

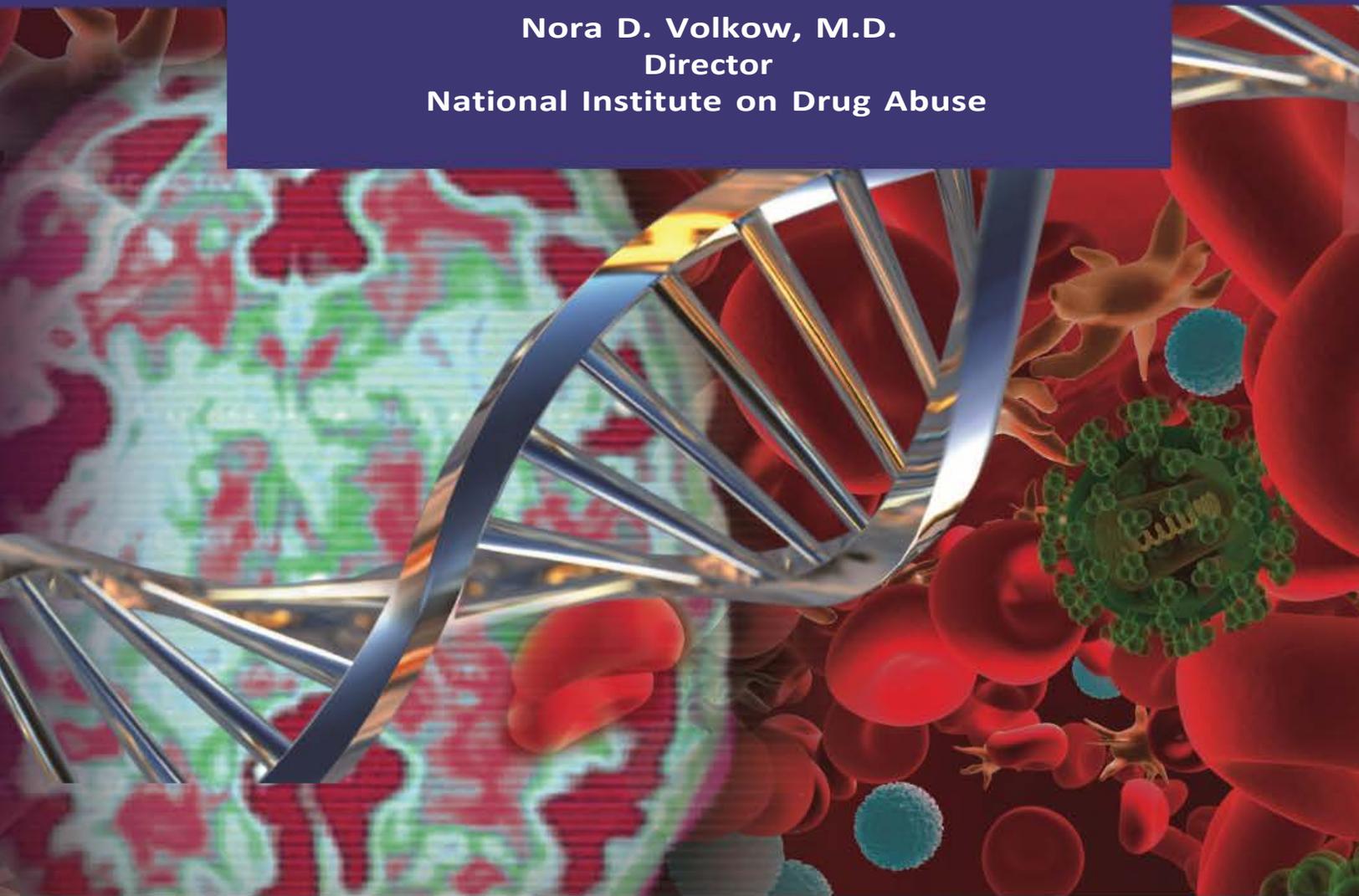


# DIRECTOR'S REPORT

\_\_\_\_\_ *to the* \_\_\_\_\_  
National Advisory Council on Drug Abuse

\_\_\_\_\_ *September 12, 2023* \_\_\_\_\_

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## **RESEARCH HIGHLIGHTS**

### **BASIC AND BEHAVIORAL RESEARCH**

**[A Human Stem Cell-Derived Neuronal Model Of Morphine Exposure Reflects Brain Dysregulation In Opioid Use Disorder: Transcriptomic And Epigenetic Characterization Of Postmortem-Derived iPSC Neurons](#)** Mendez EF, Grimm SL, Stertz L, Gorski D, Movva SV, Najera K, Moriel K, Meyer TD, Fries GR, Coarfa C, Walss-Bass C. *Front Psychiatry*. February 16, 2023; 14: 1070556. eCollection.

Human-derived induced pluripotent stem cell (iPSC) models of brain promise to advance our understanding of neurotoxic consequences of drug use. However, how well these models recapitulate the actual genomic landscape and cell function, as well as the drug-induced alterations, remains to be established. New *in vitro* models of drug exposure are needed to advance our understanding of how to protect or reverse molecular changes related to substance use disorders. We engineered a novel induced pluripotent stem cell-derived model of neural progenitor cells and neurons from cultured postmortem human skin fibroblasts, and directly compared these to isogenic brain tissue from the donor source. We assessed the maturity of the cell models across differentiation from stem cells to neurons using RNA cell type and maturity deconvolution analyses as well as DNA methylation epigenetic clocks trained on adult and fetal human tissue. As proof-of-concept of this model's utility for substance use disorder studies, we compared morphine- and cocaine-treated neurons to gene expression signatures in postmortem Opioid Use Disorder (OUD) and Cocaine Use Disorder (CUD) brains, respectively. Within each human subject (N = 2, 2 clones each), brain frontal cortex epigenetic age parallels that of skin fibroblasts and closely approximates the donor's chronological age; stem cell induction from fibroblast cells effectively sets the epigenetic clock to an embryonic age; and differentiation of stem cells to neural progenitor cells and then to neurons progressively matures the cells *via* DNA methylation and RNA gene expression readouts. In neurons derived from an individual who died of opioid overdose, morphine treatment induced alterations in gene expression similar to those previously observed in OUD *ex-vivo* brain tissue, including differential expression of the immediate early gene *EGR1*, which is known to be dysregulated by opioid use. In summary, we introduce an iPSC model generated from human postmortem fibroblasts that can be directly compared to corresponding isogenic brain tissue and can be used to model perturbation exposure such as that seen in opioid use disorder. Future studies with this and other postmortem-derived brain cellular models, including cerebral organoids, can be an invaluable tool for understanding mechanisms of drug-induced brain alterations.

**[Structure-Activity Relationship Study Of Cannabidiol-Based Analogs As Negative Allosteric Modulators Of The  \$\mu\$ -Opioid Receptor](#)** Bosquez-Berger T, Gudorf JA, Kuntz CP, Desmond JA, Schleich JP, VanNieuwenhze MS, Straiker A. *J Med Chem*. 2023; 66(14): 9466-9494.

The US faces an unprecedented surge in fatal drug overdoses. Naloxone, the only antidote for opiate overdose, competes at the mu opioid receptor ( $\mu$ OR) orthosteric site. Naloxone struggles against fentanyl-class synthetic opioids that now cause ~80% of deaths. Negative allosteric modulators (NAMs) targeting secondary sites may noncompetitively downregulate  $\mu$ OR activation. (-)-Cannabidiol ((-)-CBD) is a candidate  $\mu$ OR NAM. To explore its therapeutic potential, we evaluated the structure-activity relationships among CBD analogs to identify NAMs with increased potency. Using a cyclic AMP assay, we characterize reversal of  $\mu$ OR activation by 15 CBD analogs, several of which proved more potent than (-)-CBD. Comparative docking investigations suggest that potent compounds interact with a putative allosteric pocket to stabilize the inactive  $\mu$ OR conformation.

Finally, these compounds enhance naloxone displacement of fentanyl from the orthosteric site. Our results suggest that CBD analogs offer considerable potential for the development of next-generation antidotes for opioid overdose.

[Circuit Coordination Of Opposing Neuropeptide And Neurotransmitter Signals](#) Soden ME, Yee JX, Zweifel LS. *Nature*. 2023; 619(7969): 332-337.

Fast-acting neurotransmitters and slow, modulatory neuropeptides are co-released from neurons in the central nervous system, albeit from distinct synaptic vesicles. The mechanisms of how co-released neurotransmitters and neuropeptides that have opposing actions—for example, stimulatory versus inhibitory—work together to exert control of neural circuit output remain unclear. This has been difficult to resolve owing to the inability to selectively isolate these signaling pathways in a cell- and circuit-specific manner. Here we developed a genetic-based anatomical disconnect procedure that utilizes distinct DNA recombinases to independently facilitate CRISPR-Cas9 mutagenesis of neurotransmitter- and neuropeptide-related genes in distinct cell types in two different brain regions simultaneously. We demonstrate that neurons within the lateral hypothalamus that produce the stimulatory neuropeptide neurotensin and the inhibitory neurotransmitter GABA ( $\gamma$ -aminobutyric acid) utilize these signals to coordinately activate dopamine-producing neurons of the ventral tegmental area. We show that GABA release from lateral hypothalamus neurotensin neurons inhibits GABA neurons within the ventral tegmental area, disinhibiting dopamine neurons and causing a rapid rise in calcium, whereas neurotensin directly generates a slow inactivating calcium signal in dopamine neurons that is dependent on the expression of neurotensin receptor 1 (Ntsr1). We further show that these two signals work together to regulate dopamine neuron responses to maximize behavioural responding. Thus, a neurotransmitter and a neuropeptide with opposing signals can act on distinct timescales through different cell types to enhance circuit output and optimize behaviour.

[A Multivariate Regressor Of Patterned Dopamine Release Predicts Relapse To Cocaine](#)

Luján MÁ, Oliver BL, Young-Morrison R, Engi SA, Zhang LY, Wenzel JM, Li Y, Zlebnik NE, Cheer JF. *Cell Rep*. 2023; 42(6): 112553.

