or discharge diagnosis of opioid use disorder or opioid poisoning/adverse effects, were hospitalized at least 1 night in a medical/surgical inpatient unit and were not receiving MOUD before hospitalization. **Results**: Of 2315 adults, 628 (27.1%) were female, and the mean (SD) age was 47.0 (12.4) years. Initiation of MOUD was 11.0% in the Consult for Addiction Treatment and Care in Hospitals (CATCH) program vs 6.7% in TAU, engagement was 7.4% vs 5.3%, respectively, and continuation for 6 months was 3.2% vs 2.4%. Patients hospitalized during CATCH had 7.96 times higher odds of initiating MOUD (log-odds ratio, 2.07; 95% credible interval, 0.51-4.00) and 6.90 times higher odds of MOUD engagement (log-odds ratio, 1.93; 95% credible interval, 0.09-4.18). **Conclusions**: This randomized clinical trial found that interprofessional addiction consultation services significantly increased post-discharge MOUD initiation and engagement among patients with opioid use disorder. However, the observed rates of MOUD initiation and engagement were still low; further efforts are still needed to improve hospital-based and community-based services for MOUD treatment.

Reduced Drug Use As An Alternative Valid Outcome In Individuals With Stimulant Use Disorders: Findings From 13 Multisite Randomized Clinical Trials Amin-Esmaeili M, Farokhnia M, Susukida R, Leggio L, Johnson RM, Crum RM, Mojtabai R. Addiction. 2024; 119(5): 833–843.

Background and Aims: Total abstinence has historically been the goal of treatment for substance use disorders; however, there is a growing recognition of the health benefits associated with reduced use as a harm reduction measure in stimulant use disorders treatment. This study aimed to assess the validity of reduced stimulant use as an outcome measure in randomized controlled trials (RCTs) of pharmacological interventions for stimulant use disorder. **Design:** A secondary analysis of a pooled dataset of 13 RCTs of individuals seeking treatment for cocaine or methamphetamine use disorders ($N = 2062$) in a wide range of treatment facilities in the United States. **Measurements:** Reduced stimulant use was validated against a set of clinical indicators drawn from harmonized measurements, including severity of problems caused by drug use, comorbid depression, global severity of substance use and improvement, severity of drug-seeking behavior, craving and high-risk behaviors, all assessed at the end of the trial, as well as follow-up urine toxicology. A series of mixed effect regression models was conducted to validate reduction in frequency of use against no reduction in use and abstinence. **Findings:** More participants reduced frequency of primary drug use than achieved abstinence (18.0% vs. 14.2%, respectively). Reduced use was significantly associated with decreases in craving for the primary drug [60.1%, 95% confidence interval (CI) = 54.3%–64.7%], drug seeking behaviors (41.0%, 95% CI = 36.6%–45.7%), depression severity (39.9%, 95% CI = 30.9%–48.3%), as well as multiple measures of global improvement in psychosocial functioning and severity of drug-related problems, albeit less strongly so than abstinence. Moreover, reduced use was associated with sustained clinical benefit at follow-up, as confirmed by negative urine tests (adjusted odds ratio compared with those with no reduction in use: 0.50, 95% CI = 0.35–0.71). **Conclusion:** Reduced frequency of stimulant use appears to be

associated with meaningful improvement in various clinical indicators of recovery. Assessment of reduced use, in addition to abstinence, could broaden the scope of outcomes measured in randomized controlled trials of stimulant use disorders and facilitate the development of more diverse treatment approaches.

TREATMENT RESEARCH

Xylazine Does Not Enhance Fentanyl Reinforcement In Rats: A Behavioral Economic Analysis St Onge CM, Canfield JR, Ortiz A, Sprague JE, Banks ML. Drug and Alcohol Dependence. 2024; 258: 111282.
The adulteration of illicit fentanyl with the alpha-2 agonist xylazine has been designated an emerging public health threat. The clinical rationale for combining fentanyl with xylazine is currently unclear, and the inability to study fentanyl/xylazine interactions in humans warrants the need for preclinical research. We studied fentanyl and xylazine pharmacodynamic and pharmacokinetic interactions in male and female rats using drug self-administration behavioral economic methods. Fentanyl, but not xylazine, functioned as a reinforcer under both fixed-ratio and progressive-ratio drug self-administration procedures. Xylazine combined with fentanyl at three fixed dose-proportion mixtures did not significantly alter fentanyl reinforcement as measured using behavioral economic analyses. Xylazine produced a proportion-dependent decrease in the behavioral economic Q0 endpoint compared to fentanyl alone. However, xylazine did not significantly alter fentanyl self-administration at FR1. Fentanyl and xylazine co-administration did not result in changes to pharmacokinetic endpoints. The present results demonstrate that xylazine does not enhance the addictive effects of fentanyl or alter fentanyl plasma concentrations. The premise for why illicitly manufacture fentanyl has been adulterated with xylazine remains to be determined.

Cocaine Self-Administration Behavior Is Associated With Subcortical And Cortical Morphometry Measures In Individuals With Cocaine Use Disorder Kohler RJ, Zhornitsky S, Potenza MN, Yip SW, Worhunsky P, Angarita GA. The American Journal of Drug and Alcohol Abuse. 2024; 50(3): 1–12.
Background: Individual differences in gray-matter morphometry in the limbic system and frontal cortex have been linked to clinical features of cocaine use disorder (CUD). Self-administration paradigms can provide more direct measurements of the relationship between the regulation of cocaine use and gray-matter morphometry when compared to self-report assessments. **Objectives:** Our goal was to investigate associations with self-administration behavior in subcortical and cortical brain regions. We hypothesized the number of cocaine infusions self-administered would be correlated with gray-matter volumes (GMVs) in the striatum, amygdala, and hippocampus. Due to scarcity in human studies, we did not hypothesize subcortical directionality. In the frontal cortex, we hypothesized thickness would be negatively correlated with self-administered cocaine. **Methods:** We conducted an analysis of cocaine self-administration and structural MRI data from 33 (nFemales = 10) individuals with moderate-to-severe CUD. Self-administration lasted 60-minutes and cocaine (8, 16, or 32 mg/70 kg) was delivered on an FR1 schedule (5-minute lockout). Subcortical and cortical regression analyses were performed that included combined bilateral regions and age, experimental variables and use history as confounders. **Results:** Self-administered cocaine infusions were positively associated with caudal GMV ($b = 0.18$, $p = 0.030$) and negatively with putamenal GMV ($b = -0.10$, $p = 0.041$). In the cortical model, infusions were positively

associated with insular thickness (b = 0.39, p = 0.008) and women appeared to self-administer cocaine more frequently (b = 0.23, p = 0.019). **Conclusions:** Brain morphometry features in the striatum and insula may contribute to cocaine consumption in CUD. These differences in morphometry may reflect consequences of prolonged use, predisposed vulnerability, or other possibilities. Clinical Trial Numbers: NCT01978431; NCT03471182.

