



# DIRECTOR'S REPORT

*to the*

National Advisory Council on Drug Abuse

*May 10, 2022*

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## **RESEARCH HIGHLIGHTS**

### **BASIC AND BEHAVIORAL RESEARCH**

#### **Angiotensin-converting Enzyme Gates Brain Circuit-specific Plasticity Via An Endogenous**

**Opioid** Trieu BH, Remmers BC, Toddes C, Brandner DD, Lefevre EM, Kocharian A, Retzlaff CL, Dick RM, Mashal MA, Gauthier EA, Xie W, Zhang Y, More SS, Rothwell PE. *Science*. 2022; 375(6585): 1177-1182.

Angiotensin-converting enzyme (ACE) regulates blood pressure by cleaving angiotensin I to produce angiotensin II. In the brain, ACE is especially abundant in striatal tissue, but the function of ACE in striatal circuits remains poorly understood. We find that ACE degrades an unconventional enkephalin heptapeptide, Met-enkephalin-Arg-Phe, in the nucleus accumbens of mice. ACE inhibition enhanced mu opioid receptor activation by Met-enkephalin-Arg-Phe, causing a cell type-specific long-term depression of glutamate release onto medium spiny projection neurons expressing the Drd1 dopamine receptor. Systemic ACE inhibition was not intrinsically rewarding but decreased the conditioned place preference caused by fentanyl administration, and enhanced reciprocal social interaction. Our results raise the enticing prospect that central ACE inhibition can boost endogenous opioid signaling for clinical benefit, while mitigating risk of addiction.

#### **Functional Dissection Of Neural Circuitry Using A Genetic Reporter For fMRI**

Ghosh S, Li N, Shwalm M, Bartelle BB, Xie T, Daher JI, Singh UD, Xie K, DiNapoli N, Evans NB, Chung K, Jasanoff A. *Nature Neuroscience*. 2022; 25(3): 390-398.

The complex connectivity of the mammalian brain underlies its function but understanding how interconnected brain regions interact in neural processing remains a formidable challenge. Here we address this problem by introducing a genetic probe that permits selective functional imaging of distributed neural populations defined by viral labeling techniques. The probe is an engineered enzyme that transduces cytosolic calcium dynamics of probe-expressing cells into localized hemodynamic responses that can be specifically visualized by functional magnetic resonance imaging. Using a viral vector that undergoes retrograde transport, we apply the probe to characterize a brain-wide network of presynaptic inputs to the striatum activated in a deep brain stimulation paradigm in rats. The results reveal engagement of surprisingly diverse projection sources and inform an integrated model of striatal function relevant to reward behavior and therapeutic neurostimulation approaches. Our work thus establishes a strategy for mechanistic analysis of multiregional neural systems in the mammalian brain.

#### **Dysregulated Expression Of The Alternatively Spliced Variant MRNAs Of The Mu Opioid Receptor Gene, OPRM1, In The Medial Prefrontal Cortex Of Male Human Heroin Abusers and Heroin Self-administering Male Rats**

Brown TG, Xu J, Hurd YL, Pan Y-X. *J Neurosci Res*. 2022; 100(1): 35-47.

Heroin, a mu agonist, acts through the mu opioid receptor. The mu opioid receptor gene, OPRM1, undergoes extensive alternative splicing, creating an array of splice variants that are conserved from rodent to humans. Increasing evidence suggests that these OPRM1 splice variants are pharmacologically important in mediating various actions of mu opioids, including analgesia, tolerance, physical dependence, rewarding behavior, as well as addiction. In the present study, we examine expression of the OPRM1 splice variant mRNAs in the medial prefrontal cortex (mPFC),

one of the major brain regions involved in decision-making and drug-seeking behaviors, of male human heroin abusers and male rats that developed stable heroin-seeking behavior using an intravenous heroin self-administration (SA) model. The results show similar expression profiles among multiple OPRM1 splice variants in both human control subjects and saline control rats, illustrating conservation of OPRM1 alternative splicing from rodent to humans. Moreover, the expressions of several OPRM1 splice variant mRNAs were dysregulated in the postmortem mPFCs from heroin abusers compared to the control subjects. Similar patterns were observed in the rat heroin SA model. These findings suggest potential roles of the OPRM1 splice variants in heroin addiction that could be mechanistically explored using the rat heroin SA model.

**[A Diencephalic Circuit In Rats For Opioid Analgesia But Not Positive Reinforcement](#)** Waung MW, Maanum KA, Cirino TJ, Driscoll JR, O'Brien C, Bryant S, Mansourian KA, Morales M, Barker DJ, Margolis EB. *Nat Commun.* 2022; 13(1): 764.

Mu opioid receptor (MOR) agonists are potent analgesics, but also cause sedation, respiratory depression, and addiction risk. The epithalamic lateral habenula (LHb) signals aversive states including pain, and here we found that it is a potent site for MOR-agonist analgesia-like responses in rats. Importantly, LHb MOR activation is not reinforcing in the absence of noxious input. The LHb receives excitatory inputs from multiple sites including the ventral tegmental area, lateral hypothalamus, entopeduncular nucleus, and the lateral preoptic area of the hypothalamus (LPO). Here we report that LHb-projecting glutamatergic LPO neurons are excited by noxious stimulation and are preferentially inhibited by MOR selective agonists. Critically, optogenetic stimulation of LHb-projecting LPO neurons produces an aversive state that is relieved by LHb MOR activation, and optogenetic inhibition of LHb-projecting LPO neurons relieves the aversiveness of ongoing pain.

**[The Role Of The Anterior Insular During Targeted Helping Behavior In Male Rats](#)** Cox SS, Kearns AM, Woods SK, Brown BJ, Brown SJ, Reichel CM. *Scientific Reports.* 2022; 12(1): 1-11. Empathy, the understanding of the emotional state of others, can be examined across species using the Perception Action Model, where shared affect promotes an action by “Observers” to aid a distressed “Target”. The anterior insula (AI) has garnered interest in empathic behavior due to its role integrating sensory and emotional information of self and other. In the following studies, the AI was inhibited pharmacologically and chemogenetically during targeted helping. We demonstrate the insula is active during, and is necessary for the maintenance of, targeted helping. Analysis of ultrasonic vocalizations revealed distress calls from Targets increased when Observers’ helping was attenuated due to insula inhibition. Targets’ elevated distress was directly correlated to Observers’ diminished helping behavior, suggesting emotional transfer between Observer and Target is blunted following Observer AI inhibition. Finally, the AI may selectively blunt targeted helping, as social exploration did not change in a social reward place conditioning task. These studies help further establish the anterior insula as a critical node in the empathic brain during targeted helping, even in the absence of direct social contact.

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

### **Examining the Unique and Additive Effect Of Trauma and Racial Microaggressions On Substance Use Risk Among Black Young Adults**

Zapolski TCB, Rowe AT, Clifton RL, Khazvand S, Crichlow QJ, Faidley M. *Cultur Divers Ethnic Minor Psychol*. 2021 Dec 23. Epub ahead of print.

Objective: Exposure to traumatic events is linked to adverse health outcomes, including substance use. Contemporary models have conceptualized racism, including racial microaggressions, as a form of trauma. However, few studies have been conducted examining the unique and additive effect of racial microaggressions within models that include exposure to traditional forms of trauma on substance use outcomes, as well as whether effects vary by gender. Method: Three hundred and ninety-nine Black young adults between 18 and 29 (61% female, mean age 20.7) completed measures on problem alcohol and cannabis use, and experiences of trauma and racial microaggressions. Results: Controlling for age, gender, income, race (i.e., monoracial vs. multiracial), and recruitment source, regression analyses showed that racial microaggressions predicted problem substance use above the effect of trauma exposure. Moreover, exoticization/assumptions of similarity and workplace/school microaggressions primarily accounted for the effect of racial microaggressions on substance use risk. One gender effect was found, with trauma exposure associated with lower cannabis use for Black males and a nonsignificant effect found for Black females. Conclusions: Racial microaggressions provide unique and additive understanding in risk for substance use outcomes among Black young adults above effects observed from exposure to traditional forms of trauma. This finding highlights the significance of racial microaggression on health outcomes for Black young adults and can inform future research in the area of trauma exposure and substance use risk among this population of young people.

### **A Comparison Of Methods To Identify Antenatal Substance Use Within Electronic Health Records**

Tang LA, Jeffery AD, Leech AA, Osmundson SS, Schirle L, Phillippi JC. *Am J Obstet Gynecol MFM*. 2022; 4(2): 100535.

Substance misuse during pregnancy is associated with poor maternal and fetal outcomes. The incidences of maternal substance use disorder (SUD) and related neonatal outcomes are rising dramatically and are likely underestimated. Tracking the timing and amount of perinatal care for individuals with SUD in pregnancy is critical in assessing policy initiatives and access to services. Electronic health records (EHRs) are a resource for evaluating such policy initiatives. However, current methods for identifying individuals with SUD in the EHRs often rely on inconsistently documented SUD diagnosis codes and fail to detect individuals not utilizing SUD treatment services. Natural language processing (NLP) can be used to locate important words or phrases within EHR-based clinical notes. The presence of such important words has been combined with diagnosis codes to identify nonpregnant individuals with SUD. In some cases, the evidence of substance use may only occur in clinical notes, thus necessitating NLP methods to identify and extract substance use information. However, NLP methods have not been widely tested among pregnant patients. This study describes the development of an NLP-based algorithm for detecting antenatal substance use among individuals receiving perinatal care. This method was compared with International Classification of Diseases (ICD) codes alone and in concert with the ICD codes.