Understanding mesolimbic dopamine adaptations underlying vulnerability to drug relapse is essential to inform prognostic tools for effective treatment strategies. However, technical limitations have hindered the direct measurement of sub-second dopamine release in vivo for prolonged periods of time, making it difficult to gauge the weight that these dopamine abnormalities have in determining future relapse incidence. Here, we use the fluorescent sensor GrabDA to record, with millisecond resolution, every single cocaine-evoked dopamine transient in the nucleus accumbens (NAc) of freely moving mice during self-administration. We reveal low-dimensional features of patterned dopamine release that are strong predictors of cue-induced reinstatement of cocaine seeking. Additionally, we report sex-specific differences in cocaine-related dopamine responses related to a greater resistance to extinction in males compared with females. These findings provide important insights into the sufficiency of NAc dopamine signaling dynamics—in interaction with sex—for recapitulating persistent cocaine seeking and future relapse vulnerability.

[A Shared Neural Basis Underlying Psychiatric Comorbidity](#) Xie C, Xiang S, Shen C, et al.; IMAGEN Consortium; STRATIFY Consortium; ZIB Consortium. *Nat Med*. 2023; 29(5): 1232-1242.

Recent studies proposed a general psychopathology factor underlying common comorbidities among psychiatric disorders. However, its neurobiological mechanisms and generalizability remain

elusive. In this study, we used a large longitudinal neuroimaging cohort from adolescence to young adulthood (IMAGEN) to define a neuropsychopathological (NP) factor across externalizing and internalizing symptoms using multitask connectomes. We demonstrate that this NP factor might represent a unified, genetically determined, delayed development of the prefrontal cortex that further leads to poor executive function. We also show this NP factor to be reproducible in multiple developmental periods, from preadolescence to early adulthood, and generalizable to the resting-state connectome and clinical samples (the ADHD-200 Sample and the Stratify Project). In conclusion, we identify a reproducible and general neural basis underlying symptoms of multiple mental health disorders, bridging multidimensional evidence from behavioral, neuroimaging and genetic substrates. These findings may help to develop new therapeutic interventions for psychiatric comorbidities.

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

### **Adolescent Advertising Exposure To Cannabis Products In Rural Oklahoma Via Medical Dispensaries**

Livingston M, Barry C, Walker A, Livingston B, Talavera-Brown SL, Harmon M, Wagenaar A, Kominsky T, Komro KA. *J Stud Alcohol Drugs*. May 18, 2023. Online ahead of print. We assess cannabis advertising exposure among adolescents in rural Oklahoma from medical dispensaries. **Methods:** Our mixed-methods study identified medical dispensaries within a 15-minute drive-time of rural Oklahoma high schools. Study staff completed observational data collection forms and took photographs of each dispensary. Quantitative data from the forms and qualitative coding of photographs were used to describe dispensary characteristics and likely advertising exposure for adolescents. **Results:** Ninety-two dispensaries were identified across 20 rural communities. The majority presented as retail spaces (n=71). Product (n=22) and price promotions (n=27) were common. Coding of dispensary photographs found that product promotions advertised cannabis use modalities, with cannabis flower being the most common (n=15) followed by edibles (n=9) and concentrates (n=9). Among dispensaries with price promotions, discounts (n=19) and prices under \$10 (n=14) were common. **Conclusions:** Sampled rural medical dispensaries present as retail spaces and are a likely source of adolescent cannabis advertising exposure. **Public health implications:** Cannabis advertising via dispensaries likely modifies the adolescent perceived risk environment, even in states where recreational use is illegal.

### **Long-Term Prospects For Telemedicine In Opioid Use Disorder (OUD) Treatment: Results From A Longitudinal Survey Of OUD Clinicians**

Huskamp HA, Riedel L, Campa I, Busch AB, Rose S, Mehrotra A, Uscher-Pines L. *J Gen Intern Med*. 2023; 38(9): 2139-2146. During the pandemic, there was a dramatic shift to telemedicine for opioid use disorder (OUD) treatment. Little is known about how clinician attitudes about telemedicine use for OUD treatment are evolving or their preferences for future use. To understand OUD clinician views of and preferences regarding telemedicine. Longitudinal survey (wave 1, December 2020; wave 2, March 2022). National sample of 425 clinicians who treat OUD. Self-reported proportion of OUD visits delivered via telemedicine (actual vs. preferred), comfort in using video visits for OUD, impact of telemedicine on work-related well-being. The mean reported percentage of OUD visits delivered via telemedicine (vs. in person) dropped from 56.9% in December 2020 to 41.5% in March 2022; the mean preferred post-pandemic percentage of OUD visits delivered via telemedicine was 34.8%. Responses about comfort in using video visits for different types of OUD patients remained similar over time despite clinicians having substantially more experience with telemedicine by spring 2022 (e.g., 35.8% vs. 36.0% report being comfortable using video visits for new patients). Almost three-quarters (70.9%) reported that most of their patients preferred to have the majority of their visits via

telemedicine, and 76.7% agreed that the option to do video visits helped their patients remain in treatment longer. The majority (58.7%) reported that telemedicine had a positive impact on their work-related well-being, with higher rates of a positive impact among those who completed training more recently (68.5% of those with < 10 years, 62.1% with 10-19 years, and 45.8% with 20 + years,  $p < 0.001$ ). While many surveyed OUD clinicians were not comfortable using telemedicine for all types of patients, most wanted telemedicine to account for a substantial fraction of OUD visits, and most believed telemedicine has had positive impacts for themselves and their patients.

**[Buprenorphine Utilization And Prescribing Among New Jersey Medicaid Beneficiaries After Adoption Of Initiatives Designed To Improve Treatment Access](#)** Treitler P, Nowels M, Samples H, Crystal S. JAMA Netw Open. 2023; 6(5): e2312030.

Buprenorphine is underutilized as a treatment for opioid use disorder (OUD); state policies may improve buprenorphine access and utilization. To assess buprenorphine prescribing trends following New Jersey Medicaid initiatives designed to improve access. This cross-sectional interrupted time series analysis included New Jersey Medicaid beneficiaries who were prescribed buprenorphine and had 12 months continuous Medicaid enrollment, OUD diagnosis, and no Medicare dual eligibility, as well as physician or advanced practitioners who prescribed buprenorphine to Medicaid beneficiaries. The study used Medicaid claims data from 2017 to 2021. Implementation of New Jersey Medicaid initiatives in 2019 that removed prior authorizations, increased reimbursement for office-based OUD treatment, and established regional Centers of Excellence. Rate of buprenorphine receipt per 1000 beneficiaries with OUD; percentage of new buprenorphine episodes lasting at least 180 days; buprenorphine prescribing rate per 1000 Medicaid prescribers, overall and by specialty. Of 101,423 Medicaid beneficiaries (mean [SD] age, 41.0 [11.6] years; 54,726 [54.0%] male; 30,071 [29.6%] Black, 10,143 [10.0%] Hispanic, and 51,238 [50.5%] White), 20,090 filled at least 1 prescription for buprenorphine from 1,788 prescribers. Policy implementation was associated with an inflection point in buprenorphine prescribing trend; after implementation, the trend increased by 36%, from 1.29 (95% CI, 1.02-1.56) prescriptions per 1000 beneficiaries with OUD to 1.76 (95% CI, 1.46-2.06) prescriptions per 1000 beneficiaries with OUD. Among beneficiaries with new buprenorphine episodes, the percentage retained for at least 180 days was stable before and after initiatives were implemented. The initiatives were associated with an increase in the growth rate of buprenorphine prescribers (0.43 per 1000 prescribers; 95% CI, 0.34 to 0.51 per 1000 prescribers). Trends were similar across specialties, but increases were most pronounced among primary care and emergency medicine physicians (e.g, primary care: 0.42 per 1000 prescribers; 95% CI, 0.32-0.53 per 1000 prescribers). Advanced practitioners accounted for a growing percentage of buprenorphine prescribers, with a monthly increase of 0.42 per 1000 prescribers (95% CI, 0.32-0.52 per 1000 prescribers). A secondary analysis to test for changes associated with non-state-specific secular trends in prescribing found that quarterly trends in buprenorphine prescriptions increased in New Jersey relative to all other states following initiative implementation. In this cross-sectional study of state-level New Jersey Medicaid initiatives designed to expand buprenorphine access, implementation was associated with an upward trend in buprenorphine prescribing and receipt. No change was observed in the percentage of new buprenorphine treatment episodes lasting 180 or more days, indicating that retention remains a challenge. Findings support implementation of similar initiatives but highlight the need for efforts to support long-term retention.

**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.* 2023; 29(3): 289-301. 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.

**TREATMENT RESEARCH**

**Pharmacokinetic Properties Of An FDA-Approved Intranasal Nalmefene Formulation For The Treatment Of Opioid Overdose**

Crystal R, Ellison M, Purdon C, Skolnick P. *Clin Pharmacol Drug Dev.* July 27, 2023; 10.1002/cpdd.1312. Published online ahead of print.

Nalmefene is a high-affinity, long-duration opioid antagonist that was approved in 1995 as an injection for the treatment of opiate overdose, but subsequently withdrawn (2008) for reasons other than safety or effectiveness. The dramatic rise in opioid overdose deaths over the past 7-8 years catalyzed the development of an intranasal (IN) formulation of nalmefene for the emergency treatment of opioid overdose. The studies described here compare the pharmacokinetic properties and safety profiles of an IN formulation containing nalmefene (2.7 mg in 0.1 mL) to an approved 1 mg intramuscular (IM) dose. IN nalmefene produced maximum plasma concentrations that were significantly higher than observed following the IM dose (12.2 and 1.77 ng/mL, respectively). The time to reach maximum plasma concentrations was also faster following IN administration (0.25 and 0.33 hours, respectively) with significant differences in plasma concentrations manifested as early as 2.5 minutes after administration (NCT04759768). The plasma half-life of nalmefene was similar following IM and IN administration (10.6-11.4 hours). Furthermore, dose-normalized nalmefene exposure was similar for both 1 spray in each nostril and 2 sprays in the same nostril compared to a single spray in each nostril (NCT05219669). There were no sex differences in the pharmacokinetic properties of either IN or IM nalmefene. In an era when almost 90% of opioid overdose deaths have been linked to high-potency synthetic opioids, the ability to rapidly deliver high concentrations of nalmefene could represent an important tool for reducing both morbidity and mortality.

**Percentage Of Negative Urine Drug Screens As A Clinically Meaningful Endpoint For RCTs Evaluating Treatment For Cocaine Use**

Loya JM, Babuscio TA, Nich C, Alessi SM, Rash C, Kiluk BD. *Drug Alcohol Depend.* 2023; 248: 109947.