Cannabinoid Hyperemesis Syndrome: Clinical Trajectories And Patterns Of Use Three Months Following A Visit To The Emergency Department Wightman RS, Metrik J, Lin TR, Collins AB, Beaudoin FL. Academic Emergency Medicine. 2024; 31(5): 463–470.
OBJECTIVES: Cannabinoid hyperemesis syndrome (CHS) is a clinical condition of cyclic vomiting, nausea, and abdominal pain associated with chronic cannabis use. Despite increased recognition of CHS, there are limited details on cannabis use practices and symptoms over time. Understanding what happens in the period surrounding the emergency department (ED) visit, including any changes in symptoms and cannabis use practices following the visit, can help inform the development of patient-centered interventions around cannabis use disorder for patients with CHS. **METHODS:** A prospective observational cohort (n = 39) of patients with suspected CHS recruited from the ED at the time of a symptomatic cyclic vomiting episode was followed for 3 months. Disease progression, cannabis use practices, and health care utilization were monitored. **RESULTS:** Participants reported high rates of persistent CHS symptoms (abdominal pain, nausea, or cyclic vomiting) in the 2-week period immediately following an ED visit with a median duration of 7 days. Cannabis use frequency and quantity were reduced immediately after the ED visit, but most participants returned to pre-ED visit cannabis use patterns within a few days. Recurrent ED visits for cyclic vomiting were reported by 25% of participants who completed follow-up during the 3-month follow-up period. **CONCLUSIONS:** Participants continued to have ongoing symptoms after the ED visit, but most managed symptoms on their own and did not return to the ED. Longitudinal studies beyond 3 months are needed to better understand the clinical course of patients with suspected CHS.

Withdrawal During Outpatient Low Dose Buprenorphine Initiation In People Who Use Fentanyl: A Retrospective Cohort Study Jones BLH, Geier M, Neuhaus J, Coffin PO, Snyder HR, Soran CS, Knight KR, Suen LW. Harm Reduction Journal. 2024; 21(1): 80.
BACKGROUND: Buprenorphine is an effective treatment for opioid use disorder (OUD); however, buprenorphine initiation can be complicated by withdrawal symptoms including precipitated withdrawal. There has been increasing interest in using low dose initiation (LDI) strategies to reduce this withdrawal risk. As there are limited data on withdrawal symptoms during LDI, we characterize withdrawal symptoms in people with daily fentanyl use who underwent initiation using these strategies as outpatients. **METHODS:** We conducted a retrospective chart review of patients with OUD using daily fentanyl who were prescribed 7-day or 4-day LDI at 2 substance use disorder treatment clinics in San Francisco. Two addiction medicine experts assessed extracted chart documentation for withdrawal severity and precipitated withdrawal, defined as acute worsening of withdrawal symptoms immediately after taking buprenorphine. A third expert adjudicated disagreements. Data were analyzed using descriptive statistics. **RESULTS:** There were 175 initiations in 126 patients. The mean age was 37 (SD 10 years). 71% were men, 26% women, and 2% non-binary. 21% identified as Black, 16% Latine, and 52% white. 60% were unstably housed and 75% had Medicaid insurance. Substance co-use included 74% who used amphetamines, 29% cocaine, 22% benzodiazepines, and 19% alcohol. Follow up was available for 118 (67%) initiations. There was deviation from protocol instructions in 22% of these initiations with follow

up. 31% had any withdrawal, including 21% with mild symptoms, 8% moderate and 2% severe. Precipitated withdrawal occurred in 10 cases, or 8% of initiations with follow up. Of these, 7 had deviation from protocol instructions; thus, there were 3 cases with follow up (3%) in which precipitated withdrawal occurred without protocol deviation. **CONCLUSIONS:** Withdrawal was relatively common in our cohort but was mostly mild, and precipitated withdrawal was rare. Deviation from instructions, structural barriers, and varying fentanyl use characteristics may contribute to withdrawal. Clinicians should counsel patients who use fentanyl that mild withdrawal symptoms are likely during LDI, and there is still a low risk for precipitated withdrawal. Future studies should compare withdrawal across initiation types, seek ways to support patients in initiating buprenorphine, and qualitatively elicit patients' withdrawal experiences.

HIV RESEARCH

Weight Loss Associated With Semaglutide Treatment Among People With HIV Haidar L, Crane HM, Nance RM, Webel A, Ruderman SA, Whitney BM, Willig AL, Napravnik S, Mixson LS, Leong C, Lavu A, Aboulatta L, Dai M, Hahn A, Saag MS, Bamford L, Cachay E, Kitahata MM, Mayer KH, Jacobson J, Moore RD, Delaney JAC, Drumright LN, Eltonsy S. AIDS. 2024; 38(4): 531–535.

OBJECTIVE: There is limited real-world evidence about the effectiveness of semaglutide for weight loss among people with HIV (PWH). We aimed to investigate weight change in a US cohort of PWH who initiated semaglutide treatment. **DESIGN:** Observational study using the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. **METHODS:** We identified adult PWH who initiated semaglutide between 2018 and 2022 and with at least two weight measurements. The primary outcome was within-person bodyweight change in kilograms at 1 year. The secondary outcome was within-person Hemoglobin A1c percentage (HbA1c) change. Both outcomes were estimated using multivariable linear mixed model. **RESULTS:** In total, 222 new users of semaglutide met inclusion criteria. Mean follow-up was 1.1 years. Approximately 75% of new semaglutide users were men, and at baseline, mean age was 53 years [standard deviation (SD): 10], average weight was 108 kg (SD: 23), mean BMI was 35.5 kg/m 2, mean HbA1c was 7.7% and 77% had clinically recognized diabetes. At baseline, 97% were on ART and 89% were virally suppressed (viral load < 50 copies/ml). In the adjusted mixed model analysis, treatment with semaglutide was associated with an average weight loss of 6.47 kg at 1 year (95% CI -7.67 to -5.18) and with a reduction in HbA1c of 1.07% at 1 year (95% CI -1.64 to -0.50) among the 157 PWH with a postindex HbA1c value. **CONCLUSION:** Semaglutide was associated with significant weight loss and HbA1c reduction among PWH, comparable to results of previous studies from the general population.

