



DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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Director
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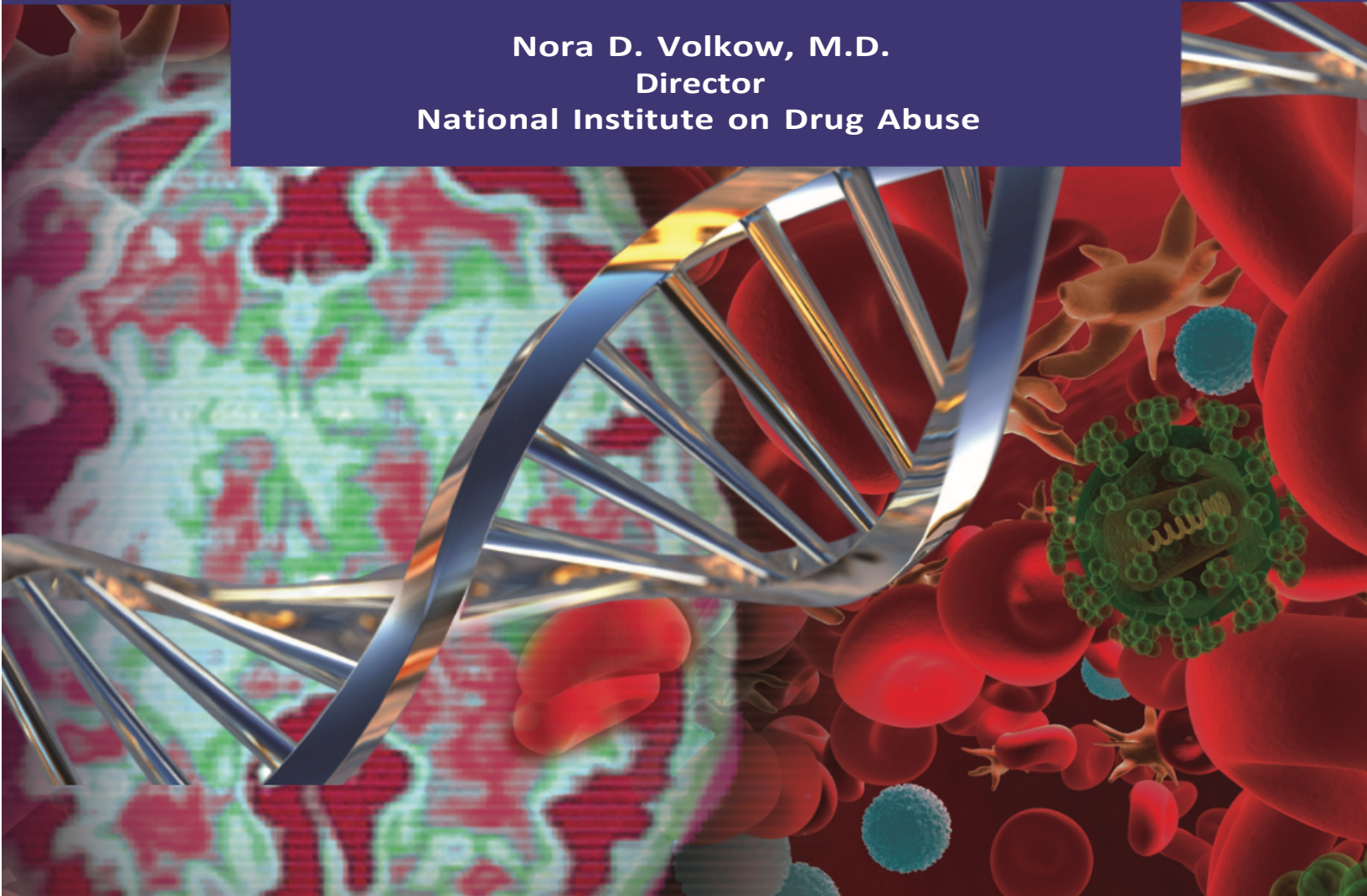


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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Structures Of The Entire Human Opioid Receptor Family Wang Y, Zhuang Y, DiBerto JF, Zhou XE, Schmitz GP, Yuan Q, Jain MK, Liu W, Melcher K, Jiang Y, Roth BL, Xu HE. Cell. January 19, 2023; 186(2): 413-427.