**Parent ENDS Use Predicts Adolescent And Young Adult Offspring ENDS Use Above And Beyond Parent Cigarette Use** Bailey JA, Epstein M, Kosterman R. *Addictive Behaviors*. 2022; 125: 107157.

Prior research has shown that parent combustible cigarette use predicts cigarette use among their offspring. This study used prospective longitudinal data from parents and offspring to test whether parent electronic nicotine delivery system (ENDS) use predicted a higher probability of ENDS use among their offspring. Data were drawn from the Seattle Social Development Project - The Intergenerational Project (SSDP-TIP). Analyses included 295 families; 7% of parents were Native American/Alaskan Native, 18% were Asian American, 28% were African American, and 47% were European American. Multilevel modeling (in 2020) of data collected in 2015, 2016, and 2017 tested associations between parent self-reported ENDS use and concurrent self-reported ENDS use among offspring ages 10-25 years (53% female). Parent combustible cigarette use was controlled. Analyses also examined the role of parent and offspring perceptions of the safety of ENDS in predicting offspring ENDS use. About 12% of offspring and 8% of parents reported past-month ENDS use. Parent ENDS use predicted a higher probability of child ENDS use (Odds Ratio 5.68,  $p = .01$ ), even after controlling parent past month cigarette use. Beyond parent nicotine product use, offspring perceptions of ENDS safety - but not parent perceptions of ENDS safety - contributed independently to offspring probability of past-month ENDS use. It is important for parents, health providers, and policymakers to focus on preventing ENDS use among offspring of parents who use ENDS.

**Clinical Impact, Costs, And Cost-Effectiveness Of Hospital-Based Strategies For Addressing The US Opioid Epidemic: A Modelling Study** Barocas JA, Savinkina A, Adams J, Jawa R, Weinstein ZM, Samet JH, Linas BP. *Lancet Public Health*. 2022; 7(1): e56-e64.

This study evaluated the clinical impact, costs, and cost-effectiveness of hospital-based strategies to address the US opioid epidemic using a microsimulation model to compare the cost-effectiveness of: standard hospital care-detoxification for opioids, no addiction consult service (status quo); expanded inpatient prescribing of medications for opioid use disorder, including bridge prescriptions (i.e., medication until they can see an outpatient provider) when possible (medications for opioid use disorder with bridge); implementation of addiction consult services within the hospital (addiction consult services alone); and a combined medication for opioid use disorder with addiction consult services strategy (combined). Outcomes were life-years, discounted costs, incremental cost-effectiveness ratios, hospitalizations, and deaths. Among people who inject opioids in the USA, expanding medications for opioid use disorder with bridge prescriptions was estimated to reduce hospitalizations and overdose deaths by 3.2% and 3.6%, respectively, and the combination of expanded medications with opioid use disorder along with addiction consult services was estimated to reduce hospitalizations and overdoses by 5.2% and 6.6%, respectively, compared with the status quo. The combined interventions of expanding hospital-based prescribing of medications for opioid use disorder and implementing addiction consult services could improve life expectancy, be cost-effective, and could be the basis for a comprehensive hospital-based strategy for addressing the opioid epidemic in the USA and countries with similar opioid epidemics.

**[Substitution Of Nonpharmacologic Therapy With Opioid Prescribing For Pain During the COVID-19 Pandemic](#)** Lee B, Yang KC, Kaminski P, Peng S, Odabas M, Gupta S, Green HD Jr, Ahn YY, Perry BL. JAMA Netw Open. 2021; 4(12): e2138453.

During the pandemic, access to medical care unrelated to COVID-19 was limited because of concerns about viral spread and corresponding policies. This study assessed the trends in opioid prescription and nonpharmacologic therapy (i.e., physical therapy and complementary medicine) for pain management during the COVID-19 pandemic in 2020 compared with the patterns in 2019. Among patients with diagnoses of limb, extremity, or joint pain, back pain, and neck pain for each week, patterns of treatment use were identified and evaluated. During the COVID-19 pandemic, the proportion of patients receiving a pain diagnosis was smaller than that for the same period in 2019. Patients with pain were more likely to receive opioids and less likely to receive nonpharmacologic therapy, and opioid prescriptions were longer and more potent during the early pandemic in 2020 relative to 2019. Analysis of individuals' transitions between treatment options for pain found that patients were more likely to transition out of nonpharmacologic therapy, replacing it with opioid prescriptions for pain management during the COVID-19 pandemic than in the year before. These findings suggest that it is imperative to investigate the implications of limited medical access on treatment substitution, which may increase patient risk, and implement policies and guidelines to prevent those substitutions.

## **TREATMENT RESEARCH**

**[Cocaine Hydrolase Blocks Cocaine-induced Dopamine Transporter Trafficking To The Plasma Membrane](#)** Deng J, Kim K, Zheng X, Shang L, Zhan C-G, Zheng F. Addict Biol. 2022; 27(1): e13089.

Cocaine blocks dopamine uptake via dopamine transporter (DAT) on plasma membrane of neuron cells and, as a result, produces the high and induces DAT trafficking to plasma membrane which contributes to the drug seeking or craving. In this study, we first examined the dose dependence of cocaine-induced DAT trafficking and hyperactivity in rats, demonstrating that cocaine at an intraperitoneal dose of 10 mg/kg or higher led to redistribution of most DAT to the plasma membrane while inducing significant hyperactivity in rats. However, administration of 5-mg/kg cocaine (ip) did not significantly induce DAT trafficking or hyperactivity in rats. So the threshold (intraperitoneal) dose of cocaine that can significantly induce DAT trafficking or hyperactivity should be between 5 and 10 mg/kg. These data suggest that when a cocaine dose is high enough to induce significant hyperactivity, it can also significantly induce DAT trafficking to the plasma membrane. Further, the threshold brain cocaine concentration required to induce significant hyperactivity and DAT trafficking was estimated to be  $\sim 2.0 \pm 0.8 \mu\text{g/g}$ . Particularly, for treatment of cocaine abuse, previous studies demonstrated that an exogenous cocaine-metabolizing enzyme, for example, Coch3-Fc(M3), can effectively block cocaine-induced hyperactivity. However, it was unknown whether an enzyme could also effectively block cocaine-induced DAT trafficking to the plasma membrane. This study demonstrates, for the first time, that the enzyme is also capable of effectively blocking cocaine from reaching the brain even with a lethal dose of 60-mg/kg cocaine (ip) and, thus, powerfully preventing cocaine-induced physiological effects such as the hyperactivity and DAT trafficking.

**Deep RTMS Of The Insula And Prefrontal Cortex In Smokers With Schizophrenia: Proof-of-concept Study** Moeller SJ, Gil R, Weinstein JJ, Baumvoll T, Wengler K, Fallon N, Van Snellenberg, JX, Abeykoon S, Perlman G, Williams J, Manu L, Slifstein M, Cassidy CM, Martinez DM; Abi-Dargham A. NPJ Schizophr. 2022; 8(1): 6.

Patients with schizophrenia have a high prevalence of cigarette smoking and respond poorly to conventional treatments, highlighting the need for new therapies. We conducted a mechanistic, proof-of-concept study using bilateral deep repetitive transcranial magnetic stimulation (dTMS) of insular and prefrontal cortices at high frequency, using the specialized H4 coil. Feasibility of dTMS was tested for disruption of tobacco self-administration, insula target engagement, and insula circuit modulation, all of which were a priori outcomes of interest. Twenty patients completed the study, consisting of weekday dTMS sessions (randomization to active dTMS or sham; double-blind; 10 patients per group), a laboratory tobacco self-administration paradigm (pre/post assessments), and multimodal imaging (three MRI total sessions). Results showed that participants assigned to active dTMS were slower to initiate smoking their first cigarette compared with sham, consistent with smoking disruption. The imaging analyses did not reveal significant Time  $\times$  Group interactions, but effects were in the anticipated directions. In arterial spin labeling analyses testing for target engagement, an overall decrease in insula blood flow, measured during a post-treatment MRI versus baseline, was numerically more pronounced in the active dTMS group than sham. In fMRI analyses, resting-state connectivity between the insula and default mode network showed a numerically greater change from baseline in the active dTMS group than sham, consistent with a functional change to insula circuits. Exploratory analyses further suggested a therapeutic effect of dTMS on symptoms of psychosis. These initial observations pave the way for future confirmatory studies of dTMS in smoking patients with schizophrenia.

**A Pilot Feasibility Study Of A Behavioral Intervention For Nicotine Vaping Cessation Among Young Adults Delivered Via Telehealth** Palmer AM, Tomko RL, Squeglia LM, Gray KM, Carpenter MJ Smith TT, Dahne J, Toll BA, McClure EA. Drug Alcohol Depend. 2022; 232: 109311.