Adult Human Brain Tissue Cultures To Study NeuroHIV Van Duyne R, Irollo E, Lin A, Johnson JA, Guillem AM, O'Brien EV, Merja L, Nash B, Jackson JG, Sarkar A, Klase ZA, Meucci O. Cells. 2024; 13(13): 1127.

HIV-associated neurocognitive disorders (HAND) persist under antiretroviral therapy as a complex pathology that has been difficult to study in cellular and animal models. Therefore, we generated an ex vivo human brain slice model of HIV-1 infection from surgically resected adult brain tissue. Brain slice cultures processed for flow cytometry showed >90% viability of dissociated cells within the first three weeks in vitro, with parallel detection of astrocyte, myeloid, and neuronal populations. Neurons within brain slices showed stable dendritic spine density and mature spine

morphologies in the first weeks in culture, and they generated detectable activity in multi-electrode arrays. We infected cultured brain slices using patient-matched CD4+ T-cells or monocyte-derived macrophages (MDMs) that were exposed to a GFP-expressing R5-tropic HIV-1 in vitro. Infected slice cultures expressed viral RNA and developed a spreading infection up to 9 days post-infection, which were significantly decreased by antiretrovirals. We also detected infected myeloid cells and astrocytes within slices and observed minimal effect on cellular viability over time. Overall, this human-centered model offers a promising resource to study the cellular mechanisms contributing to HAND (including antiretroviral toxicity, substance use, and aging), infection of resident brain cells, and new neuroprotective therapeutics.

Suppression Of HIV-TAT And Cocaine-Induced Neurotoxicity And Inflammation By Cell Penetrable Itaconate Esters Cui BC, Aksenova M, Sikirzhytskaya A, Odhiambo D, Korunova E, Sikirzhytski V, Ji H, Altomare D, Broude E, Frizzell N, Booze R, Wyatt MD, Shtutman M. Journal of Neurovirology. 2024. [Online ahead of print].
HIV-associated neurological disorder (HAND) is a serious complication of HIV infection marked by neurotoxicity induced by viral proteins like Tat. Substance abuse exacerbates neurocognitive impairment in people living with HIV. There is an urgent need for therapeutic strategies to combat HAND comorbid with Cocaine Use Disorder (CUD). Our analysis of HIV and cocaine-induced transcriptomes in primary cortical cultures revealed significant overexpression of the macrophage-specific gene aconitate decarboxylase 1 (Acod1). The ACOD1 protein converts the tricarboxylic acid intermediate cis-aconitate into itaconate during the activation of inflammation. Itaconate then facilitates cytokine production and activates anti-inflammatory transcription factors, shielding macrophages from infection-induced cell death. However, the immunometabolic function of itaconate was unexplored in HIV and cocaine-exposed microglia. We assessed the potential of 4-octyl-itaconate (4OI), a cell-penetrable ester form of itaconate known for its anti-inflammatory properties. When primary cortical cultures exposed to Tat and cocaine were treated with 4OI, microglial cell number increased and the morphological altercations induced by Tat and cocaine were reversed. Microglial cells also appeared more ramified, resembling the quiescent microglia. 4OI treatment inhibited secretion of the proinflammatory cytokines IL-1α, IL 1β, IL-6, and MIP1-α induced by Tat and cocaine. Transcriptome profiling determined that Nrf2 target genes were significantly activated in Tat and 4OI treated cultures relative to Tat alone. Further, genes associated with cytoskeleton dynamics in inflammatory microglia were downregulated by 4OI treatment. Together, the results strongly suggest 4-octyl-itaconate holds promise as a potential candidate for therapeutic development to treat HAND coupled with CUD comorbidities.

Objective Neighborhood-Level Disorder Versus Subjective Safety As Predictors Of HIV Transmission Risk And Momentary Well-Being Panlilio LV, Preston KL, Bertz JW, Moran LM, Tyburski M, Hertzel SK, Husami S, Adan F, Epstein DH, Phillips KA. AIDS and Behavior. 2024. [Online ahead of print].
Mental health and HIV risk behavior have been studied with ecological momentary assessment (EMA), but this approach has not been combined with tracking of activity space (where people go and what they encounter there) in people with HIV and their social relations, who may be HIV+ or HIV-. Activity space represents a modifiable risk or protective factor for behavior related to health status and quality of life, in both clinical and nonclinical populations. We conducted an observational study with 286 participants (243 HIV+ and 43 HIV-), roughly matched for socioeconomic status and neighborhood of residence via three waves of snowball sampling. Each participant carried a smartphone for up to 4 weeks, making 5 randomly prompted entries and 1 end-

of-day entry each day, plus self-initiated event-contingent entries for sexual activity and drug use. Responses to randomly prompted items provided subjective evaluations of the safety of the participant's current social and physical environment (the place they were and the people they were with). GPS-based location tracking-coupled with publicly available statistic indicating neighborhood-level physical disorder and socioeconomic disadvantage-provided an indicator of each participant's exposure to objective psychosocial hazard. We examined possible relationships of these objective and subjective environmental exposures with risky sexual and intravenous drug-use behavior, knowledge and utilization of antiretroviral treatment and prophylaxis, and momentary mental health (mood and stress, which relate to risky behavior and overall well-being). We found that both risky behavior and mental health were more related to participants' subjective evaluations of their activity space than to objective measures of neighborhood-level disorder, suggesting that, even within an objectively hazardous neighborhood, people who find a niche they perceive as socially and physically safe may engage in less risky behavior and have better well-being. Trial registration Clinicaltrials.gov Identifier NCT01571752.

Program Director Reports Of COVID-19 Lockdown-Driven Service Changes In Community-Based STI Clinics And Syringe Services Programs In The Southeastern U.S. Hatch MA, Laschober TC, Ertl MM, Paschen-Wolff MM, Norman G, Wright L, Tross S. AIDS Education and Prevention. 2024; 36(2): 129–140.
The COVID-19 pandemic strained the U.S. health care system, posing logistical challenges for community-based programs. This study surveyed 11 program directors in sexually transmitted infection (STI) clinics and syringe services programs (SSPs) that served people who use substances and are at risk for HIV in five southeastern U.S. states. Brief survey questions asked about programs' use of in-person and telehealth services. Results indicated widespread reduction of in-person services and concomitant adoption of telehealth services. In STI clinics, telehealth replaced in-person visits for all but urgent treatment of active symptoms. In SSPs, in-person contact continued or increased from pre-pandemic volumes. In both programs, the most salient telehealth use barrier was limited device or internet access and limited technological ease. Services were sustained through innovative adaptations. This snapshot of response to the early COVID-19 lockdown phase offers actionable guidance about service preparedness for future public health catastrophes in community-based programs serving vulnerable populations.