**BACKGROUND:** This study examined a threshold based on the percentage of cocaine-negative (CN) urine drug screens (UDS) collected during treatment as a potential meaningful endpoint for clinical trials. We hypothesized that individuals providing at least 75% CN UDS would have better long-term outcomes than those providing less than 75% CN UDS. **METHODS:** Two separate pooled datasets of randomized clinical trials conducted at different institutions were used for analyses: one composed of eight trials (N = 760) and the other composed of three trials (N = 416), all evaluating behavioral and/or pharmacological treatments for cocaine use. UDS were collected at least once per week (up to three times per week) during the 8- or 12-week treatment period across all trials, with substance use and psychosocial functioning measured up to 12 months following treatment. Chi-squares and ANOVAs compared within-treatment and follow-up outcomes between the groups. **RESULTS:** Compared to those who did not achieve the threshold, participants who achieved the 75%-CN threshold were retained in treatment longer and had a longer period of continuous abstinence, and were more likely to report problem-free functioning. Additionally, participants who achieved the 75%-CN threshold were more likely to report sustained abstinence and better psychosocial functioning throughout a follow-up period up to 12 months than those who did not achieve the threshold. **CONCLUSIONS:** A threshold of 75%-CN UDS is associated with short- and long-term clinical benefits. Future clinical trials may consider this a meaningful threshold for defining treatment responders.

**Kinetic Characterization Of An Efficient Cocaine Hydrolase Against Toxic Metabolites Of Cocaine**

Zhan M, Hou S, Shang L, Chen X, Zhan CG, Zheng F. *Org Biomol Chem.* 2023; 21(17): 3650-3659.

In the presence of alcohol, cocaine metabolism produces a number of metabolites, including three toxic ones (cocaethylene, norcocaine, and norcocaethylene) which are all more toxic than cocaine itself, with the toxicity in the order of cocaine < cocaethylene < norcocaine < norcocaethylene. In this study, we performed kinetic analysis on our previously reported cocaine hydrolase (E30-6) for its catalytic activities accelerating the hydrolysis of the three toxic metabolites in comparison with cocaine. Based on the obtained kinetic data, the in vitro catalytic efficiencies of the enzyme against these substrates are in the order of cocaine > cocaethylene > norcocaine > norcocaethylene. It has been demonstrated that E30-6 can efficiently accelerate the hydrolysis of not only cocaine itself, but also all three toxic metabolites in vitro and in vivo. E30-6 is the most efficient enzyme for each of these toxic substrates (cocaine, cocaethylene, norcocaine, and norcocaethylene) among all the reported enzymes as far as we know at this point. These findings suggest that E30-6 is capable of efficiently treating cocaine toxicity even when alcohol and cocaine are used concurrently.

**Choice Between Food And Cocaine Or Fentanyl Reinforcers Under Fixed And Variable Schedules In Female And Male Rhesus Monkeys**

Doyle WS, Freeman KB, Woods J, Huskinson SL. *Psychopharmacology (Berl).* 2023; 240(7): 1573-1585.

**RATIONALE:** Illicit drugs may be unpredictable in terms of the time and effort required to obtain them, and this can be modeled with variable- (VR) vs. fixed-ratio (FR) schedules. In a recent experiment (Zamarripa et al. 2023), the potency of cocaine to maintain choice was greatest under a VR (compared with a FR) when food was available under a FR schedule. **OBJECTIVES:** The goal of the current study was to extend prior choice results with VR vs. FR schedules to a more efficient procedure with cocaine or fentanyl vs. food. Furthermore, the FR schedule of food delivery was manipulated to determine whether increased drug choice under a VR (compared with a FR)

schedule depends on the size of the schedule of nondrug reinforcement. METHODS: Adult female (n = 2) and male (n = 4) monkeys chose between cocaine (0-30 µg/kg/injection) or fentanyl (0-1.0 µg/kg/injection) and food (2 pellets/delivery) under a 5-component procedure. In different conditions, food was available under a FR 25, 50, or 100 and cocaine or fentanyl were available under FR or VR 100 schedules. RESULTS: Cocaine's potency to maintain choice was greatest under a VR 100 (compared with FR 100) when food was available under a FR 50 or 100, and fentanyl's potency to maintain choice was generally greatest under a VR 100 (compared with FR 100) when food was available under a FR 25 or 100. However, outcomes between FR and VR schedules with fentanyl were less robust compared with cocaine. CONCLUSION: Variability in the time and effort required to obtain illicit drugs could contribute to excessive allocation of behavior toward drug use at the expense of more predictable nondrug alternatives, supporting treatment or policies aimed at making drug access more predictable through agonist medications or a safe supply. The impact of variable requirements on drug choice may be reduced if nondrug reinforcers are relatively less costly, supporting the use of low-cost reinforcers in behavioral therapies like contingency management.

**Development And Clinical Feasibility Study Of A Brief Version Of An Addiction-focused Phenotyping Battery In Females Receiving Buprenorphine For Opioid Use Disorder** Parlier-Ahmad AB, Eglovitch M, Legge C, Keyser-Marcus LA, Bjork JM, Adams A, Ramey T, Moeller FG, Martin CE. Brain Behav. 2023; 13(8): e3128.

INTRODUCTION: We aimed to streamline the NIDA Phenotyping Assessment Battery (PhAB), a package of self-report scales and neurobehavioral tasks used in substance use disorder (SUD) clinical trials, for clinical administration ease. Tailoring the PhAB to shorten administration time for a treatment setting is critical to expanding its acceptability in SUD clinical trials. This study's primary objectives were to develop a brief version of PhAB (PhAB-B) and assess its operational feasibility and acceptability in a female clinical treatment sample. METHODS: Assessments of the original PhAB were evaluated along several criteria to identify a subset for the PhAB-B. Non-pregnant females (N=55) between ages 18-65, stabilized on buprenorphine for opioid use disorder (OUD) at an outpatient addiction clinic, completed this abbreviated battery remotely or after a provider visit in clinic. Participant satisfaction questions were administered. REDCap recorded the time to complete PhAB-B measures. RESULTS: The PhAB-B included 11 measures that probed reward, cognition, negative emotionality, interoception, metacognition, and sleep. Participants who completed the PhAB-B (N =55) were  $36.1 \pm 8.9$  years of age, White (54.5%), Black (34.5%), and non-Latinx (96.0%). Most participants completed the PhAB-B remotely (n = 42, 76.4%). Some participants completed it in-person (n = 13, 23.6%). PhAB-B mean completion time was  $23.0 \pm 12.0$  min. Participant experiences were positive, and 96% of whom reported that they would participate in the study again. CONCLUSION: Our findings support the clinical feasibility and acceptability of the PhAB-B among a female opioid use disorder outpatient addiction treatment sample. Future studies should assess the PhAB-B psychometric properties among broader treatment samples.

## **HIV RESEARCH**

### **MRP8/14 Is A Molecular Signature Triggered By Dopamine In HIV Latent Myeloid Targets That Increases HIV Transcription And Distinguishes HIV+ Methamphetamine Users With Detectable CSF Viral Load And Brain Pathology**

Basova LV, Lindsey A, McGovern A, Rosander A, Delorme-Walker V, ElShamy WM, Pendyala VV, Gaskill PJ, Ellis RJ, Cherner M, Iudicello JE, Marcondes MCG. *Viruses*. 2023; 15(6): 1363.

There is a significant overlap between HIV infection and substance-use disorders. Dopamine (DA) is the most abundantly upregulated neurotransmitter in methamphetamine abuse, with receptors (DRD1-5) that are expressed by neurons as well as by a large diversity of cell types, including innate immune cells that are the targets of HIV infection, making them responsive to the hyperdopaminergic environment that is characteristic of stimulant drugs. Therefore, the presence of high levels of dopamine may affect the pathogenesis of HIV, particularly in the brain. The stimulation of HIV latently infected U1 promonocytes with DA significantly increased viral p24 levels in the supernatant at 24 h, suggesting effects on activation and replication. Using selective agonists to different DRDs, we found that DRD1 played a major role in activating viral transcription, followed by DRD4, which increased p24 with a slower kinetic rate compared to DRD1. Transcriptome and systems biology analyses led to the identification of a cluster of genes responsive to DA, where S100A8 and S100A9 were most significantly correlated with the early increase in p24 levels following DA stimulation. Conversely, DA increased the expression of these genes' transcripts at the protein level, MRP8 and MRP14, respectively, which form a complex also known as calprotectin. Interestingly, MRP8/14 was able to stimulate HIV transcription in latent U1 cells, and this occurred via binding of the complex to the receptor for an advanced glycosylation end-product (RAGE). Using selective agonists, both DRD1 and DRD4 increased MRP8/14 on the surface, in the cytoplasm, as well as secreted in the supernatants. On the other hand, while DRD1/5 did not affect the expression of RAGE, DRD4 stimulation caused its downregulation, offering a mechanism for the delayed effect via DRD4 on the p24 increase. To cross-validate MRP8/14 as a DA signature with a biomarker value, we tested its expression in HIV+ Meth users' postmortem brain specimens and peripheral cells. MRP8/14+ cells were more frequently identified in mesolimbic areas such as the basal ganglia of HIV+ Meth+ cases compared to HIV+ non-Meth users or to controls. Likewise, MRP8/14+ CD11b+ monocytes were more frequent in HIV+ Meth users, particularly in specimens from participants with a detectable viral load in the CSF. Overall, our results suggest that the MRP8 and MRP14 complex may serve as a signature to distinguish subjects using addictive substances in the context of HIV, and that this may play a role in aggravating HIV pathology by promoting viral replication in people with HIV who use Meth.

### **HIV Gp120 Impairs Nucleus Accumbens Neuroimmune Function and Dopamine D3 Receptor-Mediated Inhibition Of Cocaine Seeking In Male Rats**

Namba MD, Phillips MN, Chen PJ, Blass BE, Olive MF, Neisewander JL. *Addict Neurosci*. 2023; 5: 100062.