Opioids are effective analgesics, but their use is beset by serious side effects, including addiction and respiratory depression, which contribute to the ongoing opioid crisis. The human opioid system contains four opioid receptors (μ OR, δ OR, κ OR, and NOPR) and a set of related endogenous opioid peptides (EOPs), which show distinct selectivity toward their respective opioid receptors (ORs). Despite being key to the development of safer analgesics, the mechanisms of molecular recognition and selectivity of EOPs to ORs remain unclear. Here, we systematically characterize the binding of EOPs to ORs and present five structures of EOP-OR-Gi complexes, including β -endorphin- and endomorphin-bound μ OR, deltorphin-bound δ OR, dynorphin-bound κ OR, and nociceptin-bound NOPR. These structures, supported by biochemical results, uncover the specific recognition and selectivity of opioid peptides and the conserved mechanism of opioid receptor activation. These results provide a structural framework to facilitate rational design of safer opioid drugs for pain relief.

High Frequency DBS-Like Optogenetic Stimulation Of Nucleus Accumbens Dopamine D2 Receptor-Containing Neurons Attenuates Cocaine Reinstatement In Male Rats

Swinford-Jackson SE, Huffman PJ, Knouse MC, Thomas AS, Rich MT, Mankame S, Worobey SJ, Sarmiento M, Coleman A, Pierce RC. Neuropsychopharmacology. February 2023; 48(3): 459-467.

Previous work indicated that deep brain stimulation (DBS) of the nucleus accumbens shell in male rats attenuated reinstatement of cocaine seeking, an animal model of craving. However, the potential differential impact of DBS on specific populations of neurons to drive the suppression of cocaine seeking is unknown. Medium spiny neurons in the nucleus accumbens are differentiated by expression of dopamine D1 receptors (D1DRs) or D2DRs, activation of which promotes or inhibits cocaine-related behaviors, respectively. The advent of transgenic rat lines expressing Cre recombinase selectively in D1DR-containing or D2DR-containing neurons, when coupled with Cre-dependent virally mediated gene transfer of channelrhodopsin (ChR2), enabled mimicry of DBS in a selective subpopulation of neurons during complex tasks. We tested the hypothesis that high frequency DBS-like optogenetic stimulation of D1DR-containing neurons in the accumbens shell would potentiate, whereas stimulation of D2DR-containing neurons in the accumbens shell would attenuate, cocaine-primed reinstatement of cocaine seeking. Results indicated that high frequency, DBS-like optogenetic stimulation of D2DR-containing neurons attenuated reinstatement of cocaine seeking in male rats, whereas DBS-like stimulation of D1DR-containing neurons did not alter cocaine-primed reinstatement. Surprisingly, DBS-like optogenetic stimulation did not alter reinstatement of cocaine seeking in female rats. In rats which only expressed eYFP, intra-accumbens optogenetic stimulation did not alter cocaine reinstatement, indicating that the effect of DBS-like stimulation to attenuate cocaine reinstatement is mediated specifically by ChR2 rather than by prolonged light delivery. These results suggest that DBS of the accumbens may attenuate cocaine-primed reinstatement in male rats through the selective manipulation of D2DR-containing neurons.

An Optimized Bioluminescent Substrate For Non-Invasive Imaging In The Brain Su Y, Walker JR, Hall MP, Klein MA, Wu X, Encell LP, Casey KM, Liu LX, Hong G, Lin MZ, Kirkland TA. Nat Chem Biol. February 9, 2023. Online ahead of print.

Bioluminescence imaging (BLI) allows non-invasive visualization of cells and biochemical events in vivo and thus has become an indispensable technique in biomedical research. However, BLI in the central nervous system remains challenging because luciferases show relatively poor performance in the brain with existing substrates. Here, we report the discovery of a NanoLuc substrate with improved brain performance, cephalofurimazine (CFz). CFz paired with Antares luciferase produces greater than 20-fold more signal from the brain than the standard combination of D-luciferin with firefly luciferase. At standard doses, Antares-CFz matches AkaLuc-AkaLuc/TokeOni in brightness, while occasional higher dosing of CFz can be performed to obtain threefold more signal. CFz should allow the growing number of NanoLuc-based indicators to be applied to the brain with high sensitivity. Using CFz, we achieve video-rate non-invasive imaging of Antares in brains of freely moving mice and demonstrate non-invasive calcium imaging of sensory-evoked activity in genetically defined neurons.