Decentralized HIV Testing: Comparing Peer And Mail-Based Distribution Strategies To Improve The Reach Of HIV Self-Testing Among People Who Use Drugs In Florida Eger WH, Mutchler A, Santamour T, Meaders S, Pines HA, Bazzi AR, Tookes HE, Bartholomew TS. Harm Reduction Journal. 2024; 21(1): 116.
Introduction: People who use drugs (PWUD) are at increased risk for HIV infection. HIV self-testing (HIVST) is a promising method for identifying new infections, but optimal distribution strategies remain understudied. **Methods:** To characterize PWUD by HIVST distribution strategy (peers vs. mail), we examined data from July 2022 to June 2023 collected from a real-world HIVST program led by the non-profit, Florida Harm Reduction Collective. We used descriptive statistics and Poisson regressions with robust error variance to compare those who received HIVST through peers or via mail by socio-demographics, Ending the HIV Epidemic (EHE) county designation, and HIV testing experience. **Results:** Among 728 participants, 78% received HIVST from peers, 47% identified as cisgender female, 48% as heterosexual, and 45% as non-White; 66% resided in an EHE county, and 55% had no HIV testing experience. Compared to those who received an HIV self-test from peers, those who received tests via mail were less likely to be cisgender male (vs.

cisgender female; prevalence ratio [PR] = 0.59, 95% confidence interval [CI]: 0.43, 0.81), non-Hispanic Black (vs. non-Hispanic White; PR = 0.57, 95% CI: 0.36, 0.89) or from EHE counties (vs. non-EHE counties; PR = 0.33, 95% CI: 0.25, 0.44). Those who received tests via mail were also more likely to identify their sexual orientation as "Other/Undisclosed" (vs. straight/heterosexual; PR = 2.00, 95% CI: 1.51, 2.66). **Conclusion:** Our findings support the role of community-based HIVST distribution strategies in increasing HIV testing coverage among PWUD. Additional research could help inform the equitable reach of HIVST.

HIV Risk And Interest In Preexposure Prophylaxis In Justice-Involved Persons Nijhawan AE, Pulitzer Z, Torres B, Noreen N, Schultheis A, Frank C, Colon R, Brooks R, Proffitt R, Pankow J, Bennett A, Salyards M, Kuo I, Knight K, Springer SA. Emerging Infectious Diseases. 2024; 30(13): S68–S74.
Abstract: Preexposure prophylaxis (PrEP) is underused in persons who use drugs and justice-involved persons. In an ongoing randomized controlled trial in 4 US locations comparing patient navigation versus mobile health unit on time to initiation of HIV medication or PrEP for justice-involved persons who use stimulants or opioids and who are at risk for or living with HIV, HIV risk factors, perceived HIV risk, and interest in PrEP were assessed. Participants without HIV (n = 195) were 77% men, 65% White, 23% Black, and 26% Hispanic; 73% reported a recent history of condomless sex, mainly with partners of unknown HIV status. Of 34% (67/195) reporting injection drug use, 43% reported sharing equipment. Despite risk factors, many persons reported their risk for acquiring HIV as low (47%) or no (43%) risk, although 51/93 (55%) with PrEP indications reported interest in PrEP. Justice-involved persons who use drugs underestimated their HIV risk and might benefit from increased PrEP education efforts.

Engineered Deletions Of HIV Replicate Conditionally To Reduce Disease In Nonhuman Primates Pitchai FNN, Tanner EJ, Khetan N, Vasen G, Levrel C, Kumar AJ, Pandey S, Ordonez T, Barnette P, Spencer D, Jung SY, Glazier J, Thompson C, Harvey-Vera A, Son HI, Son HI, Strathdee SA, Holguin L, Urak R, Burnett J, Burgess W, Busman-Sahay K, Estes JD, Hessell A, Fennessey CM, Keele BF, Haigwood NL, Weinberger LS. Science. 2024; 385(6709): eadn5866.
Antiviral therapies with reduced frequencies of administration and high barriers to resistance remain a major goal. For HIV, theories have proposed that viral-deletion variants, which conditionally replicate with a basic reproductive ratio [R0] > 1 (termed “therapeutic interfering particles” or “TIPs”), could parasitize wild-type virus to constitute single-administration, escape-resistant antiviral therapies. We report the engineering of a TIP that, in rhesus macaques, reduces viremia of a highly pathogenic model of HIV by >3log10 following a single intravenous injection. Animal lifespan was significantly extended, TIPs conditionally replicated and were continually detected for >6 months, and sequencing data showed no evidence of viral escape. A single TIP injection also suppressed virus replication in humanized mice and cells from persons living with HIV. These data provide proof of concept for a potential new class of single-administration antiviral therapies.

Adult Human Brain Tissue Cultures To Study NeuroHIV Van Duyne R, Irollo E, Lin A, Johnson JA, Guillem AM, O’Brien EV, Merja L, Nash B, Jackson JG, Sarkar A, Klase ZA, Meucci O. Cells. 2024, 13(13): 1127.
HIV-associated neurocognitive disorders (HAND) persist under antiretroviral therapy as a complex pathology that has been difficult to study in cellular and animal models. Therefore, we generated an ex vivo human brain slice model of HIV-1 infection from surgically resected adult brain tissue. Brain slice cultures processed for flow cytometry showed >90% viability of dissociated cells within

the first three weeks in vitro, with parallel detection of astrocyte, myeloid, and neuronal populations. Neurons within brain slices showed stable dendritic spine density and mature spine morphologies in the first weeks in culture, and they generated detectable activity in multi-electrode arrays. We infected cultured brain slices using patient-matched CD4+ T-cells or monocyte-derived macrophages (MDMs) that were exposed to a GFP-expressing R5-tropic HIV-1 in vitro. Infected slice cultures expressed viral RNA and developed a spreading infection up to 9 days post-infection, which were significantly decreased by antiretrovirals. We also detected infected myeloid cells and astrocytes within slices and observed minimal effect on cellular viability over time. Overall, this human-centered model offers a promising resource to study the cellular mechanisms contributing to HAND (including antiretroviral toxicity, substance use, and aging), infection of resident brain cells, and new neuroprotective therapeutics.