Cocaine Use Disorders (CUDs) are associated with an increased risk of human immunodeficiency virus (HIV) infection. Cocaine and the HIV envelope protein gp120 each induce distinct deficits to mesocorticolimbic circuit function and motivated behavior; however, little is known regarding how they interact to dysregulate these functions or how such interactions impact pharmacotherapeutic efficacy. We have previously shown that the selective, weak partial agonist of the dopamine D3 receptor (D3R), MC-25-41, attenuates cocaine-seeking behavior in male rats. Here, we sought to characterize changes in striatal neuroimmune function in gp120- exposed rats across abstinence from operant access to cocaine (0.75 mg/kg, i.v.) or sucrose (45 mg/pellet), and to examine the

impact of gp120 exposure on MC-25-41-reduced cocaine seeking. After establishing a history of cocaine or sucrose self-administration, rats received intracerebroventricular gp120 infusions daily the first 5 days of abstinence and were sacrificed either on day 6 or after 21 days of forced abstinence and a cue-induced cocaine seeking test. We demonstrated that MC-25-41 treatment attenuated cue-induced cocaine seeking among control rats but not gp120-exposed rats. Moreover, postmortem analysis of nucleus accumbens (NAc) core neuroimmune function indicated cocaine abstinence- and gp120-induced impairments, and the expression of several immune factors within the NAc core significantly correlated with cocaine seeking behavior. We conclude that cocaine abstinence dysregulates striatal neuroimmune function and interacts with gp120 to inhibit the effectiveness of a D3R partial agonist in reducing cocaine seeking. These findings highlight the need to consider comorbidities, such as immune status, when evaluating the efficacy of novel pharmacotherapeutics.

### [Implementation Strategies To Screen, Refer And Link Women Involved In The Carceral System To PrEP For HIV Prevention](#)

Dauria E, Rodriguez C, Bauerle Bass S, Tolou-Shams M, Christopoulos K. Int J Prison Health. May 1, 2023. Epub ahead of print.

**Purpose:** Women involved in the carceral system (CS) experience several conditions that increase their risk for HIV (e.g. high rates of substance use, psychiatric disorders, histories of victimization). The purpose of this study is to explore perspectives on potential strategies to connect women in the CS to pre-exposure prophylaxis (PrEP) services. **Design/methodology/approach:** This study conducted in-depth interviews with 27 women involved in the CS eligible for PrEP. Using vignettes, interviews explored attitudes, barriers and facilitators toward PrEP screening, referral and linkage facilitated via a CS stakeholder, an mHealth application or providing PrEP service referrals during detention via a navigator. **Findings:** Most women were, on average, 41.3 years, from racial and ethnic minority groups (56% black/African American; 19% Latinx). Inductive thematic analysis revealed CS involved women expressed mostly positive attitudes toward CS-based PrEP implementation. Younger women were more accepting of and interested in mHealth interventions. Implementation facilitators included leveraging relationships with trusted allies (e.g. "peers") and existing systems collaborations. Recommended implementation strategies included providing HIV and PrEP-specific education and training for system stakeholders and addressing issues related to privacy, system mistrust and stigma. **Originality/value:** Results provide a critical foundation for the implementation of interventions to improve PrEP access for women involved in the CS and have important implications for implementation strategies for all adults involved in the CS. Improving access to PrEP among this population may also support progress toward addressing national disparities in PrEP uptake, where women, black and Latinx populations have substantial unmet need.

### [Chronic Pain And Substance Use Disorders Among Older Sexual Minority Men Living With HIV: Implications For HIV Disease Management Across The HIV Care Continuum](#)

Taylor SW, McKetchnie SM, Batchelder AW, Justice A, Safren SA, O'Cleirigh C. AIDS Care. 2023; 35(4): 614-623.

HIV continues to be a critical health issue for sexual minority men (SMM) in the USA. Chronic pain is common in individuals with HIV, including older SMM, and is associated with substance use behaviors. This cross-sectional study sought to address a gap in the literature by characterizing interrelationships among chronic pain, substance use disorders (SUDs), medication adherence, and engagement in HIV care among older ( $\geq 50$ ) SMM living with HIV and chronic pain (N = 63). The unadjusted relationship between an opioid use disorder and pain indicated that participants with an opioid use disorder reported higher pain ratings than those without. Presence of alcohol use disorder

was significantly associated with missed HIV-care appointments due to chronic pain or substance use, showing that individuals with an alcohol use disorder reported more missed appointments in the past year. Higher pain was significantly associated with the same missed appointments variable, such that those reporting higher pain ratings also reported more missed appointments in the past year. These findings provide preliminary evidence of the interrelationships among chronic pain, SUDs, and engagement in HIV care among older SMM living with HIV and suggest that pain management in this population might support fuller engagement in HIV care.

**Cocaine Use May Moderate The Associations Of HIV And Female Sex With Neurocognitive Impairment In A Predominantly African American Population Disproportionately Impacted By HIV And Substance Use** Lai H, Celentano DD, Treisman G, Khalsa J, Gerstenblith G, Page B, Mandler RN, Yang Y, Salmeron B, Bhatia S, Chen S, Lai S, Goodkin K, Charurat M. AIDS Patient Care STDS. 2023; 37(5): 243-252.

HIV-associated neurocognitive disorders (HAND) remain a major challenge for people with HIV in the antiretroviral therapy era. Cocaine use may trigger/exacerbate HAND among African American (AA) adults, especially women. Between 2018 and 2019, 922 adults, predominantly AAs, with/without HIV and with/without cocaine use in Baltimore, Maryland, were enrolled in a study investigating the association of HIV and cocaine use with neurocognitive impairment (NCI). Neurocognitive performance was assessed with the NIH Toolbox Cognition Battery (NIHTB-CB). NCI was considered to be present if the fully adjusted standard score for at least two cognitive domains was 1.0 standard deviation below the mean. Although the overall analysis showed HIV and female sex were associated with NCI, the associations were dependent on cocaine use. Neither HIV [adj prevalence ratio (PR): 1.12, confidence interval (95% CI): 0.77-1.64] nor female sex (adj PR: 1.07, 95% CI: 0.71-1.61) was associated with NCI among cocaine nonusers, while both HIV (adj PR: 1.39, 95% CI: 1.06-1.81) and female sex (adj PR: 1.53, 95% CI: 1.18-1.98) were associated with NCI in cocaine users. HIV was associated with two NIHTB-CB measures overall. In addition, HIV was associated with a lower dimensional change card sort score (an executive function measure) in cocaine users and not in nonusers. Cognitive performance was poorer in female than in male cocaine users. The adverse effect of HIV on cognitive performance predominantly affected cocaine users. However, cocaine use may moderate the impact of HIV and female sex on cognitive performance, highlighting the importance of reducing cocaine use in NCI prevention among the AA population.

**Missed Opportunities For HIV And Hepatitis C Screening Among Emergency Department Patients With Untreated Opioid Use Disorder** Lyons MS, Chawarski MC, Rothman R, Whiteside L, Cowan E, Richardson LD, Hawk K, Tsui JI, Schwartz RP, O'Connor P, D'Onofrio G, Fiellin DA, Edelman EJ. J Addict Med. 2023; 17(2): 210-214.

**Objective:** We assessed the frequency of emergency department (ED) HIV and hepatitis C (HCV) screening in a high-risk cohort of ED patients with untreated opioid use disorder (OUD). **Methods:** This analysis used data from a prospective, observational study of English-speaking adults with untreated OUD enrolled from April 2017 to December 2018 in 4 urban, academic EDs. Two cohorts were defined for this analysis by self-reported negative/unknown status for HIV (cohort 1) and HCV (cohort 2). Sites featured structured screening programs throughout the entire enrollment period for HIV and during at least part of the enrollment period for HCV. We calculated the proportion tested for HIV and HCV during the study enrollment ED visit. **Results:** Among 394 evaluated ED patients, 328 of 394 (83.2%) were not tested for HIV or HCV and 244 of 393 (62.1%)

lacked a usual medical care provider. In cohort 1, 375 reported negative or unknown HIV status; 59/375 (15.7%) overall and 33/218 (15.1%) of those reporting recent injection drug use were tested for HIV. In cohort 2, 231 reported negative or unknown HCV status; 22/231 (9.5%) overall and 9/98 (9.2%) of those reporting recent injection drug use were tested for HCV. The proportion tested by the ED ranged from 3% to 25% for HIV and 4% to 32% for HCV across study sites.

**Conclusions:** Emergency department HIV and HCV screening remains infrequent among patients with untreated OUD, including those who inject drugs, even in EDs committed to screening. Targeted HIV/HCV screening should be considered as an adjunct strategy until the ideal of universal screening is more fully achieved.

## **CLINICAL TRIALS NETWORK RESEARCH**

**[Exploring The Performance Of During-Treatment Substance Use Outcome Measures In Predicting Longer-Term Psychosocial Functioning And Post-Treatment Abstinence](#)** Brandt L, Hu MC, Nunes EV, Campbell ANC. Drug Alcohol Depend. 2023; 248: 109918.

**Background:** The selection of appropriate efficacy endpoints in clinical trials has been a long-standing challenge for the substance use disorder field. Using data from a large, multi-site National Drug Abuse Treatment Clinical Trials Network trial (CTN-0044; n=474), this secondary data analysis aimed to explore whether specific proximal (during-treatment) substance use outcome measures predict longer-term improvements in psychosocial functioning and post-treatment abstinence, and whether predictions vary depending on the specific substance (cannabis, cocaine/stimulants, opioids, and alcohol). **Methods:** Generalized linear mixed models examined associations between six during-treatment substance use outcome measures and social functioning impairment (Social Adjustment Scale Self-Report) and severity of psychiatric symptoms (Brief Symptom Inventory-18) at end-of-treatment, and 3- and 6-months after treatment as well as post-treatment abstinence. **Results:** Maximum days of consecutive abstinence, proportion of days abstinent,  $\geq 3$  weeks of continuous abstinence, and the proportion of urine specimens negative for the primary substance were associated with post-treatment psychiatric and social functioning improvement and abstinence. However, only the effects of abstinence during the last 4 weeks of the treatment period on all three post-treatment outcomes was stable over time and did not differ between primary substance groups. In contrast, complete abstinence during the 12-week treatment period was not consistently associated with functioning improvements. **Conclusions:** Substance use outcome measures capturing the duration of primary substance abstinence during treatment are suitable predictors of post-treatment abstinence and longer-term psychosocial functioning improvement. Binary outcomes, such as end-of-treatment abstinence, may be particularly stable predictors and attractive given their ease of computation and straightforward clinical interpretability.

**[Care Coordination Between Rural Primary Care And Telemedicine To Expand Medication Treatment For Opioid Use Disorder: Results From A Single-Arm, Multisite Feasibility Study](#)** Hser YI, Mooney LJ, Baldwin LM, Ober A, Marsch LA, Sherman S, Matthews A, Clingan S, Fei Z, Zhu Y, Dopp A, Curtis ME, Osterhage KP, Hichborn EG, Lin C, Black M, Calhoun S, Holtzer CC, Nesen N, Bouchard D, Ledgerwood M, Gehring MA, Liu Y, Ha NA, Murphy SM, Hanano M, Saxon AJ. J Rural Health. April 19, 2023. Epub ahead of print.