BACKGROUND: Nicotine vaping among youth has increased, warranting concern from tobacco control proponents. Many youth who vape indicate interest in quitting; however, few empirically supported vaping cessation interventions exist. This pilot feasibility study adapted an established behavioral intervention, contingency management (CM), delivered via telehealth to promote vaping cessation among young adults. METHODS: Participants (N = 27; ages 17-21) vaping nicotine regularly were recruited via social media and digital advertisements from across the US (June 2020-January 2021). Participants were randomized at approximately 4:1 to CM or Monitoring control (22:5). CM was delivered through DynamiCare Health's smartphone app for 4 weeks, in which financial incentives were delivered contingent on abstinent cotinine samples after the quit day until the end of treatment (EOT; Days 7-28; 10 expected submissions). Control participants earned incentives for submitting cotinine, regardless of abstinence. Feasibility, acceptability, and abstinence was collected throughout treatment, at EOT, and at 1-month follow-up. RESULTS: The majority of enrolled participants completed treatment (Monitoring: 5/5; CM: 20/22), and intervention components were rated favorably overall (> 80%). CM participants submitted 112/220 (55%) abstinent cotinine samples throughout the quit attempt, while the Monitoring group submitted 4/50 (8%) negative samples. There were no differences in abstinence between groups at EOT or follow-up. CONCLUSION: This pilot study of a telehealth-based youth vaping cessation intervention demonstrated preliminary feasibility and acceptability. These results suggest that CM



for young adult vaping cessation, delivered remotely, is a promising direction for future work and fully powered trials are warranted to assess intervention efficacy.

**Characterizing Cannabis Use Reduction And Change In Functioning During Treatment: Initial Steps On The Path To New Clinical Endpoints**

Borodovsky JT, Sofis MJ, Sherman BJ, Gray KM, Budney AJ. Psychol Addict Behav. Jan 27, 2022. Online ahead of print.

Reduction-based cannabis use endpoints are needed to better evaluate treatments for cannabis use disorder (CUD). This exploratory, secondary analysis aimed to characterize cannabis frequency and quantity reduction patterns and corresponding changes in psychosocial functioning during treatment. We analyzed 16 weeks (4 prerandomization, 12 postrandomization) of data (n = 302) from both arms of a randomized clinical trial assessing pharmacotherapy for CUD. Cannabis consumption pattern classes were extracted with latent profile modeling using self-reported (a) past-week days used (i.e., frequency) and (b) past-week average grams used per using day (i.e., quantity). Changes in mean Marijuana Problem Scale (MPS) and Hospital Anxiety and Depression Scale (HADS) scores were examined among classes. Urine cannabinoid levels were examined in relation to self-reported consumption as a validity check. Two-, three-, four-, and five-class solutions each provided potentially useful conceptualizations of associations between frequency and quantity. Regardless of solution, reductions in MPS scores varied in magnitude across classes and closely tracked class-specific reductions in consumption (e.g., larger MPS reduction corresponded to larger frequency/quantity reductions). Changes in HADS scores were less pronounced and less consistent with consumption patterns. Urine cannabinoid levels closely matched class-specific self-reported consumption frequency. Findings illustrate that frequency and quantity can be used in tandem within mixture model frameworks to summarize heterogeneous cannabis use reduction patterns that may correspond to improved psychosocial functioning. Going forward, similar analytic strategies applied to alternative metrics of cannabis consumption may facilitate construction of useful reduction-based clinical endpoints.

**Cocaethylene, Simultaneous Alcohol and Cocaine Use, And Liver Fibrosis In People Living With And Without HIV**

Tamargo JA, Sherman KE, Sékaly R-P, Bordi R, Schlatzer D, Lai S, Khalsa JH, Mandler RN, Ehman RL, Baum MK. Drug Alcohol Depend. 2022; 232: 109273.

**BACKGROUND:** The simultaneous consumption of cocaine and alcohol results in the production of cocaethylene (CE) in the liver, a highly toxic metabolite. Prior research suggests that cocaine use contributes to liver disease and its concomitant use with alcohol may increase its hepatotoxicity, but studies in humans are lacking. We evaluated the role of cocaine, its simultaneous use with alcohol, and CE on liver fibrosis. **METHODS:** We performed a cross-sectional analysis of the Miami Adult Studies on HIV (MASH) cohort. Cocaine use was determined via self-report, urine screen, and blood metabolites, using liquid chromatography with tandem mass spectrometry. Hazardous drinking was determined with the AUDIT-C and liver fibrosis with the Fibrosis-4 Index (FIB-4). **RESULTS:** Out of 649 participants included in this analysis, 281 (43.3%) used cocaine; of those, 78 (27.8%) had CE in blood. Cocaine users with CE had higher concentrations of cocaine metabolites in blood and were more likely to drink hazardously than cocaine users without CE and cocaine non-users. Overall, cocaine use was associated with liver fibrosis. CE in blood was associated with 3.17 (95% CI: 1.61, 6.23; p = 0.0008) times the odds of liver fibrosis compared to cocaine non-users, adjusting for covariates including HIV and HCV infection. The effect of CE on liver fibrosis was significantly greater than that of cocaine or alcohol alone. **CONCLUSIONS:** CE is a reliable marker

of simultaneous use of cocaine and alcohol that may help identify individuals at risk of liver disease and aid in the prevention of its development or progression.

**Therapeutic Potentials Of NOP And MOP Receptor Coactivation For The Treatment Of Pain And Opioid Abuse** Kiguchi N, Ding H, Ko M-C. J Neurosci Res. 2022; 100(1): 191-202.

Following the identification of the nociceptin/orphanin FQ (N/OFQ) peptide (NOP) as an endogenous ligand for the NOP receptor, ample evidence has revealed unique functional profiles of the N/OFQ-NOP receptor system. NOP receptors are expressed in key neural substrates involved in pain and reward modulation. In nonhuman primates (NHPs), NOP receptor activation effectively exerts antinociception and anti-hypersensitivity at the spinal and supraspinal levels. Moreover, NOP receptor activation inhibits dopaminergic transmission and synergistically enhances mu-opioid peptide (MOP) receptor-mediated analgesia. In this article, we have discussed the functional profiles of ligands with dual NOP and MOP receptor agonist activities and highlight their optimal functional efficacy for pain relief and drug abuse treatment. Through coactivation of NOP and MOP receptors, bifunctional NOP/MOP receptor "partial" agonists (e.g., AT-121, BU08028, and BU10038) reveal a wider therapeutic window with fewer side effects. These newly developed ligands potently induce antinociception without MOP receptor agonist-associated side effects such as abuse potential, respiratory depression, itching sensation, and physical dependence. In addition, in both rodent and NHP models, bifunctional NOP/MOP receptor agonists can attenuate reward processing and/or the reinforcing effects of opioids and other abused drugs. While a mixed NOP/opioid receptor "full" agonist cebranopadol is undergoing clinical trials, bifunctional NOP/MOP "partial" agonists exhibit promising therapeutic profiles in translational NHP models for the treatment of pain and opioid abuse. This class of drugs demonstrates the therapeutic advantage of NOP and MOP receptor coactivation, indicating a greater potential for future development.

**The GLT-1 Enhancer Clavulanic Acid Suppresses Cocaine Place Preference Behavior And Reduces GCPII Activity And Protein Levels In The Rat Nucleus Accumbens** Philogene-Khalid

HL, Morrison MF, Darbinian N, Selzer ME, Schroeder J, Rawls SM. Drug Alcohol Depend. 2022; 232: 109306.

The  $\beta$ -lactam antibiotic ceftriaxone (CTX) is a glutamate transporter subtype 1 (GLT-1) enhancer that reduces cocaine reinforcing efficacy and relapse in rats, but pharmacokinetic liabilities limit translational utility. An attractive alternative is clavulanic acid (CLAV), a structurally related  $\beta$ -lactamase inhibitor and component of FDA-approved Augmentin. CLAV retains the GLT-1 enhancing effects of CTX but displays greater oral bioavailability, brain penetrability and negligible antibacterial activity. CLAV reduces morphine conditioned place preference (CPP) and ethanol consumption in rats, but knowledge about the efficacy of CLAV in preclinical models of drug addiction remains sparse. Here, we investigated effects of CLAV (10 mg/kg, IP) on the acquisition, expression, and maintenance of cocaine CPP in rats, and on two glutamate biomarkers associated with cocaine dependence, GLT-1 and glutamate carboxypeptidase II (GCPII). CLAV administered during cocaine conditioning (10 mg/kg, IP x 4 d) did not affect the development of cocaine CPP. However, a single CLAV injection, administered after the conditioning phase, reduced the expression of cocaine CPP. In rats with established cocaine preference, repeated CLAV administration facilitated extinction of cocaine CPP. In the nucleus accumbens, acute CLAV exposure reduced GCPII protein levels and activity, and a 10-d CLAV treatment regimen enhanced GLT-1 levels. These results suggest that CLAV reduces expression and maintenance of cocaine CPP but lacks effect against development of CPP. Moreover, the ability of a single injection of

CLAV to reduce both GCPII activity and protein levels, as well as expression of cocaine CPP, points toward studying GCPII as a therapeutic target of CLAV.

**[Increasing Cessation Motivation And Treatment Engagement Among Smokers In Pain: A Pilot Randomized Controlled Trial](#)** Zale EL, Maisto S, De Vita MJ, Hooten WM, Ditre JW. *Exp Clin Psychopharmacol.* 2021; 29(6): 593-604.