Multivariate Genome-Wide Association Meta-Analysis Of Over 1 Million Subjects Identifies Loci Underlying Multiple Substance Use Disorders

Hatoum AS, Colbert SMC, Johnson EC, Huggett SB, Deak JD, Pathak GA, Jennings MV, Paul SE, Karcher NR, Hansen I, Baranger DAA, Edward A, Grotzinger AD, Substance Use Disorder Working Group of the Psychiatric Genomics Consortium, Tucker-Drob, E, Kranzler HR, Davis LK, Sabchez-Roige S, Polimanti R, Gelernter J, Edenberg, HJ, Bogdan R, Agrawal A. Nature Mental Health. March 22, 2023; 1: 210–223.

Genetic liability to substance use disorders can be parsed into loci that confer general or substance-specific addiction risk. We report a multivariate genome-wide association meta-analysis that disaggregates general and substance-specific loci from published summary statistics of problematic alcohol use, problematic tobacco use, cannabis use disorder and opioid use disorder in a sample of 1,025,550 individuals of European descent and 92,630 individuals of African descent. Nineteen independent single-nucleotide polymorphisms were genome-wide significant ($P < 5 \times 10^{-8}$) for the general addiction risk factor (addiction-rf), which showed high polygenicity. Across ancestries, PDE4B was significant (among other genes), suggesting dopamine regulation as a cross-substance vulnerability. An addiction-rf polygenic risk score was associated with substance use disorders, psychopathologies, somatic conditions and environments associated with the onset of addictions. Substance-specific loci (9 for alcohol, 32 for tobacco, 5 for cannabis and 1 for opioids) included metabolic and receptor genes. These findings provide insight into genetic risk loci for substance use disorders that could be leveraged as treatment targets.

Adaptations In Nucleus Accumbens Neuron Subtypes Mediate Negative Affective Behaviors In Fentanyl Abstinence

Fox ME, Wulff AB, Franco D, Choi EY, Calarco CA, Engeln M, Turner MD, Chandra R, Rhodes VM, Thompson SM, Ament SA, Lobo MK. Biol Psychiatry. March 15, 2023; 93(6): 489-501.

BACKGROUND: Opioid discontinuation generates a withdrawal syndrome marked by increased negative affect. Increased symptoms of anxiety and dysphoria during opioid discontinuation are significant barriers to achieving long-term abstinence in opioid-dependent individuals. While adaptations in the nucleus accumbens are implicated in opioid abstinence syndrome, the precise neural mechanisms are poorly understood. Additionally, our current knowledge is limited to changes following natural and semisynthetic opioids, despite recent increases in synthetic opioid use and overdose. METHODS: We used a combination of cell subtype-specific viral labeling and electrophysiology in male and female mice to investigate structural and functional plasticity in

nucleus accumbens medium spiny neuron (MSN) subtypes after fentanyl abstinence. We characterized molecular adaptations after fentanyl abstinence with subtype-specific RNA sequencing and weighted gene co-expression network analysis. We used viral-mediated gene transfer to manipulate the molecular signature of fentanyl abstinence in D1-MSNs. RESULTS: Here, we show that fentanyl abstinence increases anxiety-like behavior, decreases social interaction, and engenders MSN subtype-specific plasticity in both sexes. D1-MSNs, but not D2-MSNs, exhibit dendritic atrophy and an increase in excitatory drive. We identified a cluster of coexpressed dendritic morphology genes downregulated selectively in D1-MSNs that are transcriptionally coregulated by E2F1. E2f1 expression in D1-MSNs protects against loss of dendritic complexity, altered physiology, and negative affect-like behaviors caused by fentanyl abstinence. CONCLUSIONS: Our findings indicate that fentanyl abstinence causes unique structural, functional, and molecular changes in nucleus accumbens D1-MSNs that can be targeted to alleviate negative affective symptoms during abstinence.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Enhancing Use Of Medications For Opioid Use Disorder Through External Coaching

Molfenter T, Kim H, Kim JS, Kisicki A, Knudsen HK, Horst J, Brown R, Madden LM, Toy A, Haram E, Jacobson N. Psychiatr Serv. March 1, 2023; 74(3): 265-271.