**Purpose:** The use of telemedicine (TM) has accelerated in recent years, yet research on the implementation and effectiveness of TM-delivered medication treatment for opioid use disorder (MOUD) has been limited. This study investigated the feasibility of implementing a care

coordination model involving MOUD delivered via an external TM provider for the purpose of expanding access to MOUD for patients in rural settings. **Methods:** The study tested a care coordination model in 6 rural primary care sites by establishing referral and coordination between the clinic and a TM company for MOUD. The intervention spanned approximately 6 months from July/August 2020 to January 2021, coinciding with the peak of the COVID-19 pandemic. Each clinic tracked patients with OUD in a registry during the intervention period. A pre-/post-intervention design (N = 6) was used to assess the clinic-level outcome as patient-days on MOUD based on patient electronic health records. **Findings:** All clinics implemented critical components of the intervention, with an overall TM referral rate of 11.7% among patients in the registry. Five of the 6 sites showed an increase in patient-days on MOUD during the intervention period compared to the 6-month period before the intervention (mean increase per 1,000 patients: 132 days, P = .08, Cohen's d = 0.55). The largest increases occurred in clinics that lacked MOUD capacity or had a greater number of patients initiating MOUD during the intervention period. **Conclusions:** To expand access to MOUD in rural settings, the care coordination model is most effective when implemented in clinics that have negligible or limited MOUD capacity.

[Sexual Orientation Differences Among Men In A Randomized Clinical Trial Of Extended-Release Naltrexone And Bupropion For Methamphetamine Use Disorder](#) Kidd JD, Smiley SL, Coffin PO, Carmody TJ, Levin FR, Nunes EV, Shoptaw SJ, Trivedi MH. Drug Alcohol Depend. 2023; 250: 110899.

**Background:** Methamphetamine use disorder (MethUD) disproportionately affects men who have sex exclusively with men or with men and women (collectively MSM/W), compared to men who have sex with women (MSW). This study is the first MethUD medication trial to compare treatment effect for these groups, hypothesizing that extended-release injectable naltrexone 380mg every 3 weeks plus oral extended-release bupropion 450mg daily would be less effective for MSM/W than MSW. **Methods:** Data come from men (N = 246) in a multi-site, double-blind, randomized, placebo-controlled trial with sequential parallel comparison design. In Stage 1 (6-weeks), participants were randomized to active treatment or placebo. In Stage 2 (6-weeks), Stage 1 placebo non-responders were rerandomized. Treatment response was  $\geq 3$  methamphetamine-negative urine samples, out of four obtained at the end of Stages 1 and 2. Treatment effect was the active-versus-placebo between-group difference in the weighted average Stages 1 and 2 responses.

**Results:** MSM/W (n = 151) were more likely than MSW (n = 95) to be Hispanic, college-educated, and living with HIV. Adjusting for demographics, among MSM/W, response rates were 13.95 % (active treatment) and 2.78 % (placebo) in Stage 1; 23.26 % (active treatment) and 4.26 % (placebo) in Stage 2. Among MSW, response rates were 7.69 % (active treatment) and 5.80 % (placebo) in Stage 1; 3.57 % (active treatment) and 0 % (placebo) in Stage 2. Treatment effect was significantly larger for MSM/W (h = 0.1479) than MSW (h = 0.0227) (p = 0.04). **Conclusions:** Findings suggest efficacy of extended-release naltrexone plus bupropion for MSM/W, a population heavily burdened by MethUD. While a secondary outcome, this intriguing finding merits testing in prospective trials.

[Implementing Programs To Initiate Buprenorphine For Opioid Use Disorder Treatment In High-Need, Low-Resource Emergency Departments: A Nonrandomized Controlled Trial](#)

McCormack RP, Rotrosen J, Gauthier P, D'Onofrio G, Fiellin DA, Marsch LA, Novo P, Liu D, Edelman EJ, Farkas S, Matthews AG, Mulatya C, Salazar D, Wolff J, Knight R, Goodman W, Williams J, Hawk K. Ann Emerg Med. 2023; 82(3): 272-287.

**Objective:** We hypothesized that implementation facilitation would enable us to rapidly and effectively implement emergency department (ED)-initiated buprenorphine programs in rural and urban settings with high-need, limited resources and dissimilar staffing structures. **Methods:** This

multicenter implementation study employed implementation facilitation using a participatory action research approach to develop, introduce, and refine site-specific clinical protocols for ED-initiated buprenorphine and referral in 3 EDs not previously initiating buprenorphine. We assessed feasibility, acceptability, and effectiveness by triangulating mixed-methods formative evaluation data (focus groups/interviews and pre/post surveys involving staff, patients, and stakeholders), patients' medical records, and 30-day outcomes from a purposive sample of 40 buprenorphine-receiving patient-participants who met research eligibility criteria (English-speaking, medically stable, locator information, nonprisoners). We estimated the primary implementation outcome (proportion receiving ED-initiated **buprenorphine** among candidates) and the main secondary outcome (30-day treatment engagement) using Bayesian methods. **Results:** Within 3 months of initiating the implementation facilitation activities, each site implemented buprenorphine programs. During the 6-month programmatic evaluation, there were 134 ED-buprenorphine candidates among 2,522 encounters involving opioid use. A total of 52 (41.6%) practitioners initiated buprenorphine administration to 112 (85.1%; 95% confidence interval [CI] 79.7% to 90.4%) unique patients. Among 40 enrolled patient-participants, 49.0% (35.6% to 62.5%) were engaged in addiction treatment 30 days later (confirmed); 26 (68.4%) reported attending one or more treatment visits; there was a 4-fold decrease in self-reported overdose events (odds ratio [OR] 4.03; 95% CI 1.27 to 12.75). The ED clinician readiness increased by a median of 5.02 (95% CI: 3.56 to 6.47) from 1.92/10 to 6.95/10 (n(pre)=80, n(post)=83). **Conclusions:** The implementation facilitation enabled us to effectively implement ED-based buprenorphine programs across heterogeneous ED settings rapidly, which was associated with promising implementation and exploratory patient-level outcomes.

### [Naltrexone Plus Bupropion Reduces Cigarette Smoking In Individuals With Methamphetamine Use Disorder: A Secondary Analysis From The CTN ADAPT-2 Trial](#)

Schmitz JM, Stotts AL, Yoon JH, Northrup TF, Villarreal YR, Yammine L, Weaver MF, Carmody T, Shoptaw S, Trivedi MH. J Subst Use Addict Treat. 2023; 151: 208987.

**Introduction:** Methamphetamine (MA) use is marked by high rates of comorbid tobacco smoking, which is associated with more severe drug use and worse clinical outcomes compared to single use of either drug. Research has shown the combination of naltrexone plus oral bupropion (NTX-BUP) improves smoking cessation outcomes in non-MA-using populations. In the Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT-2) study, NTX-BUP successfully reduced MA use. Our aim in this secondary data analysis was to examine changes in cigarette smoking among the subgroup of participants reporting comorbid tobacco use in the ADAPT-2 trial. **Methods:** The multi-site ADAPT-2 study used a randomized, double blind, sequential parallel comparison design to evaluate treatment with extended-release injectable NTX (380 mg every 3 weeks) combined with once-daily oral extended-release BUP (450 mg/day) vs matching injectable and oral placebo in outpatients with moderate or severe MA use disorder. The study assessed smoking outcomes, based on self-reported timeline followback (TLFB) data, twice/week for 13 weeks. **Results:** Of the 403 participants in the ADAPT-2 trial, 290 reported being current cigarette smokers (71.9 %). The study found significant differences ( $p$ 's < 0.0001) for each smoking outcome indicating greater change in the proportion of nonsmoking days, number of cigarettes smoked per week, and consecutive nonsmoking days, all favoring the group receiving NTX-BUP versus placebo. **Conclusions:** NTX-BUP was associated with significant reductions in self-reported cigarette smoking in the context of concurrent treatment for MA use disorder. These off-target medication effects warrant prospective investigation using biochemically confirmed measures of smoking abstinence. The development of NTX-BUP as a co-addiction treatment strategy has a potential for high public health impact.

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

### **State-Level Macro-Economic Factors Moderate The Association Of Low Income With Brain Structure And Mental Health In U.S. Children**

Weissman DG, Hatzenbuehler ML, Cikara M, Barch DM, McLaughlin KA. Nat Commun. 2023; 14(1): 2085.

Macrostructural characteristics, such as cost of living and state-level anti-poverty programs relate to the magnitude of socioeconomic disparities in brain development and mental health. In this study we leveraged data from the Adolescent Brain and Cognitive Development (ABCD) study from 10,633 9-11 year old youth (5115 female) across 17 states. Lower income was associated with smaller hippocampal volume and higher internalizing psychopathology. These associations were stronger in states with higher cost of living. However, in high cost of living states that provide more generous cash benefits for low-income families, socioeconomic disparities in hippocampal volume were reduced by 34%, such that the association of family income with hippocampal volume resembled that in the lowest cost of living states. We observed similar patterns for internalizing psychopathology. State-level anti-poverty programs and cost of living may be confounded with other factors related to neurodevelopment and mental health. However, the patterns were robust to controls for numerous state-level social, economic, and political characteristics. These findings suggest that state-level macrostructural characteristics, including the generosity of anti-poverty policies, are potentially relevant for addressing the relationship of low income with brain development and mental health.

### **Longitudinal Associations Between Perceived Discrimination And Suicidality In Youth**

Pearlman AT, Murphy MA, Raiciulescu S, Johnson N, Klein DA, Gray JC, Schvey NA. J Pediatr. 2023; 262: 113642.

Research among adults reveals robust associations between discrimination and suicidality. The relationship between discrimination and suicidality is understudied in youth. Participants in the Adolescent Brain Cognitive Development (ABCD) study completed a measure of discrimination based on multiple attributes. The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) was administered one-year later to assess depressive disorders and suicidality (ideation and behavior). Logistic regressions, adjusting for age, sex, race/ethnicity, family income, lifetime depressive disorders, and body composition were conducted. Adjusting for covariates, discrimination based on weight (OR: 2.19), race/ethnicity/color (OR: 3.21), and sexual orientation (OR: 3.83) were associated with greater odds of reporting suicidality one year later ( $p < 0.025$ ). Nationality-based discrimination was not significantly associated with suicidality. Compared with those reporting no discrimination, youths reporting discrimination based on two or more attributes had nearly five times greater odds of recent suicidality (OR: 4.72;  $p < 0.001$ ). The current study highlights the deleterious impacts of discrimination on mental health among youths reporting multiple forms of discrimination.