CLINICAL TRIALS NETWORK RESEARCH

Offering Nurse Care Management For Opioid Use Disorder In Primary Care: Impact On Emergency And Hospital Utilization In A Cluster-Randomized Implementation Trial Bobb JF, Idu AE, Qiu H, Yu O, Boudreau DM, Wartko PD, Matthews AG, McCormack J, Lee AK, Campbell CI, Saxon AJ, Liu DS, Altschuler A, Samet JH, Northrup TF, Braciszewski JM, Murphy MT, Arnsten JH, Cunningham CO, Horigian VE, Szapocznik J, Glass JE, Caldeiro RM, Tsui JI, Burganowski RP, Weinstein ZM, Murphy SM, Hyun N, Bradley KA. Drug and Alcohol Dependence. 2024; 261: 111350.
Patients with opioid use disorder (OUD) have increased emergency and hospital utilization. The PROUD trial showed that implementation of office-based addiction treatment (OBAT) increased OUD medication treatment compared to usual care but did not decrease acute care utilization in patients with OUD documented pre-randomization. This paper reports secondary emergency and hospital utilization outcomes in patients with documented OUD in the PROUD trial. Among 1,988 patients with documented OUD seen pre-randomization, days of emergency care or hospitalization did not differ between intervention and usual care; OUD treatment also did not differ. In secondary analyses among 1,347 patients with OUD post-randomization, there remained no difference in emergency or hospital utilization despite intervention patients receiving 32.2 more days of OUD treatment relative to usual care. Implementation of OBAT did not reduce emergency or hospital utilization among patients with OUD, even in the sample with OUD first documented post-randomization in whom the intervention increased treatment.

Extended-Release 7-Day Injectable Buprenorphine For Patients With Minimal To Mild Opioid Withdrawal D'Onofrio G, Herring AA, Perrone J, Hawk K, Samuels EA, Cowan E, Anderson E, McCormack R, Huntley K, Owens P, Martel S, Schactman M, Lofwall MR, Walsh SL, Dziura J, Fiellin DA. JAMA Network Open. 2024; 7(7): e2420702.
A 7-day injectable formulation of extended-release buprenorphine offers a method to initiate buprenorphine that does not require stabilization on sublingual buprenorphine and therefore provides an opportunity to surmount many of the barriers associated with the sublingual formulation. A 7-day single injection avoids unnecessary delays to full induction and addresses the often-fragmented and barrier-laden health care system that may thwart rapid access to follow-up care. In this nonrandomized trial of 100 adult patients with opioid use disorder presenting with minimal to mild Clinical Opiate Withdrawal Scale scores (0-7), 7% of patients experienced precipitated withdrawal within 4 hours of 7-day extended-release buprenorphine administration,

which included 3% with higher scores (4-7) and 14% with lower scores (0-3). Results of this study suggest that 7-day extended-release buprenorphine may be feasible in patients with opioid use disorder presenting with minimal to mild Clinical Opiate Withdrawal Scale scores (4-7), This new medication formulation could substantially increase the number of patients with OUD receiving buprenorphine.

Predictability Of Buprenorphine-Naloxone Treatment Retention: A Multi-Site Analysis Combining Electronic Health Records And Machine Learning Nateghi Haredasht F, Fouladvand S, Tate S, Chan MM, Yeow JJL, Griffiths K, Lopez I, Bertz JW, Miner AS, Hernandez-Boussard T, Chen CA, Deng H, Humphreys K, Lembke A, Vance LA, Chen JH. Addiction. 2024. [Online ahead of print].
Opioid use disorder (OUD) and opioid dependence lead to significant morbidity and mortality, yet treatment retention, crucial for the effectiveness of medications like buprenorphine-naloxone, remains unpredictable. Our objective was to determine the predictability of 6-month retention in buprenorphine-naloxone treatment using electronic health record (EHR) data from diverse clinical settings and to identify key predictors. US patients with opioid use disorder or opioid dependence treated with buprenorphine-naloxone prescriptions appear to have a high (~60%) treatment attrition by 6 months. Machine learning models trained on diverse electronic health record datasets appear to be able to predict treatment continuity with accuracy comparable to that of clinical experts. This capability to maintain predictive accuracy across different patient cohorts suggests these models could be effectively deployed across various health-care settings, enhancing personalized treatment strategies. Treatment retention is a complex and heterogeneous phenomenon, but the feasibility of distinguishing high versus low-risk patients can allow for individualized patient management and follow-up engagement strategies while offering a means of risk-adjusting different treatment programs.

Wiidookaage'win: Beta-Test Of A Facebook Group Intervention For Native Women To Support Opioid Use Recovery Roche AI, Young A, Sabaque C, Kelpin SS, Sinicrope P, Pham C, Marsch LA, Campbell ANC, Venner K, Baker-DeKrey L, Wyatt T, WhiteHawk S, Nord T, Resnicow K, Young C, Brown A, Bart G, Patten C. Journal of Substance Use Addiction Treatment. 2024; 163: 209396.
The ongoing opioid misuse epidemic has had a marked impact on American Indian/Alaska Native (AI/AN) communities. Culture- and gender-specific barriers to medically assisted recovery from opioid use disorder (OUD) have been identified, exacerbating its impact for AI/AN women. Wiidookaage'win is a community-based participatory research study that aims to develop a culturally tailored, moderated, private Facebook group intervention to support Minnesotan AI/AN women in medically assisted recovery from OUD. This study assessed the preliminary feasibility and acceptability of the intervention in a beta-test to inform refinements before conducting a pilot randomized controlled trial (RCT). Ten AI/AN women taking medication for OUD (MOUD) were accrued. The beta-test indicated that the Facebook platform and study procedures generally worked as intended and that the intervention was largely acceptable to study participants. The results of this study phase provided valuable insights to inform refinements prior to conducting a pilot RCT to further assess the feasibility, acceptability, and potential efficacy of the intervention.