This randomized controlled trial tested whether external coaching influences addiction treatment providers' utilization of medications to treat opioid use disorder (MOUDs). Methods: This study recruited 75 unique clinical sites in Florida, Ohio, and Wisconsin, including 61 sites in specialty treatment agencies and 14 behavioral health sites within health systems. The trial used external coaching to increase use of MOUDs in the context of a learning collaborative and compared it with no coaching and no learning collaborative (control condition). Outcome measures of MOUD capacity and utilization were monthly tabulations of licensed buprenorphine slots (i.e., the number of patients who could be treated based on the buprenorphine waiver limits of the site's providers), buprenorphine use, and injectable naltrexone administration. Results: The coaching and control arms showed no significant difference at baseline. Although buprenorphine slots increased in both arms during the 30-month trial, growth increased twice as fast at the coaching sites, compared with the control sites (average monthly rate of 6.1% vs. 3.0%, respectively, $p,0.001$). Buprenorphine use showed a similar pattern; the monthly growth rate in the coaching arm was more than twice the rate in the control arm (5.3% vs. 2.4%, $p,0.001$). Coaching did not have an impact on injectable naltrexone, which grew less than 1% in both arms over the trial period. Conclusions: External coaching can increase organizational capacity for and growth of buprenorphine use. Future research should explore the dimensions of coaching practice, dose, and delivery modality to better understand and enhance the coaching function.

Population-Based Opioid Prescribing And Overdose Deaths In The USA: An Observational Study Olfson M, Waidmann T, King M, Pancini V, Schoenbaum M. J Gen Intern Med. February 2023; 38(2): 390-398.

Rising opioid-related death rates have prompted reductions of opioid prescribing, yet limited data exist on population-level associations between opioid prescribing and opioid-related deaths. To evaluate population-level associations between five opioid prescribing measures and opioid-related deaths. An ecological panel analysis was performed using linear regression models with year and commuting zone fixed effects. People ≥ 10 years aggregated into 886 commuting zones, which are geographic regions collectively comprising the entire USA. Annual opioid prescriptions were

measured with IQVIA Real World Longitudinal Prescription Data including 76.5% (2009) to 90.0% (2017) of US prescriptions. Prescription measures included opioid prescriptions per capita, percent of population with ≥ 1 opioid prescription, percent with high-dose prescription, percent with long-term prescription, and percent with opioid prescriptions from ≥ 3 prescribers. Outcomes were age- and sex-standardized associations of change in opioid prescriptions with change in deaths involving any opioids, synthetics other than methadone, heroin but not synthetics or methadone, and prescription opioids, but not other opioids. Change in total regional opioid-related deaths was positively correlated with change in regional opioid prescriptions per capita ($\beta=.110$, $p<.001$), percent with ≥ 1 opioid prescription ($\beta=.100$, $p=.001$), and percent with high-dose prescription ($\beta=.081$, $p<.001$). Change in total regional deaths involving prescription opioids was positively correlated with change in all five opioid prescribing measures. Conversely, change in total regional deaths involving synthetic opioids was negatively correlated with change in percent with long-term opioid prescriptions and percent with ≥ 3 prescribers, but not for persons ≥ 45 years. Change in total regional deaths in heroin was not associated with change in any prescription measure. Regional decreases in opioid prescriptions were associated with declines in overdose deaths involving prescription opioids but were also associated with increases in deaths involving synthetic opioids (primarily fentanyl). Individual-level inferences are limited by the ecological nature of the analysis.

Adult Use Of Highly-Potent $\Delta 9$ -THC Cannabis Concentrate Products By U.S. State Cannabis Legalization Status, 2021

Hasin DS, Borodovsky J, Shmulewitz D, Walsh C, Struble CA, Livne O, Habib MI, Fink DS, Aharonovich E, Budney A. *Addict Behav.* May 2023; 140: 107617.

Background: Compared to plant/flower cannabis products, cannabis concentrates have higher average potency of delta-9-tetrahydrocannabinol ($\Delta 9$ -THC), which may be associated with greater likelihood of cannabis-related harms. Information on factors associated with use of cannabis concentrates is needed.