### **Mapping Human Brain Charts Cross-Sectionally And Longitudinally**

Di Biase MA, Tian YE, Bethlehem RAI, Seidlitz J, Alexander-Bloch AF, Yeo BTT, Zalesky A. Proc Natl Acad Sci U S A. 2023; 120(20): e2216798120.

Brain scans acquired across large, age-diverse cohorts have facilitated recent progress in establishing normative brain aging charts. Here, we ask the critical question of whether cross-sectional estimates of age-related brain trajectories resemble those directly measured from longitudinal data. We show that age-related brain changes inferred from cross-sectionally mapped brain charts can substantially underestimate actual changes measured longitudinally. We further

find that brain aging trajectories vary markedly between individuals and are difficult to predict with population-level age trends estimated cross-sectionally. Prediction errors relate modestly to neuroimaging confounds and lifestyle factors. Our findings provide explicit evidence for the importance of longitudinal measurements in ascertaining brain development and aging trajectories.

[Characteristics Associated With Cannabis Use Initiation By Late Childhood And Early Adolescence In The Adolescent Brain Cognitive Development \(ABCD\) Study](#) Miller AP, Baranger DAA, Paul SE, Hatoum AS, Rogers C, Bogdan R, Agrawal A. JAMA Pediatr. 2023; 177(8): 861-863.

Early-onset cannabis use is common (e.g., 12% of 14- to 15-year-olds in the US report lifetime use) and is associated with increased risk for cannabis use disorder, other psychiatric disorders, and other problems (e.g, early school dropout) during childhood and adulthood. Prospective risk factors of early-onset cannabis use remain poorly understood. Here, using data from the Adolescent Brain Cognitive Development (ABCD) Study, we identified characteristics associated with cannabis use initiation by early adolescence (mean [SD] age, 13.43 [0.62] years). As expected, initiation of alcohol and tobacco use by 3.5-year follow-up exhibited the greatest effect sizes (odds ratio [OR], 17.46; 95% CI, 11.10-27.47 and OR, 35.85; 95% CI, 23.21-55.37, respectively). Outside of these associations, prenatal cannabis exposure was associated with the largest risk for cannabis use initiation (OR, 2.60; 95% CI, 1.62-4.17); this association remained when additionally controlling for alcohol and tobacco use initiation, family or parent alcohol or drug problems, and prenatal alcohol and tobacco exposure (OR, 2.16; 95% CI, 1.17-3.97). Several cannabis-specific factors at 1-year follow-up (mean [SD] age, 10.92 [0.64] years), including ease of obtaining, positive expectancies, number of friends using, and greater peer tolerance, were associated with greater odds of early initiation of cannabis use. Greater externalizing symptomatology, depressed mood, and anhedonia at baseline were also significantly prospectively associated with cannabis use initiation.

[Early-Initiated Childhood Reading For Pleasure: Associations With Better Cognitive Performance, Mental Well-Being And Brain Structure In Young Adolescence](#) Sun YJ, Sahakian BJ, Langley C, Yang A, Jiang Y, Kang J, Zhao X, Li C, Cheng W, Feng J. Psychol Med. June 28, 2023; 1-15. Epub ahead of print.

**Background:** Childhood is a crucial neurodevelopmental period. We investigated whether childhood reading for pleasure (RfP) was related to young adolescent assessments of cognition, mental health, and brain structure. **Methods:** We conducted a cross-sectional and longitudinal study in a large-scale US national cohort (10 000 + young adolescents), using the well-established linear mixed model and structural equation methods for twin study, longitudinal and mediation analyses. A 2-sample Mendelian randomization (MR) analysis for potential causal inference was also performed. Important factors including socio-economic status were controlled. **Results:** Early-initiated long-standing childhood RfP (early RfP) was highly positively correlated with performance on cognitive tests and significantly negatively correlated with mental health problem scores of young adolescents. These participants with higher early RfP scores exhibited moderately larger total brain cortical areas and volumes, with increased regions including the temporal, frontal, insula, supramarginal; left angular, para-hippocampal; right middle-occipital, anterior-cingulate, orbital areas; and subcortical ventral-diencephalon and thalamus. These brain structures were significantly related to their cognitive and mental health scores, and displayed significant mediation effects. Early RfP was longitudinally associated with higher crystallized cognition and lower attention symptoms at follow-up. Approximately 12 h/week of youth regular RfP was cognitively optimal. We further observed a moderately significant heritability of early RfP, with considerable contribution from environments. MR analysis revealed beneficial causal associations of early RfP

with adult cognitive performance and left superior temporal structure. **Conclusions:** These findings, for the first time, revealed the important relationships of early RfP with subsequent brain and cognitive development and mental well-being.

## **INTRAMURAL RESEARCH**

### **AI-Based Analysis Of Social Media Language Predicts Addiction Treatment Dropout At 90 Days**

Curtis B, Giorgi S, Ungar L, Vu H, Yaden D, Liu T, Yadeta K, Schwartz HA.

Neuropsychopharmacology. April 24, 2023. Epub ahead of print.

The reoccurrence of use (relapse) and treatment dropout is frequently observed in substance use disorder (SUD) treatment. In the current paper, we evaluated the predictive capability of an AI-based digital phenotype using the social media language of patients receiving treatment for substance use disorders (N = 269). We found that language phenotypes outperformed a standard intake psychometric assessment scale when predicting patients' 90-day treatment outcomes. We also use a modern deep learning-based AI model, Bidirectional Encoder Representations from Transformers (BERT) to generate risk scores using pre-treatment digital phenotype and intake clinic data to predict dropout probabilities. Nearly all individuals labeled as low-risk remained in treatment while those identified as high-risk dropped out (risk score for dropout AUC = 0.81;  $p < 0.001$ ). The current study suggests the possibility of utilizing social media digital phenotypes as a new tool for intake risk assessment to identify individuals most at risk of treatment dropout and relapse.

### **Dopaminergic Prediction Errors In The Ventral Tegmental Area Reflect A Multithreaded Predictive Model**

Takahashi YK, Stalnaker TA, Mueller LE, Harootonian SK, Langdon AJ, Schoenbaum G. Nat Neurosci. 2023; 26(5): 830-839.

Dopamine neuron activity is tied to the prediction error in temporal difference reinforcement learning models. These models make significant simplifying assumptions, particularly with regard to the structure of the predictions fed into the dopamine neurons, which consist of a single chain of timepoint states. Although this predictive structure can explain error signals observed in many studies, it cannot cope with settings where subjects might infer multiple independent events and outcomes. In the present study, we recorded dopamine neurons in the ventral tegmental area in such a setting to test the validity of the single-stream assumption. Rats were trained in an odor-based choice task, in which the timing and identity of one of several rewards delivered in each trial changed across trial blocks. This design revealed an error signaling pattern that requires the dopamine neurons to access and update multiple independent predictive streams reflecting the subject's belief about timing and potentially unique identities of expected rewards.

### **PPAR $\alpha$ And PPAR $\gamma$ Are Expressed In Midbrain Dopamine Neurons And Modulate Dopamine- And Cannabinoid-Mediated Behavior In Mice**

Hempel B, Crissman M, Pari S, Klein B, Bi GH, Alton H, Xi ZX. Mol Psychiatry. July 21, 2023. Epub ahead of print.

Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptors that regulate gene expression.  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) is a PPAR $\gamma$  agonist and some endocannabinoids are natural activators of PPAR $\alpha$  and PPAR $\gamma$ . However, little is known regarding their cellular distributions in the brain and functional roles in cannabinoid action. Here, we first used RNAscope in situ hybridization and immunohistochemistry assays to examine the cellular distributions of PPAR $\alpha$  and PPAR $\gamma$  expression in the mouse brain. We found that PPAR $\alpha$  and PPAR $\gamma$  are expressed

in ~70% of midbrain dopamine (DA) neurons. In the amygdala, PPAR $\alpha$  is expressed in ~60% of glutamatergic neurons, while PPAR $\gamma$  is expressed in ~60% of GABA neurons. However, no PPAR $\alpha/\gamma$  signal was detected in GABA neurons in the nucleus accumbens. We then used a series of behavioral assays to determine the functional roles of PPAR $\alpha/\gamma$  in the CNS effects of  $\Delta^9$ -THC. We found that optogenetic stimulation of midbrain DA neurons was rewarding as assessed by optical intracranial self-stimulation (oICSS) in DAT-cre mice.  $\Delta^9$ -THC and a PPAR $\gamma$  (but not PPAR $\alpha$ ) agonist dose-dependently inhibited oICSS. Pretreatment with PPAR $\alpha$  or PPAR $\gamma$  antagonists attenuated the  $\Delta^9$ -THC-induced reduction in oICSS and  $\Delta^9$ -THC-induced anxiogenic effects. In addition, a PPAR $\gamma$  agonist increased, while PPAR $\alpha$  or PPAR $\gamma$  antagonists decreased open-field locomotion. Pretreatment with PPAR $\alpha$  or PPAR $\gamma$  antagonists potentiated  $\Delta^9$ -THC-induced hypoactivity and catalepsy but failed to alter  $\Delta^9$ -THC-induced analgesia, hypothermia and immobility. These findings provide the first anatomical and functional evidence supporting an important role of PPAR $\alpha/\gamma$  in DA-dependent behavior and cannabinoid action.

**Role Of Piriform Cortex And Its Afferent Projections In Relapse To Fentanyl Seeking After Food Choice-Induced Voluntary Abstinence** Claypool SM, Reiner DJ, Behdin S, Orihuel J, Batista A, Caldwell KE, Chow JJ, Bossert JM, Rubio FJ, Hope BT, Shaham Y. J Neurosci. 2023; 43(14): 2597-2614.