Tobacco smokers with co-occurring pain report greater difficulty quitting, face unique cessation challenges, and may benefit from targeted smoking interventions. We developed and tested a brief motivational intervention aimed at increasing knowledge of pain-smoking interrelations, motivation to quit, and cessation treatment engagement among smokers in pain. Nontreatment seeking daily cigarette smokers with chronic pain (N = 76, 57.9% women, 52.6% White) were randomized to the targeted or ask, advise, refer (AAR) intervention. The targeted intervention included personalized feedback and pain-smoking psychoeducation to help participants develop discrepancy between continued smoking and desired pain outcomes. At postintervention, the targeted intervention (vs. AAR) increased knowledge of pain-smoking interrelations and several indices of motivation to quit smoking ( $p < .01$ ). Participants who received the targeted intervention were also more likely to accept information about and report intention to engage evidence-based cessation treatments ( $p < .05$ ). Increased knowledge of pain-smoking interrelations mediated postintervention effects on motivation to quit and willingness to learn about treatments. At 1-month follow up, gains in knowledge of pain-smoking interrelations were maintained ( $p = .009$ ). Participants who received the targeted intervention were more likely to report having subsequently engaged cessation treatment ( $p = .019$ ), but this was not mediated by increased knowledge of pain-smoking interrelations. Smokers with chronic pain may benefit from targeted interventions that address smoking in the context of pain. Smokers in pain may become increasingly motivated to quit and engage cessation treatment as they become aware of how smoking may exacerbate their pain.

**[A Pilot Randomized Clinical Trial Of Brief Behavioral Treatment For Insomnia To Reduce Problematic Cannabis Use Among Trauma-exposed Young Adults](#)** Short NA, Zvolensky MJ, Schmidt NB. *J Subst Abuse Treat.* 2021; 131: 108537.

**BACKGROUND:** Insomnia symptoms may be an important etiological factor for substance use disorders; however, whether improving sleep leads to reductions in problematic substance use among at-risk populations remains unclear. **METHOD:** As such, the current pilot study used a randomized controlled design to test the effects of Brief Behavioral Treatment for Insomnia (BBTI) against a waitlist control among a sample of trauma-exposed young adults with elevated insomnia symptoms who regularly use cannabis (N = 56). **RESULTS:** Intent-to-treat multilevel modeling analyses indicated that BBTI may be more efficacious than waitlist control in reducing self-reported insomnia symptoms, with large effects three months post-treatment ( $d = 1.34$ ). Further, our initial evidence suggested that BBTI resulted in reductions in cannabis-related problems with medium to large effects at three months post-treatment ( $d = 0.75$ ). The current pilot analyses indicated BBTI also reduced cravings to use cannabis to reduce negative emotions in response to trauma cues with a large effect size. **CONCLUSION:** This pilot study suggests BBTI may be efficacious not only in improving insomnia symptoms among cannabis users but also in reducing cannabis-related problems and cravings over three months. Future research should replicate these results in a larger, fully powered sample with improved follow-up rates designed to test temporal mediation using multimethod assessments of insomnia symptoms and problematic cannabis use. Overall, BBTI may

be a promising intervention for trauma-exposed cannabis users to improve sleep and reduce cannabis-related problems.

**[Examining The Impact Of Social Distancing And Methamphetamine Use On Sexual Risk And Intimate Partner Violence In Sexual And Gender Minority Young Adults During The COVID-19 Pandemic](#)** Xavier Hall CD, Javanbakht M, Iyer C, Costales C, Napolitano JC, Johnson T, Castro CF, Newcomb ME, Kipke MD, Shoptaw S, Gorbach P, Mustanski B. *Drug Alcohol Depend.* 2022; 232: 109231.

**BACKGROUND:** During the COVID-19 pandemic in 2020, concerns were raised about the potential impact of pandemic-related social distancing measures on existing health disparities among sexual and gender minority (SGM) young adults, including HIV transmission risk and intimate partner violence (IPV). Another concern was the potential for increased methamphetamine use during the pandemic, which is a known risk factor for HIV transmission and IPV. **METHODS:** The present analysis examines the impact of COVID-19 social distancing (social distancing and quarantining) and methamphetamine use on HIV risk and IPV in a combined dataset from 3 cohort studies of SGM young adults (two in Los Angeles and one in Chicago) from May 2020 to April 2021 (n = 1142). Bivariate analyses and multivariable logistic regressions were estimated. **RESULTS:** The median age was 26. All participants were assigned male at birth and most participants were men (93.8%). The largest racial groups were Hispanic/Latinx (44.6%) and Black (29.0%). In adjusted models methamphetamine use was consistently associated with having a new sex partner, higher numbers of sex partners, and experience of IPV, during the pandemic. Reporting no social distancing and reporting one social distancing behavior, were associated with experience of IPV relative to reporting 2 social distancing behaviors. Social distancing was not associated with sexual risk behavior or Pre-exposure Prophylaxis use. **CONCLUSIONS:** SGM young adults live at the intersection of multiple vulnerabilities during the COVID-19 pandemic. Addiction services, HIV prevention services, and violence support services should be prepared to support young adult SGM needs, particularly those who use methamphetamine.

## **HIV RESEARCH**

**[Parallel Analysis Of Transcription, Integration, And Sequence Of Single HIV-1 Proviruses](#)** Einkauf KB, Osborn MR, Gao C, Sun W, Sun X, Lian X, Parsons EM, Gladkov GT, Seiger KW, Blackmer JE, Jiang C, Yuki SA, Rosenberg ES, Yu XG, Lichterfeld M. *Cell.* 2022; 185:266-282. HIV-1-infected cells that persist despite antiretroviral therapy (ART) are frequently considered “transcriptionally silent,” but active viral gene expression may occur in some cells, challenging the concept of viral latency. Applying an assay for profiling the transcriptional activity and the chromosomal locations of individual proviruses, we describe a global genomic and epigenetic map of transcriptionally active and silent proviral species and evaluate their longitudinal evolution in persons receiving suppressive ART. Using genome-wide epigenetic reference data, we show that proviral transcriptional activity is associated with activating epigenetic chromatin features in linear proximity of integration sites and in their inter- and intrachromosomal contact regions. Transcriptionally active proviruses were actively selected against during prolonged ART; however, this pattern was violated by large clones of virally infected cells that may outcompete negative selection forces through elevated intrinsic proliferative activity. Our results suggest that

transcriptionally active proviruses are dynamically evolving under selection pressure by host factors.

**Mitochondrial Dysfunction: A Prelude To Neuropathogenesis Of SARS-CoV-2** Pliss A, Kuzmin AN, Prasad PN, Mahajan SD. ACS Chem Neurosci. 2022; 13(3):308-312.

The SARS-CoV-2 virus is notorious for its neuroinvasive capability, causing multiple neurological conditions. The neuropathology of SARS-CoV-2 is increasingly attributed to mitochondrial dysfunction of brain microglia cells. However, the changes in biochemical content of mitochondria that drive the progression of neuro-COVID remain poorly understood. Here we introduce a Raman microspectrometry approach that enables the molecular profiling of single cellular organelles to characterize the mitochondrial molecular makeup in the infected microglia cells. We found that microglia treated with either spike protein or heat-inactivated SARS-CoV-2 trigger a dramatic reduction in mtDNA content and an increase in phospholipid saturation levels. At the same time, no significant changes were detected in Golgi apparatus and in lipid droplets, the organelles that accommodate biogenesis and storage of lipids. We hypothesize that transformations in mitochondria are caused by increased synthesis of reactive oxygen species in these organelles. Our findings call for the development of mitochondria-targeted therapeutic approaches to limit neuropathology associated with SARS-CoV-2.

**Stimulant Use Interventions May Strengthen ‘Getting To Zero’ HIV Elimination Initiatives In Illinois: Insights From A Modeling Study** Lee F, Sheeler D, Hotton A, Del Vecchio N, Flores R, Fujimoto K, Harawa N, Schneider JA, Khanna AS. International Journal of Drug Policy. 2022; 103: 103628.

Objective(s): Getting to Zero (GTZ) is an Illinois-based HIV elimination initiative. GTZ identifies younger Black men who have sex with men (YBMSM) as a population who have experienced disproportionate HIV incidence. Rising stimulant use among YBMSM has been determined to impede engagement in the HIV prevention and treatment continua for reducing onward HIV transmission. Given the limited development of dedicated or culturally appropriate interventions for this population, this modeling study explores the impact of stimulant use on HIV incidence among YBMSM and assesses the impact of interventions to treat stimulant use on downstream HIV transmission to achieve GTZ goals. Methods: A previously developed agent-based network model (ABNM), calibrated using data for YBMSM in Illinois, was extended to incorporate the impact of stimulant use (methamphetamines, crack/cocaine, and ecstasy) on sexual networks and engagement in HIV treatment and prevention continua. The model simulated the impact of a residential behavioral intervention (BI) for reducing stimulant use and an outpatient biomedical intervention (mirtazapine) for treating methamphetamine use. The downstream impact of these interventions on population-level HIV incidence was the primary intervention outcome. Results: Baseline simulated annual HIV incidence in the ABNM was 6.93 [95% Uncertainty Interval (UI): 6.83,7.04] per 100 person years (py) and 453 [95% UI: 445.9,461.2] new infections annually. A residential rehabilitation intervention targeted to 25% of stimulant using persons yielded a 27.1% reduction in the annual number of new infections. Initiating about 50% of methamphetamine using persons on mirtazapine reduced the overall HIV incidence among YBMSM by about 11.2%. A 30% increase in antiretroviral treatment (ART) and pre-exposure prophylaxis (PrEP) uptake in the non-stimulant using YBMSM population combined with a 25% uptake of BI for stimulant using persons produces

an HIV incidence consistent with HIV elimination targets (about 200 infections/year) identified in the GTZ initiative. Conclusions: Behavioral and biomedical interventions to treat stimulant use, in addition to expanding overall ART and PrEP uptake, are likely to enhance progress towards achieving GTZ goals.