Methods: Respondents were 4,328 adult past-7-day cannabis users from all 50 U.S. states and Washington DC (DC) who participated in an online 2021 survey. Using logistic regression to generate adjusted odds ratios (aOR), we investigated whether participants in states that enacted recreational cannabis laws (RCL, 12 states plus DC [treated as a state], $n = 1,236$) or medical cannabis laws (MCL-only, 23 states, $n = 2,030$) by December 31, 2020 were more likely than those in states without cannabis laws (no-CL, 15 states, $n = 1,062$) to use cannabis concentrate products in the prior 7 days. Results: Most participants (92.4%) used plant material in the prior 7 days; 57.0% used cannabis concentrates. In RCL, MCL and no-CL states, concentrate use was reported by 61.5%, 56.6%, and 52.5%, respectively. Compared to participants in no-CL states, odds of using cannabis concentrate products were greater among those in RCL states (aOR = 1.47; CI = 1.17-1.84) and MCL-only states (aOR = 1.29; CI = 1.08-1.55). Whether states had legally-authorized dispensaries had little effect on results. Conclusion: Results suggest that individuals in MCL-only and RCL states are more likely to use cannabis concentrate products. Determining mechanisms underlying these results, e.g., commercialization, could provide important information for prevention. Clinicians should be alert to patient use of concentrates, especially in MCL-only and RCL states. Continued monitoring is warranted as additional states legalize cannabis use.

Familias Unidas Prevents Youth Internalizing Symptoms: A Baseline Target Moderated Mediation (BTMM) Study

Brincks A, Perrino T, Howe G, Estrada Y, Robles N, Prado G. *Prev Sci.* February 2023; 24(2): 204-213.

Abstract: Family-based preventive interventions have been found to prevent youth internalizing symptoms, yet they operate through diverse mechanisms with heterogeneous effects for different youth. To better target preventive interventions, this study examines the effects of the Familias

Unidas preventive intervention on reducing internalizing symptoms with a universal sample of Hispanic youth in a real-world school setting (i.e., effectiveness trial). The study utilizes emerging methods in baseline target moderated mediation (BTMM) to determine whether the intervention reduces internalizing symptoms through its impact on three distinct mechanisms: family functioning, parent stress, and social support for parents. Data are from a randomized controlled effectiveness trial of 746 Hispanic eighth graders and their parents assessed at baseline, 6-, 18-, and 30-month post-baseline. BTMM models examined three moderated mechanisms through which the intervention might influence 30-month adolescent internalizing symptoms. The intervention decreased youth internalizing symptoms through improvements in family functioning in some models, but there was no evidence of moderation by baseline level of family functioning. There was some evidence of mediation through increasing social support for parents for those intervention parents presenting with lower baseline support. However, there was no evidence of mediation through parent stress. Post hoc analyses suggest a possible cascading of effects where improvements in support for parents strengthened parental monitoring of youth and ultimately reduced youth internalizing symptoms. Findings support the intervention's effects on internalizing symptoms in a universal, real-world setting, and the value of BTMM methods to improve the targeting of preventive interventions.

[ED-Home: Pilot Feasibility Study Of A Targeted Homelessness Prevention Intervention For Emergency Department Patients With Drug Or Unhealthy Alcohol Use](#) Fazio D, Zuiderveen S, Guyet D, Reid A, Lalane M, McCormack RP, Wall SP, Shelley D, Mijanovich T, Shinn M, Doran KM. Acad Emerg Med. December 2022; 29(12): 1453-1465.

Background: Housing insecurity is prevalent among emergency department (ED) patients. Despite a surge of interest in screening for patients' social needs including housing insecurity, little research has examined ED social needs interventions. We worked together with government and community partners to develop and pilot test a homelessness prevention intervention targeted to ED patients with drug or unhealthy alcohol use.

Methods: We approached randomly sampled patients at an urban public hospital ED, May to August 2019. Adult patients were eligible if they were medically stable, not incarcerated, spoke English, had unhealthy alcohol or any drug use, and were not currently homeless but screened positive for risk of future homelessness using a previously developed risk screening tool. Participants received a three-part intervention: (1) brief counseling and referral to treatment for substance use delivered through a preexisting ED program; (2) referral to Homebase, an evidence-based community homelessness prevention program; and (3) up to three troubleshooting phone calls by study staff. Participants completed surveys at baseline and 6 months. **Results:** Of 2183 patients screened, 51 were eligible and 40 (78.4%) participated; one later withdrew, leaving 39 participants. Participants were diverse in age, gender, race, and ethnicity. Of the 32 participants reached at 6 months, most said it was very or extremely helpful to talk to someone about their housing situation (n = 23, 71.9%) at the baseline ED visit. Thirteen (40.6%) said their housing situation had improved in the past 6 months and 16 (50.0%) said it had not changed. Twenty participants (62.5%) had made contact with a Homebase office. Participants shared ideas of how to improve the intervention. **Conclusions:** This pilot intervention was feasible and well received by participants though it required a large amount of screening to identify potentially eligible patients. Our findings will inform a larger future trial and may be informative for others seeking to develop similar interventions.