Rapid Initiation Of Injection Naltrexone For Opioid Use Disorder: A Stepped-Wedge Cluster Randomized Clinical Trial Shulman M, Greiner MG, Tafessu HM, Opara O, Ohrtman K, Potter K, Hefner K, Jelstrom E, Rosenthal RN, Wenzel K, Fishman M, Rotrosen J, Ghitza UE, Nunes EV, Bisaga A. JAMA Network Open. 2024 ;7(5): e249744.
Injectable extended-release (XR)-naltrexone is an effective treatment option for opioid use disorder (OUD), but the need to withdraw patients from opioid treatment prior to initiation is a barrier to implementation. Improving the rate of XR-naltrexone initiation using the rapid procedure (RP) in community-based treatment settings could be an important step to ensure more patients with OUD have the option of initiating XR-naltrexone, if this is their preferred medication treatment. This trial was conducted to test the effectiveness of the rapid XR-naltrexone initiation procedure compared with usual care at community-based inpatient addiction treatment units. This cluster trial demonstrated that an RP for initiating XR-naltrexone consisting of minimal buprenorphine, use of higher doses of nonopioid medications for opioid withdrawal, and titration of low doses of oral naltrexone is feasible, relatively safe, and noninferior, compared with the SP recommended in the XR-naltrexone prescribing information. The RP requires close medical monitoring. Due to its shorter duration, the RP may be cost-effective and a better fit within constraints on the duration of inpatient stays imposed by third-party payers. It is noteworthy that only 10.4% of all patients entering treatment chose to attempt XR-naltrexone initiation and even in the RP 37.3% of participants did not initiate XR-naltrexone. In future studies, the implementation strategies used in the present trial could be broadened to encompass initiation of buprenorphine and methadone, addressing the larger goal of maximizing the proportion of patients with OUD admitted to inpatient or residential treatment who emerge stabilized on MOUD.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

Differences In Educational Opportunity Predict White Matter Development Roy E, Van Rinsveld A, Nedelec P, Richie-Halford A, Rauschecker AM, Sugrue LP, Rokem A, McCandliss BD, Yeatman JD. Differences in educational opportunity predict white matter development. Developmental Cognitive Neuroscience. 2024; 67: 101386.
Coarse measures of socioeconomic status, such as parental income or parental education, have been linked to differences in white matter development. However, these measures do not provide insight into specific aspects of an individual's environment and how they relate to brain development. On the other hand, educational intervention studies have shown that changes in an individual's educational context can drive measurable changes in their white matter. These studies, however, rarely consider socioeconomic factors in their results. In the present study, we examined the unique relationship between educational opportunity and white matter development, when controlling other known socioeconomic factors. To explore this question, we leveraged the rich demographic and neuroimaging data available in the ABCD study, as well the unique data-crosswalk between ABCD and the Stanford Education Data Archive (SEDA). We find that educational opportunity is related to accelerated white matter development, even when accounting for other socioeconomic factors, and that this relationship is most pronounced in white matter tracts associated with academic skills. These results suggest that the school a child attends has a measurable relationship with brain development for years to come.

Do Traumatic Events And Substance Use Co-Occur During Adolescence? Testing Three Causal Etiologic Hypotheses Patel H, Tapert SF, Brown SA, Norman SB, Pelham WE 3rd. Journal of Child Psychology and Psychiatry. 2024. [Online ahead of print].

Background: Why do potentially traumatic events (PTEs) and substance use (SU) so commonly co-occur during adolescence? Causal hypotheses developed from the study of posttraumatic stress disorder (PTSD) and substance use disorder (SUD) among adults have not yet been subject to rigorous theoretical analysis or empirical tests among adolescents with the precursors to these disorders: PTEs and SU. Establishing causality demands accounting for various factors (e.g. genetics, parent education, race/ethnicity) that distinguish youth endorsing PTEs and SU from those who do not, a step often overlooked in previous research. **Methods:** We leveraged nationwide data from a sociodemographically diverse sample of youth (N = 11,468) in the Adolescent Brain and Cognitive Development Study. PTEs and substance use prevalence were assessed annually. To account for the many pre-existing differences between youth with and without PTE/SU (i.e. confounding bias) and provide rigorous tests of causal hypotheses, we linked within-person changes in PTEs and SU (alcohol, cannabis, nicotine) across repeated measurements and adjusted for time-varying factors (e.g. age, internalizing symptoms, externalizing symptoms, and friends' use of substances). **Results:** Before adjusting for confounding using within-person modeling, PTEs and SU exhibited significant concurrent associations (βs = .46-1.26, ps < .05) and PTEs prospectively predicted greater SU (βs = .55-1.43, ps < .05) but not vice versa. After adjustment for confounding, the PTEs exhibited significant concurrent associations for alcohol (βs = .14-.23, ps < .05) and nicotine (βs = .16, ps < .05) but not cannabis (βs = -.01, ps > .05) and PTEs prospectively predicted greater SU (βs = .28-.55, ps > .05) but not vice versa. **Conclusions:** When tested rigorously in a nationwide sample of adolescents, we find support for a model in which PTEs are followed by SU but not for a model in which SU is followed by PTEs. Explanations for why PTSD and SUD co-occur in adults may need further theoretical analysis and adaptation before extension to adolescents.

Exposomic And Polygenic Contributions To Allostatic Load In Early Adolescence Hoffman KW, Tran KT, Moore TM, Gataviņš MM, Visoki E, Kwon O, DiDomenico GE, Chaiyachati BH, Schultz LM, Almasy L, Hayes MR, Daskalakis NP, Barzilay R. Nature Mental Health. 2024; 2: 828–839.

Allostatic load (AL) is the cumulative 'wear and tear' on the body due to chronic adversity. We tested the poly-environmental (exposomic) and polygenic contributions to AL and their combined contribution to adolescent mental health. In this cohort study of $N = 5{,}036$ diverse youth (mean age 12 years) from the Adolescent Brain Cognitive Development Study, we calculated a latent AL score, childhood exposomic risk and genetic risk. We tested the associations of exposomic and polygenic risks with AL using linear mixed-effects models, and tested the mediating role of AL on the pathway from exposomic/polygenic risk to mental health. AL was significantly lower among non-Hispanic white youth compared to Hispanic and non-Hispanic black youth. Childhood exposomic burden was associated with AL in adolescence ($\beta = 0.25$, 95% CI 0.22–0.29, $P < 0.001$). In subset analysis of participants of European-like genetic ancestry ($n = 2{,}928$), the type 2 diabetes polygenic risk score (T2D-PRS; $\beta = 0.11$, 95% CI 0.07–0.14, $P < 0.001$) and major depressive disorder (MDD)-PRS ($\beta = 0.05$, 95% CI 0.02–0.09, $P = 0.003$) were associated with AL. Both PRSs showed significant gene–environment interactions such that, with greater polygenic risk, associations between exposome and AL were stronger. AL significantly mediated the indirect path from exposomic risk at age 11 years, and from both MDD-PRS and T2D-PRS to psychopathology at age 12 years. Our findings show that AL can be quantified in youth and is associated with exposomic and polygenic burden, supporting the diathesis–stress model.