### **The Contribution Of Unstable Housing To HIV And Hepatitis C Virus Transmission Among People Who Inject Drugs Globally, Regionally, And At Country Level: A Modelling Study**

Stone J, Artenie A, Hickman M, Martin NK, Degenhardt L, Fraser H, Vickerman P. *Lancet Public Health*. 2022; 7(2): e136-e145.

A considerable proportion of people who inject drugs are unstably housed. Although unstable housing is associated with HIV and HCV infection among people who inject drugs, its contribution to transmission is unknown. The investigators estimated the global and national proportions of incident HIV and HCV infections among people who inject drugs attributed to housing instability from 2020 to 2029. The models estimated the transmission population attributable fraction (tPAF) of unstable housing to HIV and HCV transmission among people who inject drugs, defined as the percentage of infections prevented from 2020 to 2029 if the additional risk due to unstable housing was removed, for 58 countries. Globally, the investigators project unstable housing contributes 7.9% of new HIV infections and 11.2% of new HCV infections among people who inject drugs from 2020 to 2029. Unstable housing is an important modifiable risk factor for HIV and HCV transmission among people who inject drugs in many countries. The study emphasizes the importance of implementing initiatives to mitigate these risks and reduce housing instability.

### **HIV Clinic-Based Extended-Release Naltrexone Versus Treatment As Usual For People With HIV And Opioid Use Disorder: A Non-Blinded, Randomized Non-Inferiority Trial**

Korthuis PT, Cook RR, Lum PJ, Waddell EN, Tookes H, Vergara-Rodriguez P, Kunkel LE, Lucas GM, Rodriguez AE, Bielavitz S, Fanucchi LC, Hoffman KA, Bachrach K, Payne EH, Collins JA, Matthews A, Oden N, Jacobs P, Jelstrom E, Sorensen JL, McCarty D. *Addiction*. 2022 Feb 7. Online ahead of print.

Background and aim: Opioid agonist medications for treatment of opioid use disorder (OUD) can improve human immunodeficiency virus (HIV) outcomes and reduce opioid use. We tested whether outpatient antagonist treatment with naltrexone could achieve similar results. Design: Open-label, non-inferiority randomized trial. Setting: Six US HIV primary care clinics. Participants: A total of 114 participants with untreated HIV and OUD (62% male; 56% black, 12% Hispanic; positive for fentanyl (62%), other opioids (47%) and cocaine (60%) at baseline). Enrollment halted early due to slow recruitment. Intervention: HIV clinic-based extended-release naltrexone (XR-NTX; n = 55) versus treatment as usual (TAU) with buprenorphine or methadone (TAU; n = 59).

Measurements: Treatment group differences were compared for the primary outcome of viral suppression (HIV RNA  $\leq$  200 copies/ml) at 24 weeks and secondary outcomes included past 30-day use of opioids at 24 weeks. Findings: Fewer XR-NTX participants initiated medication compared with TAU participants (47 versus 73%). The primary outcome of viral suppression was comparable for XR-NTX (52.7%) and TAU (49.2%) [risk ratio (RR) = 1.064; 95% confidence interval (CI) = 0.748, 1.514] at 24 weeks. Non-inferiority could not be demonstrated, as the lower confidence limit of the RR did not exceed the pre-specified margin of 0.75 in intention-to-treat (ITT) analysis. The main secondary outcome of past 30-day opioid use was comparable for XR-NTX versus TAU (11.7 versus 14.8 days; mean difference = -3.1; 95% CI = -8.7, 1.1) in ITT analysis. Among those

initiating medication, XR-NTX resulted in fewer days of opioid use compared with TAU in the past 30 days (6.0 versus 13.6, mean difference = -7.6; 95% CI = -13.8, -0.2). Conclusions: A randomized controlled trial found supportive, but not conclusive, evidence that human immunodeficiency virus clinic-based extended-release naltrexone is not inferior to treatment as usual for facilitating human immunodeficiency virus viral suppression. Participants who initiated extended-release naltrexone used fewer opioids than those who received treatment as usual.

## **CLINICAL TRIALS NETWORK RESEARCH**

**[The Opioid Use Disorder Core Outcomes Set \(OUD-COS\) For Treatment Research: Findings From A Delphi Consensus Study](#)** Karnik NS, Marsden J, McCluskey C, Boley RA, Bradley KA, Campbell CI, Curtis ME, Fiellin D, Ghitza U, Hefner K, Hser YI, McHugh RK, McPherson SM, Mooney LJ, Moran LM, Murphy SM, Schwartz RP, Shmueli-Blumberg D, Shulman M, Stephens KA, Watkins KE, Weiss RD, Wu LT. *Addiction*. 2022 Mar 16. Online ahead of print.

Background and aim: There is no gold-standard and considerable heterogeneity in outcome measures used to evaluate treatments for opioid use disorder (OUD) along the opioid treatment cascade. The aim of this study was to develop the US National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) opioid use disorder core outcomes set (OUD-COS). Design: Four round, e-Delphi expert panel consensus study and plenary research group discussion and targeted consultation. Setting: USA. Participants: A panel of 25 members including clinical practitioners, clinical researchers, and administrative staff from the CTN, the network's affiliated clinical and community sites, and the NIDA Centre for the CTN.

Measurements: From a pool of 24 candidate items in four domains (biomedical/disease status; behaviors, symptoms, and functioning; opioid treatment cascade; and morbidity and mortality), the panel completed an online questionnaire to rank items with defined specification, on a 9-point scale for importance, with a standard 70% consensus criterion. Findings: After the fourth round of the questionnaire and subsequent discussion, consensus was reached for five outcomes: two patient reported (global impression of improvement and incident non-fatal overdose); one clinician reported (illicit/non-medical drug toxicology); and two from administrative records (duration of treatment and fatal opioid poisoning). Conclusions: An e-Delphi consensus study has produced the US National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network opioid use disorder core outcomes set (version 1) for opioid use disorder treatment efficacy and effectiveness research.

**[Clinical Documentation Of Patient-Reported Medical Cannabis Use In Primary Care: Toward Scalable Extraction Using Natural Language Processing Methods](#)** Carrell DS, Cronkite DJ, Shea M, Oliver M, Luce C, Matson TE, Bobb JF, Hsu C, Binswanger IA, Browne KC, Saxon AJ, McCormack J, Jelstrom E, Ghitza UE, Campbell CI, Bradley KA, Lapham GT. *Subst Abus*. 2022; 43(1): 917-924.

Background: Most states have legalized medical cannabis, yet little is known about how medical cannabis use is documented in patients' electronic health records (EHRs). We used natural language processing (NLP) to calculate the prevalence of clinician-documented medical cannabis use among adults in an integrated health system in Washington State where medical and recreational use are legal. Methods: We analyzed EHRs of patients  $\geq 18$  years old screened for past-year cannabis use (November 1, 2017-October 31, 2018), to identify clinician-documented medical cannabis use. We

defined medical use as any documentation of cannabis that was recommended by a clinician or described by the clinician or patient as intended to manage health conditions or symptoms. We developed and applied an NLP system that included NLP-assisted manual review to identify such documentation in encounter notes. Results: Medical cannabis use was documented for 16,684 (5.6%) of 299,597 outpatient encounters with routine screening for cannabis use among 203,489 patients seeing 1,274 clinicians. The validated NLP system identified 54% of documentation and NLP-assisted manual review the remainder. Language documenting reasons for cannabis use included 125 terms indicating medical use, 28 terms indicating non-medical use and 41 ambiguous terms. Implicit documentation of medical use (e.g., "edible THC nightly for lumbar pain") was more common than explicit (e.g., "continues medical cannabis use"). Conclusions: Clinicians use diverse and often ambiguous language to document patients' reasons for cannabis use. Automating extraction of documentation about patients' cannabis use could facilitate clinical decision support and epidemiological investigation but will require large amounts of gold standard training data.

### **Moderation Of Buprenorphine Therapy For Cocaine Dependence Efficacy By Variation Of The Prodynorphin Gene**

Nielsen DA, Walker R, Graham DP, Nielsen EM, Hamon SC, Hillhouse M, Shmueli-Blumberg D, Lawson WB, Shores-Wilson K, Settles-Reaves BD, Rotrosen J, Trivedi MH, Saxon AJ, Ling W, Kosten TR. Eur J Clin Pharmacol. 2022; Online ahead of print.

Purpose: The aim of this secondary analysis was to identify prodynorphin (PDYN) genetic markers moderating the therapeutic response to treatment of cocaine dependence with buprenorphine/naloxone (Suboxone®; BUP). Methods: Cocaine-dependent participants (N = 302) were randomly assigned to a platform of injectable, extended-release naltrexone (XR-NTX) and one of three daily medication arms: 4 mg BUP (BUP4), 16 mg BUP (BUP16), or placebo (PLB) for 8 weeks (Parent Trial Registration: Protocol ID: NIDA-CTN-0048, ClinicalTrials.gov ID: [NCT01402492](#)). DNA was obtained from 277 participants. Treatment response was determined from weeks 3 to 7 over each 1-week period by the number of cocaine-positive urines per total possible urines. Results: In the cross-ancestry group, the PLB group had more cocaine-positive urines than the BUP16 group (P = 0.0021). The interactions of genetic variant × treatment were observed in the rs1022563 A-allele carrier group where the BUP16 group (N = 35) had fewer cocaine-positive urines (P = 0.0006) than did the PLB group (N = 26) and in the rs1997794 A-allele carrier group where the BUP16 group (N = 49) had fewer cocaine-positive urines (P = 0.0003) than did the PLB group (N = 58). No difference was observed in the rs1022563 GG or rs1997794 GG genotype groups between the BUP16 and PLB groups. In the African American-ancestry subgroup, only the rs1022563 A-allele carrier group was associated with treatment response. Conclusion: These results suggest that PDYN variants may identify patients who are best suited to treatment with XR-NTX plus buprenorphine for cocaine use disorder pharmacotherapy.