“We Want Everything In A One-Stop Shop”: Acceptability And Feasibility Of PrEP And Buprenorphine Implementation With Mobile Syringe Services For Black People Who Inject Drugs Bartholomew TS, Andraka-Cristou B, Totaram RK, Harris S, Doblecki-Lewis S, Ostrer L, Serota DP, Forrest DW, Chueng TA, Suarez E, Tookes HE. Harm Reduct J. December 3, 2022; 19(1): 133.

A recent surge in HIV outbreaks, driven by the opioid and stimulant use crises, has destabilized our progress toward targets set forth by Ending the HIV Epidemic: A Plan for America for the high-priority community of people who inject drugs (PWID), particularly Black PWID. In order to ascertain the acceptability and feasibility of using a mobile syringe services program (SSP) for comprehensive HIV prevention via PrEP and medications for opioid use disorder (MOUD), our mixed methods approach included a quantitative assessment and semi-structured qualitative interviews with Black PWID (n = 30) in Miami-Dade County who were actively engaged in mobile syringe services. Participants felt that delivery of MOUD and PrEP at a mobile SSP would be both feasible and acceptable, helping to address transportation, cost, and stigma barriers common within traditional healthcare settings. Participants preferred staff who are compassionate and nonjudgmental and have lived experience. A mobile harm reduction setting could be an effective venue for delivering comprehensive HIV prevention services to Black PWID, a community that experiences significant barriers to care via marginalization and racism in a fragmented healthcare system.

TREATMENT RESEARCH

Attenuation Of The Positive-Reinforcing Effects Of Ultra-Potent Fentanyl Analogs, Along With Those Of Fentanyl And Heroin, During Daily Treatment With Methocinnamox In Rhesus Monkeys Gerak LR, France CP. J Pharmacol Exp Ther. March 2023; 384(3): 363-371.

Without substantial intervention, the opioid crisis is projected to continue, underscoring the need to develop new treatments for opioid use disorder (OUD). One drug under development is the μ opioid receptor antagonist methocinnamox (MCAM), which appears to offer advantages over currently available medications; however, some questions remain about its potential utility, including its ability to block the effects of ultra-potent fentanyl analogs. The goal of this study was to examine its effectiveness in attenuating the abuse-related effects of the fentanyl analogs carfentanil and 3-methylfentanyl in monkeys responding for food or intravenous infusions under a choice procedure. These drugs were compared with fentanyl, heroin, methamphetamine, and cocaine. Food was preferred over saline, and there was a dose-dependent increase in responding for drug over food with no marked decrease in response rates or number of choice trials completed for any of the six drugs studied. Naltrexone (0.032 mg/kg) antagonized choice of μ opioid receptor agonists, producing rightward shifts in dose-effect curves ranging from 27-fold (carfentanil) to 71-fold (heroin). In contrast, naltrexone was less effective in attenuating choice of methamphetamine or cocaine with curves obtained in the presence of naltrexone shifted.

Interactive Effects Of M-Opioid And Adrenergic- α 2 Receptor Agonists In Rats: Pharmacological Investigation Of The Primary Kratom Alkaloid Mitragynine And Its Metabolite 7-Hydroxymitragynine Obeng S, Leon F, Patel A, et al. Interactive Effects of μ -Opioid and Adrenergic- α 2 Receptor Agonists in Rats: Pharmacological Investigation of the Primary Kratom Alkaloid Mitragynine and Its Metabolite 7-Hydroxymitragynine. J Pharmacol Exp Ther. December 2022; 383(3): 182-198.