We previously demonstrated a role of piriform cortex (Pir) in relapse to fentanyl seeking after food choice-induced voluntary abstinence. Here, we used this model to further study the role of Pir and its afferent projections in fentanyl relapse. We trained male and female rats to self-administer palatable food pellets for 6 d (6 h/day) and fentanyl (2.5  $\mu\text{g}/\text{kg}/\text{infusion}$ , i.v.) for 12 d (6 h/day). We assessed relapse to fentanyl seeking after 12 voluntary abstinence sessions, achieved through a discrete choice procedure between fentanyl and palatable food (20 trials/session). We determined projection-specific activation of Pir afferents during fentanyl relapse with Fos plus the retrograde tracer cholera toxin B (injected into Pir). Fentanyl relapse was associated with increased Fos expression in anterior insular cortex (AI) and prelimbic cortex (PL) neurons projecting to Pir. We next used an anatomical disconnection procedure to determine the causal role of these two projections (AI $\rightarrow$ Pir and PL $\rightarrow$ Pir) in fentanyl relapse. Contralateral but not ipsilateral disconnection of AI $\rightarrow$ Pir projections decreased fentanyl relapse but not reacquisition of fentanyl self-administration. In contrast, contralateral but not ipsilateral disconnection of PL $\rightarrow$ Pir projections modestly decreased reacquisition but not relapse. Fluorescence-activated cell sorting and quantitative PCR data showed molecular changes within Pir Fos-expressing neurons associated with fentanyl relapse. Finally, we found minimal or no sex differences in fentanyl self-administration, fentanyl versus food choice, and fentanyl relapse. Our results indicate that AI $\rightarrow$ Pir and PL $\rightarrow$ Pir projections play dissociable roles in nonreinforced relapse to fentanyl seeking versus reacquisition of fentanyl self-administration after food choice-induced voluntary abstinence.

**SIGNIFICANCE STATEMENT** We previously showed a role of Pir in fentanyl relapse after food choice-induced voluntary abstinence in rats, a procedure mimicking human abstinence or a significant reduction in drug self-administration because of the availability of alternative nondrug rewards. Here, we aimed to further characterize the role of Pir in fentanyl relapse by investigating the role of Pir afferent projections and analyzing molecular changes in relapse-activated Pir neurons. We identified dissociable roles of two Pir afferent projections (AI $\rightarrow$ Pir and PL $\rightarrow$ Pir) in relapse to fentanyl seeking versus reacquisition of fentanyl self-administration after voluntary abstinence. We also characterized molecular changes within Pir Fos-expressing neurons associated with fentanyl relapse.

**Comparative Appearing Neuropharmacology Of Structurally Distinct Non-Fentanyl Opioids That Are Appearing On Recreational Drug Markets Worldwide**

Vandeputte MM, Tsai MM, Chen L, Glatfelter GC, Walther D, Stove CP, Shi L, Baumann MH. Drug Alcohol Depend. 2023; 249: 109939.

**Background:** The emergence of novel synthetic opioids (NSOs) is contributing to the opioid overdose crisis. While fentanyl analogs have historically dominated the NSO market, a shift towards non-fentanyl compounds is now occurring. **Methods:** Here, we examined the neuropharmacology of structurally distinct non-fentanyl NSOs, including U-47700, isotonitazene, buprenorphine, and N-desethyl isotonitazene, as compared to morphine and fentanyl. Compounds were tested in vitro using opioid receptor binding assays in rat brain tissue and by monitoring forskolin-stimulated cAMP accumulation in cells expressing the human mu-opioid receptor (MOR). Compounds were administered subcutaneously to male Sprague-Dawley rats, and hot plate antinociception, catalepsy score, and body temperature changes were measured. **Results:** Receptor binding results revealed high MOR selectivity for all compounds, with MOR affinities comparable to those of morphine and fentanyl (i.e., nM). All drugs acted as full-efficacy MOR agonists in the cyclic AMP assay, but nitazene analogs had greater functional potencies (i.e., pM) compared to the other drugs (i.e., nM). When administered to rats, all compounds induced opioid-like antinociception, catalepsy, and body temperature changes, but nitazenes were the most potent. Similar to fentanyl, the nitazenes had faster onset and decline of in vivo effects when compared to morphine. In vivo potencies to induce antinociception and catalepsy (i.e., ED<sub>50</sub>s) correlated with in vitro functional potencies (i.e., EC<sub>50</sub>s) but not binding affinities (i.e., K<sub>i</sub>s) at MOR. **Conclusions:** Collectively, our findings indicate that non-fentanyl NSOs pose grave danger to those individuals who use opioids. Continued vigilance is needed to identify and characterize synthetic opioids as they emerge in clandestine drug markets.

## **GRANTEE HONORS AND AWARDS**

**Edythe London, Ph.D.**, University of California Los Angeles, was awarded the Nathan B. Eddy Memorial Award at the College on Problems of Drug Dependence (CPDD) 2023, which was established in memory of one of the pioneers in the field of drug dependence following his death in 1973. The award acknowledges outstanding research efforts that have advanced our knowledge of drug dependence.

**Jamie Peters, Ph.D.**, University of Colorado, was awarded the Rosalind Franklin Science Award for her seminal *Nature* paper with Dr. David Olson's group ("Tabernanthalog Reduces Motivation for Heroin and Alcohol in a Polydrug Use Model"). Jamie's work demonstrated a striking long-lasting therapeutic effect of a single treatment with the psychedelic-like compound tabernanthalog, a synthetic derivative of ibogaine, on relapse to heroin-seeking in rats.

**Justin Strickland, Ph.D.**, Johns Hopkins University School of Medicine, won the Joseph Cochin Young Investigator Award at CPDD 2023. The award, in memory of a respected leader in drug abuse research and a former Chairman and Executive Secretary of CPDD, was established in 1986 to recognize research contributions in any facet of the field of drug abuse.

## **STAFF HONORS AND AWARDS**

**Amy Newman, Ph.D.**, Director, NIDA Intramural Research Program (IRP), has been inducted into the American Chemical Society's (ACS) Medicinal Chemistry Division Hall of Fame—one of three 2023 inductees. Since its inception in 1966, Amy is the first female scientist and fifth overall from the NIH IRP to receive this honor. Amy was formally inducted during the Hall of Fame ceremony and reception at the ACS meeting in August 2023.

### **2023 Outstanding Poster Awards**

The following were honored at the 11<sup>th</sup> annual NIDA IRP Poster Day and Mentoring Awards ceremony on May 11, 2023.

**Sarah Claypool**

**Qingfang Liu, Ph.D.**

**Samanth Lee**

**Michelle Tsai**

**Ana Armenta Vega**

**Kelsey Shimoda**

**Noelle Henein**

**Laura Grasso and Kareem Woods**

**Diana Pham**

**Ivan Osnaya**

**Hadley Mills**

**Hannah Alton**

**Lacey Greer**

**Annika Quam**

**Fallon Curry**

### **2023 NIDA IRP Mentoring Awards**

The following were honored at the 11<sup>th</sup> annual NIDA Poster Day and Mentoring Awards ceremony on May 11, 2023.

**Yosuke Arima, Ph.D.** – Postdoctoral Fellow Mentoring Award

**David Epstein, Ph.D.** – Investigator Mentoring Award

**Mehdi Farokhnia, M.D., M.P.H.** – Staff Scientist Mentoring Award

**Gisela Camacho Hernandez, Ph.D.** – Diversity Mentoring Award

### **2023 NIDA IRP Women in Science Research Awardees**

The NIDA IRP Women Scientist Advisors awards ceremony is held annually to recognize the accomplishments of outstanding women scientists. The 2023 awardees are:

**Agnieszka Sulima, Ph.D.** – Excellence in Research Award.

**Gisela Andrea Camacho Hernandez, Ph.D.** – Excellence in Research Award

**Amy Janes, Ph.D.** – Research Recognition Award for Exceptional Achievement

**Melinda Hersey, Ph.D.** – Research Recognition Award for Exceptional Achievement

**Qingfang Liu, Ph.D.** – Promising Postdoctoral Fellow Award

**Erika Carlson** was selected as Highlighted Trainee Author for May 2023 by the *Journal of Pharmacology and Experimental Therapeutics (JPET)*. JPET recognized Erika's contributions to the article titled "Heroin- and Fentanyl-Induced Respiratory Depression in a Rat Plethysmography

Model: Potency, Tolerance, and Sex Differences,” which was published in the May 2023 issue. Erika co-authored this article with her mentors **Renata Marchette, Pharm.D., Ph.D., Leandro Vendruscolo, Ph.D., Pharm.D., M.Sc.,** and **George Koob, Ph.D.** while she was a post-baccalaureate in the Neurobiology of Addiction Section at the NIDA IRP.

**Jonathan Pollock, Ph.D.,** of NIDA’s Division of Neuroscience and Behavior (DNB), co-edited with **Kay Wanke, Ph.D., M.P.H.,** of NIH’s Office of Disease Prevention, a special issue in *Addiction Neuroscience* on biomarkers for nicotine and tobacco dependence. This special issue showcases current consensus measures and new biomarker advances that can be incorporated into cessation and harm reduction clinical trials.

## STAFF CHANGES

### New Appointments

**Nathaniel “Natty” Davis, M.B.A.**, was selected as the new Executive Officer and Deputy Director for Management. He joined NIDA in February 2020 and served as the Budget Officer and Chief of the Financial Management Branch. Prior to joining NIDA, Natty was the Budget Officer at the National Institute on Minority Health and Health Disparities and, before that, worked as a Budget Analyst elsewhere at NIH and with the Department of the Army. In addition to his resource management experience, Natty brings a wealth of general management and leadership experience, much of which he gained during his over 10 years as an active-duty Army officer and in a variety of assignments in the Army Reserve. Amongst the most challenging of these were serving as the director of a more than 150-person unit in Mosul, Iraq, as well as serving as the Deputy Director of a construction management office in Tel Aviv, Israel, where he helped lead a multi-national and multi-cultural project delivery team.

**Christie Brannock, M.B.A.**, transitioned to Director, Office of Education and Career Development at the NIDA IRP on July 1, 2023. Christie graduated from the College of Notre Dame of Maryland with a B.A. in Psychology (Research Track) and received her M.B.A. from Loyola University Maryland. She strongly believes in life-long learning and is currently a doctoral student at the Johns Hopkins University School of Education. Her program focuses on Entrepreneurial Leadership in Education, with an emphasis on program evaluation and curriculum development. Her dissertation examines the experiences of biomedical trainees and mentors, and she anticipates finishing her degree by 2025.

**Barbara Oudekerk, Ph.D.**, joined NIDA in January 2021 and will serve as a Scientific Program Director in DESPR’s Epidemiology Research Branch for the N CREW Program. Barbara will provide expertise in a variety of areas, including intervention research and substance use prevention. Prior to joining the N CREW Program, she was a PO in the Prevention Research Branch where she managed portfolios on prevention in social services, justice, and community settings and was the Lead Project Scientist for the NIH HEAL Preventing Opioid Use Disorder Research Program.