### **Cost Of Hepatitis C Care Facilitation For HIV/Hepatitis C Co-infected People Who Use Drugs**

Gutkind S, Starbird LE, Murphy SM, Teixeira PA, Gooden LK, Matheson T, Feaster DJ, Jain MK, Masson CL, Perlman DC, Del Rio C, Metsch LR, Schackman BR. Drug Alcohol Depend. 2022; 232: 109265. Epub 2022 Jan 10.

Background: Using data from a randomized trial, we evaluated the cost of HCV care facilitation that supports moving along the continuum of care for HIV/HCV co-infected individuals with substance use disorder. Methods: Participants were HIV patients residing in the community, initially recruited from eight US hospital sites. They received HCV care facilitation (n = 51) or treatment as usual (n = 62) for up to six months. We used micro-costing methods to evaluate costs



from the healthcare sector and patient perspectives in 2017 USD. We conducted sensitivity analyses varying care facilitator caseloads and examined offsetting savings using participant self-reported healthcare utilization. Results: The average site start-up cost was \$6320 (site range: \$4320-\$7000), primarily consisting of training. The mean weekly cost per participant was \$20 (site range: \$4-\$30) for care facilitation visits and contacts, \$360 (site range: \$130- \$700) for supervision and client outreach, and \$70 (site range: \$20-\$180) for overhead. In sensitivity analyses applying a weekly caseload of 10 participants per care facilitator (versus 1-6 observed in the trial), the total mean weekly care facilitation cost from the healthcare sector perspective decreased to \$110. Weekly participant time and travel costs averaged \$7. There were no significant differences in other healthcare service costs between participants in the intervention and control arms.

Conclusion: Weekly HCV care facilitation costs were approximately \$450 per participant, but approximately \$110 at a real-world setting maximum caseload of 10 participants per week. No healthcare cost offsets were identified during the trial period, although future savings might result from successful HCV treatment. Trial registration: ClinicalTrials.gov [NCT01612169](https://clinicaltrials.gov/ct2/show/study/NCT01612169).

**[Association Between Methadone Or Buprenorphine Use During Medically Supervised Opioid Withdrawal And Extended-Release Injectable Naltrexone Induction Failure](#)** Shulman M, Choo TH, Scodes J, Pavlicova M, Wai J, Haenlein P, Tofighi B, Campbell ANC, Lee JD, Rotrosen J, Nunes EV. J Subst Abuse Treat. 2021; 124: 108292.

Background: Extended-release naltrexone (XR-NTX) is an effective maintenance treatment for opioid use disorder, but induction from active opioid use is a challenge as individuals must complete detoxification before induction. We aimed to determine whether use of methadone or buprenorphine, long-acting agonist opioids commonly used for detoxification, were associated with decreased likelihood of induction onto XR-NTX. Methods: We performed a secondary analysis of a large open-label randomized trial of buprenorphine versus XR-NTX for treatment of individuals with opioid use disorder recruited from eight short term residential (detoxification) units. This analysis only included individuals randomized to the XR-NTX arm of the trial (N = 283). The method of detoxification varied according to usual practices at each inpatient program. Logistic regression models estimating the log-odds of induction onto XR-NTX were fit, with detoxification regimen received as the predictor. Results: In the unadjusted logistic regression model, detoxification drug received (either methadone or buprenorphine) was significantly associated with decreased likelihood of induction onto XR-NTX compared to receiving non-opioid detoxification (Overall:  $P < 0.001$ ); buprenorphine vs non-opioid detoxification: OR (95% CI) = 0.32 (0.15-0.67); methadone vs non-opioid detoxification: OR (95% CI) = 0.23 (0.11-0.46). After controlling for site as a random effect, the association of detoxification drug with induction success lost statistical significance. Conclusions: Use of agonist medication during detoxification was associated with XR-NTX induction failure. Medication choice was determined by each site's clinical practice and therefore this association could not be separated from other site level variables. Clinical trial registration: [NCT02032433](https://clinicaltrials.gov/ct2/show/study/NCT02032433).

## **ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH**

**Reproducible Brain-Wide Association Studies Require Thousands Of Individuals** Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, Donohue MR, Foran W, Miller RL, Hendrickson TJ, Malone SM, Kandala S, Feczko E, Miranda-Dominguez O, Grahamk AM, Earl EA, Perrone AJ, Cordova M, Doyle O, Moore LA, Conan GM, Uriarte J, Snider K, Lynch BJ, Wilgenbusch JC, Pengo T, Tam A, Chen J, Newbold DJ, Zheng A, Seider NA, Van AN, Metoki A, Chauvin RJ, Laumann TO, Greene DJ, Petersen SE, Garavan H, Thompson WK, Nichols TE, Yeo BTT, Barch DM, Luna B, Fair DA Dosenbach NUF. *Nature*. 2022; 603(7902): 654-660.

Magnetic resonance imaging (MRI) has transformed our understanding of the human brain through well-replicated mapping of abilities to specific structures (for example, lesion studies) and functions (for example, task functional MRI (fMRI)). Mental health research and care have yet to realize similar advances from MRI. A primary challenge has been replicating associations between inter-individual differences in brain structure or function and complex cognitive or mental health phenotypes (brain-wide association studies (BWAS)). Such BWAS have typically relied on sample sizes appropriate for classical brain mapping (the median neuroimaging study sample size is about 25), but potentially too small for capturing reproducible brain-behavioural phenotype associations. Here we used three of the largest neuroimaging datasets currently available-with a total sample size of around 50,000 individuals-to quantify BWAS effect sizes and reproducibility as a function of sample size. BWAS associations were smaller than previously thought, resulting in statistically underpowered studies, inflated effect sizes and replication failures at typical sample sizes. As sample sizes grew into the thousands, replication rates began to improve and effect size inflation decreased. More robust BWAS effects were detected for functional MRI (versus structural), cognitive tests (versus mental health questionnaires) and multivariate methods (versus univariate). Smaller than expected brain-phenotype associations and variability across population subsamples can explain widespread BWAS replication failures. In contrast to non-BWAS approaches with larger effects (for example, lesions, interventions and within-person), BWAS reproducibility requires samples with thousands of individuals.

**Cross-Ethnicity/Race Generalization Failure Of Behavioral Prediction From Resting-State Functional Connectivity** Li J, Bzdok D, Chen J, Tam A, Ooi LQR, Holmes AJ, Ge T, Patil KR, Jabbi M, Eickhoff SB, Yeo TT, Genon S. *Sci Adv*. 2022; 8(11): eabj1812.

Algorithmic biases that favor majority populations pose a key challenge to the application of machine learning for precision medicine. Here, we assessed such bias in prediction models of behavioral phenotypes from brain functional magnetic resonance imaging. We examined the prediction bias using two independent datasets (preadolescent versus adult) of mixed ethnic/racial composition. When predictive models were trained on data dominated by white Americans (WA), out-of-sample prediction errors were generally higher for African Americans (AA) than for WA. This bias toward WA corresponds to more WA-like brain-behavior association patterns learned by the models. When models were trained on AA only, compared to training only on WA or an equal number of AA and WA participants, AA prediction accuracy improved but stayed below that for WA. Overall, the results point to the need for caution and further research regarding the application of current brain-behavior prediction models in minority populations.

## **INTRAMURAL RESEARCH**

### **Detailed Mapping Of Behavior Reveals The Formation Of Prelimbic Neural Ensembles**

**Across Operant Learning** Zhang Y, Denman AJ, Liang B, Werner CT, Beacher NJ, Chen R, Li Y, Shaham Y, Barbera G, Lin DT. *Neuron*. 2022; 110(4): 674-685.e6.

The prelimbic cortex (PrL) is involved in the organization of operant behaviors, but the relationship between longitudinal PrL neural activity and operant learning and performance is unknown. Here, we developed deep behavior mapping (DBM) to identify behavioral microstates in video recordings. We combined DBM with longitudinal calcium imaging to quantify behavioral tuning in PrL neurons as mice learned an operant task. We found that a subset of PrL neurons were strongly tuned to highly specific behavioral microstates, both task and non-task related. Overlapping neural ensembles were tiled across consecutive microstates in the response-reinforcer sequence, forming a continuous map. As mice learned the operant task, weakly tuned neurons were recruited into new ensembles, with a bias toward behaviors similar to their initial tuning. In summary, our data suggest that the PrL contains neural ensembles that jointly encode a map of behavioral states that is fine grained, is continuous, and grows during operant learning.

### **Involvement Of The Ghrelin System In The Maintenance Of Oxycodone Self-Administration: Converging Evidence From Endocrine, Pharmacologic And Transgenic Approaches**

You ZB, Gardner EL, Galaj E, Moore AR, Buck T, Jordan CJ, Humburg BA, Bi GH, Xi ZX, Leggio L. *Mol Psychiatry*. 2022 Jan 21. [Epub ahead of print].