Multi-Ancestry Meta-Analysis Of Tobacco Use Disorder Identifies 461 Potential Risk Genes And Reveals Associations With Multiple Health Outcomes Toikumo S, Jennings MV, Pham BK, Lee H, Mallard TT, Bianchi SB, Meredith JJ, Vilar-Ribó L, Xu H, Hatoum AS, Johnson EC, Pazdernik VK, Jinwala Z, Pakala SR, Leger BS, Niarchou M, Ehinmowo M; Penn Medicine BioBank, Jenkins GD, Batzler A, Pendegraft R, Palmer AA, Zhou H, Biernacka JM, Coombes BJ, Gelernter J, Xu K, Hancock DB, Cox NJ, Smoller JW, Davis LK, Justice AC, Kranzler HR, Kember RL, Sanchez-Roige S. Nature Human Behaviour. 2024; 8(6): 1177–1193.
Tobacco use disorder (TUD) is the most prevalent substance use disorder in the world. Genetic factors influence smoking behaviours and although strides have been made using genome-wide association studies to identify risk variants, most variants identified have been for nicotine consumption, rather than TUD. Here we leveraged four US biobanks to perform a multi-ancestral meta-analysis of TUD (derived via electronic health records) in 653,790 individuals (495,005 European, 114,420 African American and 44,365 Latin American) and data from UK Biobank (ncombined = 898,680). We identified 88 independent risk loci; integration with functional genomic tools uncovered 461 potential risk genes, primarily expressed in the brain. TUD was genetically correlated with smoking and psychiatric traits from traditionally ascertained cohorts, externalizing behaviours in children and hundreds of medical outcomes, including HIV infection, heart disease and pain. This work furthers our biological understanding of TUD and establishes electronic health records as a source of phenotypic information for studying the genetics of TUD.

FEMA: Fast And Efficient Mixed-Effects Algorithm For Large Sample Whole-Brain Imaging Data Parekh P, Fan CC, Frei O, Palmer CE, Smith DM, Makowski C, Iversen JR, Pecheva D, Holland D, Loughnan R, Nedelec P, Thompson WK, Hagler DJ Jr, Andreassen OA, Jernigan TL, Nichols TE, Dale AM. Human Brain Mapping. 2024; 45(2): e26579.
The linear mixed-effects model (LME) is a versatile approach to account for dependence among observations. Many large-scale neuroimaging datasets with complex designs have increased the need for LME; however LME has seldom been used in whole-brain imaging analyses due to its heavy computational requirements. In this paper, we introduce a fast and efficient mixed-effects algorithm (FEMA) that makes whole-brain vertex-wise, voxel-wise, and connectome-wide LME analyses in large samples possible. We validate FEMA with extensive simulations, showing that the estimates of the fixed effects are equivalent to standard maximum likelihood estimates but obtained with orders of magnitude improvement in computational speed. We demonstrate the applicability of FEMA by studying the cross-sectional and longitudinal effects of age on region-of-interest level and vertex-wise cortical thickness, as well as connectome-wide functional connectivity values derived from resting state functional MRI, using longitudinal imaging data from the Adolescent Brain Cognitive Development^{SM} Study release 4.0. Our analyses reveal distinct spatial patterns for the annualized changes in vertex-wise cortical thickness and connectome-wide connectivity values in early adolescence, highlighting a critical time of brain maturation. The simulations and application to real data show that FEMA enables advanced investigation of the relationships between large numbers of neuroimaging metrics and variables of interest while considering complex study designs, including repeated measures and family structures, in a fast and efficient manner. The source code for FEMA is available via: **https://github.com/cmig-research-group/cmig_tools/**.

INTRAMURAL RESEARCH

Presynaptic And Postsynaptic Mesolimbic Dopamine D3 Receptors Play Distinct Roles In Cocaine Versus Opioid Reward In Mice Xi ZX, Bocarsly ME, Galaj E, Hempel B, Teresi C, Shaw M, Bi GH, Jordan C, Linz E, Alton H, Tanda G, Freyberg Z, Alvarez VA, Newman AH. Biological Psychiatry. 2024; S0006-3223(24): 01358-1. [Online ahead of print].

Background: Past research has illuminated pivotal roles of dopamine D_3 receptors (D_3R) in the rewarding effects of cocaine and opioids. However, the cellular and neural circuit mechanisms that underlie these actions remain unclear. **Methods:** We employed Cre-LoxP techniques to selectively delete D_3R from presynaptic dopamine neurons or postsynaptic dopamine D_1 receptor (D_1R)-expressing neurons in male and female mice. We utilized RNAscope in situ hybridization, immunohistochemistry, real-time polymerase chain reaction, voltammetry, optogenetics, microdialysis, and behavioral assays ($n \geq 8$ animals per group) to functionally characterize the roles of presynaptic versus postsynaptic D_3R in cocaine and opioid actions. **Results:** Our results revealed D_3R expression in ~25% of midbrain dopamine neurons and ~70% of D_1R-expressing neurons in the nucleus accumbens. While dopamine D_2 receptors (D_2R) were expressed in ~80% dopamine neurons, we found no D_2R and D_3R colocalization among these cells. Selective deletion of D_3R from dopamine neurons increased exploratory behavior in novel environments and enhanced pulse-evoked nucleus accumbens dopamine release. Conversely, deletion of D_3R from D_1R-expressing neurons attenuated locomotor responses to D_1-like and D_2-like agonists. Strikingly, deletion of D_3R from either cell type reduced oxycodone self-administration and oxycodone-enhanced brain-stimulation reward. In contrast, neither of these D_3R deletions impacted cocaine self-administration, cocaine-enhanced brain-stimulation reward, or cocaine-induced hyperlocomotion. Furthermore, D_3R knockout in dopamine neurons reduced oxycodone-induced hyperactivity and analgesia, while deletion from D_1R-expressing neurons potentiated opioid-induced hyperactivity without affecting analgesia. **Conclusions:** We dissected presynaptic versus postsynaptic D_3R function in the mesolimbic dopamine system. D_2R and D_3R are expressed in different populations of midbrain dopamine neurons, regulating dopamine release. Mesolimbic D_3R are critically involved in the actions of opioids but not cocaine.