**Liza Zeinert, M.A.**, rejoined the Center for the Clinical Trials Network (CCTN) at NIDA as a Clinical Trials Program Specialist. In this role, Liza will serve as a resource to the study investigators and Center staff and will assist in the administration and coordination of the CTN’s research portfolio. Before joining CCTN, Ms. Zeinert was with the National Institute on Aging, where she served as a Clinical Trials Specialist in the Division of Behavioral and Social Research.

### New Staff

**Amanda Burton, Ph.D.**, joined the Office of the Director of NIDA’s Division of Extramural Research as a Clinical Research Policy Program Manager on June 4. Amanda comes to NIDA from the ClinicalTrials.gov program at the NIH’s National Library of Medicine. She received her Ph.D. in Neuroscience and Cognitive Science from the University of Maryland, College Park, where her dissertation research focused on the long-term effects of drug exposure on behavior and reward-circuitry. Upon finishing her degree, she gained regulatory experience and supported efforts to

improve the transparency of clinical research. Amanda has expertise in NIH policies and regulations regarding clinical trial registration and results reporting requirements.

**Alexander Colorado** joined the Management Analysis Branch, Office of Management on May 21 as a Management Analyst. He comes from the Cybersecurity and Infrastructure Security Agency, where he supported senior leaders in critical cybersecurity and infrastructure protection initiatives. Previously, he worked for the Federal Emergency Management Agency's Process Improvement Team, enhancing the systems that deliver public assistance to federal, state, local, tribal, and territorial partners after natural and man-made disasters. He is a graduate of George Mason University, the Wake Forest University School of Business, and the Army Logistics University's Quartermaster Basic Officer Leadership Course. At NIDA, Alexander's portfolio will include the Risk Management, Records Management, and Emergency Management programs.

**Monica R. Corry, J.D.**, will join the NIDA Office of Management on September 11 as the Ethics Coordinator. Monica is coming from the FDA, where she was an Ethics Specialist for the Center for Devices and Radiological Health. Before joining the FDA, she worked at the U.S. Postal Service Office of Inspector General. She earned a bachelor's degree from the University of Maryland and a law degree from the University of Baltimore School of Law.

**Giuliana Faller** joined the NIDA Office of Acquisitions on June 20 as a Contract Specialist. She will primarily support the National Center for Advancing Translational Sciences. Giuliana has 8 years of experience in acquisitions in the private sector. She most recently worked as a Subcontracts Administrator at Leidos supporting a project focused on checkpoint screening services at all U.S. airports. Additionally, she has worked as a Contract Specialist at immixGroup, Inc. and at the Brazilian Aeronautical Commission. Giuliana received a bachelor's degree in law from Positivo University, Brazil.

**Stephanie Glynn** rejoined NIDA in the Office of Management's Administrative Management Branch as an Administrative Officer (AO) on August 27, 2023. She will be the servicing AO for DTMC and the Office of Science Policy and Communications. Prior to joining NIDA, Stephanie was a senior AO with the National Institute on Deafness and Other Communication Disorders, a Program Specialist at the NIDA IRP, and elsewhere at NIH and the Department of Health and Human Services. With more than 15 years of service, she returns with extensive experience—including travel, procurement, human resources, and training.

**Christina Hatch, Ph.D.**, recently joined NIDA's DNB as a program analyst. Christina's expertise is in the neural basis of processes related to decision-making, addiction, and Parkinson's disease. She studied perceptual decision-making and perceived confidence in humans and non-human primates using a combination of behavioral, neurophysiological, and computational approaches. Christina earned a Ph.D. from New York University, with Roozbeh Kiani, M.D., Ph.D. as her mentor. Prior to graduate school, Christina worked as a Research Associate in the Cellular Neurobiology Research Branch at the NIDA IRP. Christina holds bachelor's degrees in Physiology and Neurobiology, Psychology, and Philosophy from the University of Maryland. She will initially be working with Susan Wright, Ph.D., on data science programs and initiatives.

**Saravanan Karuppagounder, Ph.D.**, joined the Office of Translational Initiatives and Program Innovations (OTIPI) as a PO on July 16. Saru is a trained pharmacologist with extensive background in translational neuroscience. Prior to joining NIDA, he worked as a Director, Spinal

Cord Injury Core, Burke Neurological Institute, Weill Cornell Medicine. He earned his bachelor's degree in pharmacy from Madras Medical College and doctorate in Pharmacy from Indian Institute of Chemical Biology, Jadavpur University, India.

**Ernestine Lenteu** joined NIDA's OTIPI as a Program Specialist on August 27. She previously served as a Program Assistant Program Specialist at the Institute of Neurology Disorders and Stroke for the Channels Synapses and Circuits/Neural environment Clusters, Staff Assistant for Wilson Compton, M.D., M.P.E., as well as other roles within NIDA. For the past 18 months, she has worked as an Administrative Officer in the Office of Research Facilities Team.

**Jessica Mollick, Ph.D.**, came to NIDA's DNB as a new PO in the Behavioral Cognitive Neuroscience Branch. Jessica's areas of scientific interest and expertise include the neural mechanisms of reward learning, emotion, and decision-making, and how these mechanisms are influenced by substance use disorders. She is also interested in neuroimaging methods and computational models of reward learning and decision-making. Jessica received her bachelor's degree in Cognitive Science from the University of California Berkeley. She then completed a Ph.D. in Neuroscience and Psychology at the University of Colorado Boulder. Jessica completed postdoctoral training at Yale University in the Department of Psychiatry under the mentorship of Hedy Kober, Ph.D.

**Commander (CDR) Erin Parker, Ph.D.**, joined NIDA's DESPR as a Social and Behavioral Scientist Administrator in May. Prior to joining NIDA, Erin served as the Deputy Associate Director for Science in the Division of Overdose Prevention at the Centers for Disease Control and Prevention (CDC). Erin began her U.S. Public Health Service career as an Epidemic Intelligence Service Officer in the Division of Unintentional Injury Prevention at CDC. Prior to that, she served as a Health Scientist in CDC's Home, Recreation, and Transportation Branch, where she worked on projects in older adult fall prevention, global road safety, drowning, child injury, and fires/burns.

**Jane Ting** joined the Management Analysis Branch, Office of Management on June 5 as a Management Analyst. Jane's NIDA portfolio will include onboarding, exit survey, workload analysis, and the Federal Employee Viewpoint Survey. Jane recently worked as a Performance Management Data Analyst for the Montgomery County Government. Jane previously served as a Management Analyst/Project Manager as a contractor at National Heart, Lung, and Blood Institute. Jane graduated with a B.S. in Finance from George Mason University and an M.S. in Information Systems and Technology from George Washington University.

**Sarah Vidal, Ph.D.**, joined DESPR as a Social and Behavioral Scientist Administrator on August 27. Prior to joining NIH, she served as a senior study director in the behavioral health and health policy area at Westat. More recently, Sarah served as a Scientific Review Officer with the NIH Center for Scientific Review. She earned her Ph.D. in psychology with a concentration in human development and public policy from Georgetown University and completed an NIH/NIDA T32 postdoctoral fellowship in the Division of Prevention and Community Research at Yale University School of Medicine. Sarah will work with research programs related to the AI/AN community, child welfare, and criminal/juvenile justice in ERB.

**Angela Walden, Ph.D.**, joined the N CREW team on June 20 as a Social and Behavioral Sciences Administrator in ERB. Angela will work collaboratively with Native communities and allies to enhance locally driven Tribal community and organizational research capacity and infrastructure to

address substance misuse through culturally grounded methods and processes. Angela is a citizen of the Cherokee Nation and is an experienced researcher, practitioner, educator, and expert on diversity, equity, and inclusion. Her work has focused on increasing services, supports, and professional pathways for members of underrepresented communities. Angela previously worked at the University of Illinois Chicago, most recently as the Assistant Vice Chancellor for Diversity Initiatives in the Office of the Vice Chancellor for Diversity, Equity, and Engagement and served on the faculty in the Department of Psychology.

**Monica Williams** joined NIDA's Office of Management on June 5 to support our Diversity, Equity, Inclusion and Accessibility (DEIA) Program. Monica will provide project management and program coordination in the implementation of the DEIA REEP action plan and support the DEIA Steering Committee. Prior to NIDA, Monica served as the Customer Experience Reporting and Analytics Director for Bright Multiple Listing Service (MLS), where she handled all aspects of the customer relationship experience for the nation's largest MLS system. Prior to that role, Monica served as the Director of Customer Support. She graduated with a B.A. in Sociology from the University of Maryland – College Park and received her M.B.A. from Keller Graduate School of Management.

### **Staff Departures**

**Hugo Matamoros**, a Budget Analyst with the NIDA Office of Management's Financial Management Branch, left NIDA on July 29 for a position with the Department of Homeland Security.

**Christina Page**, a Program Analyst in the DER's Office of Extramural Policy, left NIDA on June 3 for a position with the National Institute of Mental Health (NIMH).

**Manny Rodriguez**, a Management Analyst in NIDA's Office of Management Analysis Branch, left on May 6 for a position with NIMH.

**Melba Rojas**, an Ethics Coordinator with NIDA's Office of Management's Office of the Director, left NIDA on July 1 for a position with the NIH Office of the Director.

**Nichole Wise**, an Administrative Officer in NIDA's Office of Management Analysis Branch, left NIDA on May 20 for a position at the National Cancer Institute.

### **Retirements**

**Stuart Berlin** retired on September 9 after working 5 years in the NIDA Office of Management, Information Resource Management Branch, as an IT Specialist/Project Manager. Stuart played a vital role in the automation and modernization of several NIDA legacy applications, NIDA's migration to the Microsoft Office 365 Cloud environment, and several projects that resulted in key cost savings and cost avoidance for the Institute.

**Stephen J. Heishman, Ph.D.**, Director, Office of Education and Career Development at the NIDA IRP, retired on June 30. Steve joined the NIDA IRP as a Staff Fellow in the Clinical Pharmacology

Branch in 1988 and was tenured in 1991, becoming Chief, of the Nicotine Psychopharmacology Section. In 1999, Steve took on the role of our first Training Director and in 2011, he officially created the Office of Education and Career Development.

**Cheryl Nathaniel** retired from NIDA's Grants Management Branch after more than 30 years of Federal Service, on August 25.



National Institute  
on Drug Abuse