Ghrelin, an orexigenic hormone, has emerged as a critical biological substrate implicated in drug reward. However, the response of the ghrelin system to opioid-motivated behaviors and the role of ghrelin in oxycodone self-administration remain to be studied. Here, we investigated the reciprocal interactions between the endogenous ghrelin system and oxycodone self-administration behaviors in rats and the role of the ghrelin system in brain stimulation reward (BSR) driven by optogenetic stimulation of midbrain reward circuits in mice. Oxycodone self-administration significantly elevated plasma ghrelin, des-acyl ghrelin and growth hormone and showed no effect on plasma LEAP2, a newly identified endogenous ghrelin receptor (GHS-R1a) antagonist. Oxycodone self-administration produced significant decreases in plasma gastric inhibitory polypeptide and insulin. Acquisition of oxycodone self-administration significantly upregulated GHS-R1a mRNA levels in dopamine neurons in the ventral tegmental area (VTA), a brain region critical in drug reward. Pretreatment with JMV2959, a selective GHS-R1a antagonist, dose-dependently reduced oxycodone self-administration and decreased the breakpoint for oxycodone under a progressive ratio reinforcement in Long-Evans rats. The inhibitory effects of JMV2959 on oxycodone self-administration is selectively mediated by GHS-R1a as JMV2959 showed a similar effect in Wistar wildtype but not in GHS-R knockout rats. JMV2959 pretreatment significantly inhibited BSR driven by selective stimulation of VTA dopamine neurons, but not by stimulation of striatal GABA neurons projecting to the VTA in mice. These findings suggest that elevation of ghrelin signaling by oxycodone or oxycodone-associated stimuli is a causal process by which oxycodone motivates oxycodone drug-taking and targeting the ghrelin system may be a viable treatment approach for opioid use disorders

**Elevation Of Extracellular Glutamate By Blockade Of Astrocyte Glutamate Transporters Inhibits Cocaine Reinforcement In Rats Via A NMDA-GluN2B Receptor Mechanism** Yang HJ, Hempel BJ, Bi GH, He Y, Zhang HY, Gardner EL, Xi ZX. *J Neurosci.* 2022; 42(11): 2327-2343.

It is well established that glutamate plays an important role in drug-induced and cue-induced reinstatement of drug seeking. However, the role of glutamate in drug reward is unclear. In this study, we systemically evaluated the effects of multiple glutamate transporter (GLT) inhibitors on extracellular glutamate and dopamine (DA) in the nucleus accumbens (NAc), intravenous cocaine self-administration, intracranial brain-stimulation reward (BSR), and reinstatement of cocaine seeking in male and female rats. Among the five GLT inhibitors we tested, TFB-TBOA was the most potent. Microinjections of TFB-TBOA into the NAc, but not the ventral tegmental area (VTA), or dorsal striatum (DS), dose-dependently inhibited cocaine self-administration under fixed-ratio and progressive-ratio (PR) reinforcement schedules, shifted the cocaine dose-response curve downward, and inhibited intracranial BSR. Selective downregulation of astrocytic GLT-1 expression in the NAc by GLT-1 antisense oligonucleotides also inhibited cocaine self-administration. The reduction in cocaine self-administration following TFB-TBOA administration was NMDA GluN2B receptor dependent, and rats self-administering cocaine showed upregulation of GluN2B expression in NAc DA- and cAMP-regulated phosphoprotein 32 (DARPP-32)-positive medium-spiny neurons (MSNs). In contrast, TFB-TBOA, when locally administered into the NAc, VTA, or ventral pallidum (VP), dose-dependently reinstated cocaine-seeking behavior. Intra-NAc TFB-TBOA-evoked drug-seeking was long-lasting and NMDA/AMPA receptor dependent. These findings, for the first time, indicate that glutamate in the NAc negatively regulates cocaine's rewarding effects, while an excess of glutamate in multiple brain regions can trigger reinstatement of drug-seeking behavior. Significance Statement: It is well known that glutamate plays an important role in relapse to drug seeking. However, the role of glutamate in drug reward is less clear. Here, we report that TFB-TBOA, a highly potent glutamate transporter (GLT) inhibitor, dose-dependently elevates extracellular glutamate and inhibits cocaine self-administration and brain-stimulation reward (BSR), when administered locally into the nucleus accumbens (NAc), but not other brain regions. Mechanistic assays indicate that cocaine self-administration upregulates NMDA-GluN2B receptor subtype expression in striatal dopaminergic neurons and activation of GluN2B by TFB-TBOA-enhanced glutamate inhibits cocaine self-administration. TFB-TBOA also reinstates cocaine-seeking behavior when administered into the NAc, ventral tegmental area (VTA), and ventral pallidum (VP). These findings demonstrate that glutamate differentially regulates cocaine reward versus relapse, reducing cocaine reward, while potentiating relapse to cocaine seeking.

**Medial Prefrontal Cortex And Anteromedial Thalamus Interaction Regulates Goal-Directed Behavior And Dopaminergic Neuron Activity** Yang C, Hu Y, Talishinsky AD, Potter CT, Calva CB, Ramsey LA, Kesner AJ, Don RF, Junn S, Tan A, Pierce AF, Nicolas C, Arima Y, Lee SC, Su C, Coudriet JM, Mejia-Aponte CA, Wang DV, Lu H, Yang Y, Ikemoto S. *Nat Commun.* 16; 13(1): 1386.

The prefrontal cortex is involved in goal-directed behavior. Here, we investigate circuits of the PFC regulating motivation, reinforcement, and its relationship to dopamine neuron activity. Stimulation of medial PFC (mPFC) neurons in mice activated many downstream regions, as shown by fMRI. Axonal terminal stimulation of mPFC neurons in downstream regions, including the anteromedial thalamic nucleus (AM), reinforced behavior and activated midbrain

dopaminergic neurons. The stimulation of AM neurons projecting to the mPFC also reinforced behavior and activated dopamine neurons, and mPFC and AM showed a positive-feedback loop organization. We also found using fMRI in human participants watching reinforcing video clips that there is reciprocal excitatory functional connectivity, as well as co-activation of the two regions. Our results suggest that this cortico-thalamic loop regulates motivation, reinforcement, and dopaminergic neuron activity.

**Corticosteroid Sensitization Drives Opioid Addiction** Carmack SA, Vendruscolo JCM, Adrienne McGinn M, Miranda-Barrientos J, Repunte-Canonigo V, Bosse GD, Mercatelli D, Giorgi FM, Fu Y, Hinrich AJ, Jodelka FM, Ling K, Messing RO, Peterson RT, Rigo F, Edwards S, Sanna PP, Morales M, Hastings ML, Koob GF, Vendruscolo LF. *Mol Psychiatry*. 2022 Mar 16. [Epub ahead of print].

The global crisis of opioid overdose fatalities has led to an urgent search to discover the neurobiological mechanisms of opioid use disorder (OUD). A driving force for OUD is the dysphoric and emotionally painful state (hyperkatifeia) that is produced during acute and protracted opioid withdrawal. Here, we explored a mechanistic role for extrahypothalamic stress systems in driving opioid addiction. We found that glucocorticoid receptor (GR) antagonism with mifepristone reduced opioid addiction-like behaviors in rats and zebrafish of both sexes and decreased the firing of corticotropin-releasing factor neurons in the rat amygdala (i.e., a marker of brain stress system activation). In support of the hypothesized role of glucocorticoid transcriptional regulation of extrahypothalamic GRs in addiction-like behavior, an intra-amygdala infusion of an antisense oligonucleotide that blocked GR transcriptional activity reduced addiction-like behaviors. Finally, we identified transcriptional adaptations of GR signaling in the amygdala of humans with OUD. Thus, GRs, their coregulators, and downstream systems may represent viable therapeutic targets to treat the "stress side" of OUD.

## **GRANTEE HONORS AND AWARDS**

**Benjamin F. Cravatt, Ph.D.**, Gilula Chair of Chemical Biology and Professor of Chemistry at Scripps Research has been selected as the winner of the 2022 Wolf Prize in Chemistry. This award is in recognition of Benjamin's contribution to the development of activity-based protein profiling as a powerful chemical proteomic strategy to characterize enzyme function in native biological systems. He used this approach to characterize numerous enzymes including the endocannabinoid hydrolases, which play critical roles in human biology and disease.

**Anders M. Dale, Ph.D.**, University of California, San Diego and Adjunct Professor at the University of Oslo, was awarded the Olav Thon Foundation's research prize within the natural sciences and medicine for his studies of brain functions, particularly age-related changes in the brain.

**Pebbles Fagan, Ph.D., M.P.H.**, University of Arkansas for Medical Sciences, received the 2022 Society for Research on Nicotine and Tobacco President's Award in recognition of her decades of scientific excellence and efforts to combat health inequities related to nicotine and tobacco use.

**Francesca Filbey, Ph.D.**, University of Texas, Dallas and **Cassandra Gipson-Reichardt, Ph.D.**, University of Kentucky, joined the College on Problems of Drug Dependence Board of Directors.

**Brandon Henderson, Ph.D.**, Marshall University, was awarded the 2022 American Society for Pharmacology and Experimental Therapeutics (ASPET) Division for Pharmacology Early Career Award in recognition of his highly innovative studies on the impact of flavorants on nicotine reward and fundamental scientific scholarship on nicotinic receptor pharmacology/drug discovery. Brandon was also recognized for his strong commitment to mentoring and public outreach.