Key Language Markers Of Depression On Social Media Depend On Race Rai S, Stade EC, Giorgi S, Francisco A, Ungar LH, Curtis B, Guntuku SC. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121(14): e2319837121.

Depression has robust natural language correlates and can increasingly be measured in language using predictive models. However, despite evidence that language use varies as a function of individual demographic features (e.g., age, gender), previous work has not systematically examined whether and how depression's association with language varies by race. We examine how race moderates the relationship between language features (i.e., first-person pronouns and negative emotions) from social media posts and self-reported depression, in a matched sample of Black and White English speakers in the United States. Our findings reveal moderating effects of race: While depression severity predicts I-usage in White individuals, it does not in Black individuals. White individuals use more belongingness and self-deprecation-related negative emotions. Machine learning models trained on similar amounts of data to predict depression severity performed poorly when tested on Black individuals, even when they were trained exclusively using the language of Black individuals. In contrast, analogous models tested on White individuals performed relatively well. Our study reveals surprising race-based differences in the expression of depression in natural

language and highlights the need to understand these effects better, especially before language-based models for detecting psychological phenomena are integrated into clinical practice.

Incubation Of Methamphetamine Craving In Punishment-Resistant Individuals Is Associated With Activation of Specific Gene Networks In The Rat Dorsal Striatum Daiwile AP, McCoy MT, Ladenheim B, Subramaniam J, Cadet JL. Molecular Psychiatry. 2024. [Online ahead of print].
Methamphetamine use disorder (MUD) is characterized by loss of control over compulsive drug use. Here, we used a self-administration (SA) model to investigate transcriptional changes associated with the development of early and late compulsivity during contingent footshocks. Punishment initially separated methamphetamine taking rats into always shock-resistant (ASR) rats that continued active lever pressing and shock-sensitive (SS) rats that reduced their lever pressing. At the end of the punishment phase, rats underwent 15 days of forced abstinence at the end of which they were re-introduced to the SA paradigm followed by SA plus contingent shocks. Interestingly, 36 percent of the initial SS rats developed delayed shock-resistance (DSR). Of translational relevance, ASR rats showed more incubation of methamphetamine craving than DSR and always sensitive (AS) rats. RNA sequencing revealed increased striatal Rab37 and Dipk2b mRNA levels that correlated with incubation of methamphetamine craving. Interestingly, Bdnf mRNA levels showed HDAC2-dependent decreased expression in the AS rats. The present SA paradigm should help to elucidate the molecular substrates of early and late addiction-like behaviors.

Involvement Of Dopamine D3 Receptor In Impulsive Choice Decision-Making In Male Rats Shen H, Ma Z, Hans E, Duan Y, Bi GH, Chae YC, Bonifazi A, Battiti FO, Newman AH, Xi ZX, Yang Y. Neuropharmacology. 2024; 257: 110051.
Impulsive decision-making has been linked to impulse control disorders and substance use disorders. However, the neural mechanisms underlying impulsive choice are not fully understood. While previous PET imaging and autoradiography studies have shown involvement of dopamine and D2/3 receptors in impulsive behavior, the roles of distinct D1, D2, and D3 receptors in impulsive decision-making remain unclear. In this study, we used a food reward delay-discounting task (DDT) to identify low- and high-impulsive rats, in which low-impulsive rats exhibited preference for large delayed reward over small immediate rewards, while high-impulsive rats showed the opposite preference. We then examined D1, D2, and D3 receptor gene expression using RNAscope in situ hybridization assays. We found that high-impulsive male rats exhibited lower levels of D2 and D3, and particularly D3, receptor expression in the nucleus accumbens (NAc), with no significant changes in the insular, prelimbic, and infralimbic cortices. Based on these findings, we further explored the role of the D3 receptor in impulsive decision-making. Systemic administration of a selective D3 receptor agonist (FOB02-04) significantly reduced impulsive choices in high-impulsive rats but had no effects in low-impulsive rats. Conversely, a selective D3 receptor antagonist (VK4-116) produced increased both impulsive and omission choices in both groups of rats. These findings suggest that impulsive decision-making is associated with a reduction in D3 receptor expression in the NAc. Selective D3 receptor agonists, but not antagonists, may hold therapeutic potentials for mitigating impulsivity in high-impulsive subjects.

VTA Glutamatergic Projections To The Nucleus Accumbens Suppress Psychostimulant-Seeking Behavior Barbano MF, Qi J, Chen E, Mohammad U, Espinoza O, Candido M, Wang H, Liu B, Hahn S, Vautier F, Morales M. Neuropsychopharmacology. 2024. [Online ahead of print].
Converging evidence indicates that both dopamine and glutamate neurotransmission within the nucleus accumbens (NAc) play a role in psychostimulant self-administration and relapse in rodent models. Increased NAc dopamine release from ventral tegmental area (VTA) inputs is critical to

psychostimulant self-administration and NAc glutamate release from prelimbic prefrontal cortex (PFC) inputs synapsing on medium spiny neurons (MSNs) is critical to reinstatement of psychostimulant-seeking after extinction. The regulation of the activity of MSNs by VTA dopamine inputs has been extensively studied, and recent findings have demonstrated that VTA glutamate neurons target the NAc medial shell. Here, we determined whether the mesoaccumbal glutamatergic pathway plays a role in psychostimulant conditioned place preference and self-administration in mice. We used optogenetics to induce NAc release of glutamate from VTA inputs during the acquisition, expression, and reinstatement phases of cocaine- or methamphetamine-induced conditioned place preference (CPP), and during priming-induced reinstatement of cocaine-seeking behavior. We found that NAc medial shell release of glutamate resulting from the activation of VTA glutamatergic fibers did not affect the acquisition of cocaine-induced CPP, but it blocked the expression, stress- and priming-induced reinstatement of cocaine- and methamphetamine CPP, as well as it blocked the priming-induced reinstatement of cocaine-seeking behavior after extinction. These findings indicate that in contrast to the well-recognized mesoaccumbal dopamine system that is critical to psychostimulant reward and relapse, there is a parallel mesoaccumbal glutamatergic system that suppresses reward and psychostimulant-seeking behavior.


DEPARTMENT OF HEALTH & HUMAN SERVICES · USA


NIH
National Institute
on Drug Abuse