**Erica Levitt, Ph.D.**, University of Florida, was awarded the 2022 ASPET Division for Pharmacology Early Career Award in recognition of her highly impactful research on the mechanisms of opioid-induced respiratory depression in the Kolliker-Fuse nucleus. Erica was also recognized for her outstanding record of opioid receptor scholarship and strong commitment to mentoring and service.

**Jens Meiler, Ph.D.**, Distinguished Research Professor of Chemistry at Vanderbilt University, was elected as a 2021 Fellow of the American Association for the Advancement of Science for his contributions to the development and widespread dissemination of methods for determining protein structure and *de novo* design and engineering of proteins.

**John Roll, Ph.D.**, Co-PI of the NIDA Clinical Trials Network Pacific Northwest Node and Professor and Vice Dean for Research for the Elson S. Floyd College of Medicine at Washington State University (WSU), has received the 2022 MED Associates Brady-Schuster Award. This lifetime achievement award is presented by the American Psychological Association's Division 28, Psychopharmacology and Substance Use. The MED Associates Brady-Schuster Award is one of the highest honors an individual can receive in the area of behavioral pharmacology. Named after Joe Brady and Bob Schuster, pioneers in the field, the award is bestowed to scientists with

an established record of outstanding research underscoring the fundamental importance of behavioral science to psychopharmacology or substance abuse. John was privileged to know each of them early in his career. John also recently was awarded the Sahlin Eminent Faculty Award at WSU, the highest honor any faculty can receive at the university, for a lifetime of achievement and scientific impact. John is a Fellow in three separate divisions of the American Psychological Association as well as a Fellow in the Association for Psychological Science, the Association for Behavior Analysis International, and the American Association for the Advancement of Science. John is also President-Elect of the Washington State Academy of Science.

## **STAFF HONORS AND AWARDS**

**Rita Valentino, Ph.D.**, received the Joseph Erlanger Distinguished Lectureship of the American Physiological Society Central Nervous System Section award at the 2022 Experimental Biology Meeting in Philadelphia, Pennsylvania.

**The Animal Program** of NIDA's Intramural Research Program (IRP) received a stellar letter from the accrediting organization American Association for Accreditation of Laboratory Animal Care following our most recent site visit in November 2021.

**Betty Jo Salmeron, M.D.**, Staff Clinician in the Neuroimaging Research Branch at the NIDA IRP, received an NIH Bench to Bedside Award for a project entitled "Hippocampal network changes following mindfulness training in tobacco vaping adolescents." Building on her laboratory's findings that connectivity in hippocampal networks central to emotion regulation is disrupted in rats after adolescent exposure to nicotine and literature pointing to alterations in overlapping networks after mindfulness training, this collaborative project with researchers at Johns Hopkins University will examine network connectivity in adolescent vapers before and after a mindfulness-based stress reduction intervention using resting state fMRI.

**Brandon Harvey, Ph.D.**, Senior Investigator and Chief of the Molecular Mechanisms of Cellular Stress and Inflammation Section in the Integrative Neuroscience Research Branch of the NIDA IRP, received an NIH Bench to Bedside Award for a project entitled "Targeting endoplasmic reticulum proteostasis to monitor and treat ischemic stroke." This project is aimed at exploring exodosi, a cellular phenomenon related to proteostasis, that Brandon's research team recently discovered as a pathophysiological mechanism of stroke. Brandon and his team will collaborate with SUNY Stony Brook researchers to study exodosi in stroke in both preclinical and clinical settings.

**The following were recently awarded K99/R00 Grants in the IRP program:**

**Kaue Costa, Ph.D.**, in Dr. Geoff Schoenbaum's Behavioral Neurophysiology Neuroscience Laboratory, Cellular Neurobiology Research Branch.

**Kirsten Smith, Ph.D.**, in Dr. David Epstein's Real-World Assessment, Prediction and Treatment Unit, Translational Addiction Medicine Branch.

**David Reiner, Ph.D.**, in Dr. Yavin Shaham's Neurobiology Relapse Section, Behavioral Neuroscience Research Branch.



## STAFF CHANGES

### New Staff

**Thorsten Kahnt, Ph.D.**, joined NIDA's IRP as Chief of Learning and Decision-Making Unit, Cellular Neurobiology Research Branch on March 27, 2022.

**Marsha Nelson-Duncan** joined the Division of Extramural Research's Office of Extramural Policy as the Training Coordinator in March 2022. Marsha comes to NIDA from a position at NCI.

**Nicole Slade-Acty** joined NIDA's Division of Extramural Research's Extramural Activities and Initiative Development Branch as a Program Specialist on March 13, 2022. Nicole comes to NIDA from a position with NCI.

**Marisa Srivareerat, Ph.D.**, is a trained scientist with over ten years of academic and industry experience. She brings in significant expertise in organizing, planning, and conducting biomedical research. Marisa obtained her Ph.D. in Pharmacology from University of Houston in 2008. She was a Clinical Manager for NuVasive Clinical Services, where she led a group conducting neurological monitoring during neurosurgical procedures in hospital settings. Marisa joined NIDA's Division of Extramural Research in February 2022.

**Brian Wolff, Ph.D.**, is a trained neuroscientist with over ten years of neuroscience research experience. Brian obtained his Ph.D. in Neuroscience from Georgetown University in 2013. Subsequently, he joined the Symptoms Biology Unit of the Intramural research program at National Institute of Nursing Research (NINR) as a postdoctoral fellow and was later promoted to a Research Fellow position. At NINR, he directed the animal model research program focused on fatigue in the context of health-related behavioral research. Brian has served as a peer reviewer for various journals and as a Graduate Course Director for the Interdisciplinary Program in Neuroscience at Georgetown University. Brian joined NIDA as a Scientific Review Officer in the Division of Extramural Research in January 2022.

**Josh Robbins** joined the Communications Branch in the Office of Science Policy and Communications (OSPC) as the new social media strategist on April 26, 2022. Prior to joining NIDA, Josh served as a prominent HIV reporter, blogger, advocate, consultant, and social media influencer with a background in marketing. His bylines as a guest contributor include Healthline, POZ, *Plus Magazine*, O&AN, and numerous regional LGBT publications.

### Staff Departures

**Matt Houle**, an Ethics Specialist in NIDA's Office of Management, left NIDA on March 26, 2022, for a position with the Bureau of Prisons.

**Ernestine Lenteu**, a Staff Assistant in NIDA's Office of the Director, left NIDA on March 26, 2022, for a position in the NIH Office of the Director.

**Janet Linton**, an IT Specialist with OSPC's Digital Communications Branch, left NIDA on April 9, 2022, for a position with the FDA.

**Liza Zeinhert**, a Clinical Trials Specialist in NIDA's Center for Clinical Trials Network left NIDA on February 2, 2022, for a position with NIA.

## **Retirements**

**David McCann, Ph.D.**, Associate Director, Division of Therapeutics and Medical Consequences (DTMC), retired on February 28, 2022, after more than 33 years of federal service at NIDA. Dave began his career at NIDA in 1988 as a Staff Fellow and then a Senior Staff Fellow at the NIDA Intramural Research Program. In 1992, he joined the extramural Medications Development Division (now DTMC), where he served as Chief of the Medications Discovery and Toxicology Branch for almost a decade, then served as Acting Division Director in 2009, and as Associate Division Director from 2010–2022. During his tenure in medications development, Dave made major contributions through his outreach to the pharmaceutical industry, where he was able generate interest in the development of medications for substance use disorders, resulting in many preclinical and clinical collaborative projects with both large and small pharma. In the preclinical program, he played a key role in the development of non-clinical safety protocols for compounds advancing to clinical trials and in ensuring the use of appropriate experimental controls in all preclinical models utilized in the Addiction Treatment Discovery Program. On the clinical side, he advanced our understanding of the effects of non-adherent subjects on clinical trial outcomes, resulting in the use of subject participant registries as well as the monitoring of adherence to medication regimens in clinical trials. Dave was also involved in the redesign of efficacy studies with the goal of managing placebo responders to insure the adequate testing of experimental hypotheses. We will miss the benefits of his multilevel experience and his broad reach in the scientific programs of the Division.

**Elliot Stein, Ph.D.**, retired as Chief of NIDA IRP Neuroimaging Research Branch on February 28, 2022. Elliot has dedicated more than 40 years to research on the neurobiology of addiction, employing both preclinical and human models. As functional magnetic resonance imaging (fMRI) was being developed at the Medical College of Wisconsin (MCW) in the early 1990s, he shifted his focus from rat studies to human work. His MCW laboratory pioneered the application of fMRI to study addiction in humans. During the past two decades, he has led a multidisciplinary team of scientists who have employed multimodal magnetic resonance imaging technologies to define the neuronal systems mediating the actions of drugs, such as nicotine and cocaine. These studies have led to discoveries of brain sites and mechanisms responsible for mediating substance craving and learning and reinforcement. Elliot's studies also examined how drugs interact with specific central executive processes—including working memory, attention, and decision-making—as a function of dependence to alter behavior. Preclinical neuroimaging models have been used to link more mechanistic animal work with human studies. Elliot was elected as a Fellow of American College of Neuropsychopharmacology in 2011. He received the NIH Director's Award in 2021. Although Elliot officially retired in February, he remains as a special volunteer and will undoubtedly continue to contribute to the work in his Branch for some time to come.



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