The primary kratom alkaloid mitragynine is proposed to act through multiple mechanisms, including actions at μ -opioid receptors (MORs) and adrenergic- α 2 receptors ($A\alpha$ 2Rs), as well as conversion in vivo to a MOR agonist metabolite (i.e., 7-hydroxymitragynine). $A\alpha$ 2R and MOR agonists can produce antinociceptive synergism. Here, contributions of both receptors to produce mitragynine-related effects were assessed by measuring receptor binding in cell membranes and, in rats, pharmacological behavioral effect antagonism studies. Mitragynine displayed binding affinity at both receptors, whereas 7-hydroxymitragynine only displayed MOR binding affinity. Compounds were tested for their capacity to decrease food-maintained responding and rectal temperature and to produce antinociception in a hotplate test. Prototypical MOR agonists and 7-hydroxymitragynine, but not mitragynine, produced antinociception. MOR agonist and 7-hydroxymitragynine rate-decreasing and antinociceptive effects were antagonized by the opioid antagonist naltrexone but not by the $A\alpha$ 2R antagonist yohimbine. Hypothermia only resulted from reference $A\alpha$ 2R agonists. The rate-decreasing and hypothermic effects of reference $A\alpha$ 2R agonists were antagonized by yohimbine but not naltrexone. Neither naltrexone nor yohimbine antagonized the rate-decreasing effects of mitragynine. Mitragynine and 7-hydroxymitragynine increased the potency of the antinociceptive effects of $A\alpha$ 2R but not MOR reference agonists. Only mitragynine produced hypothermic effects. Isobolographic analyses for the rate-decreasing effects of the reference $A\alpha$ 2R and MOR agonists were also conducted. These results suggest mitragynine and 7-hydroxymitragynine may produce antinociceptive synergism with $A\alpha$ 2R and MOR agonists. When combined with $A\alpha$ 2R agonists, mitragynine could also produce hypothermic synergism. SIGNIFICANCE STATEMENT: Mitragynine is proposed to target the μ -opioid receptor (MOR) and adrenergic- α 2 receptor ($A\alpha$ 2R) and to produce behavioral effects through conversion to its MOR agonist metabolite 7-hydroxymitragynine. Isobolographic analyses indicated supra-additivity in some dose ratio combinations. This study suggests mitragynine and 7-hydroxymitragynine may produce antinociceptive synergism with $A\alpha$ 2R and MOR agonists. When combined with $A\alpha$ 2R agonists, mitragynine could also produce hypothermic synergism.

Effects Of 2,5-Dimethoxy-4-Methylamphetamine (DOM) And 2-Piperazin-1-yl-Quinoline (Quipazine) On Fentanyl Versus Food Choice In Rhesus Monkeys Maguire DR. J Pharmacol Exp Ther. January 2023; 384(1): 155-162.

There has been increasing interest in the potential therapeutic effects of drugs with agonist properties at serotonin 2A subtype (5-HT_{2A}) receptors (e.g., psychedelics), including treatment of substance use disorders. Studying interactions between 5-HT_{2A} receptor agonists and other drugs is important for understanding potential therapeutic effects as well as adverse interactions. Direct-acting 5-HT_{2A} receptor agonists such as 2,5-dimethoxy-4-methylamphetamine (DOM) and 2-piperazin-1-yl-quinoline (quipazine) enhance some (e.g., antinociceptive) effects of opioids; however, it is unclear whether they alter the abuse-related effects of opioids. This study examined whether DOM and quipazine alter the reinforcing effects of fentanyl in rhesus monkeys (n = 6) responding under a food versus drug choice procedure. Responding on one lever delivered sucrose pellets and responding on the other lever delivered intravenous (i.v.) infusions. In one set of experiments, fentanyl (0.1-3.2 μ g/kg/infusion) versus food choice sessions were preceded by noncontingent i.v. pretreatments with DOM (0.032-0.32 mg/kg), quipazine (0.32-1.0 mg/kg), naltrexone (0.032 mg/kg), or heroin (0.1 mg/kg). In another set of experiments, fentanyl was available during choice sessions in combination with DOM (0.32-100 μ g/kg/infusion) or quipazine (3.2-320 μ g/kg/infusion) in varying dose ratios. Naltrexone decreased and heroin increased fentanyl choice, demonstrating sensitivity of responding to pharmacological manipulation. However, whether given as a pretreatment or made available in combination with fentanyl as a mixture, neither DOM nor quipazine significantly altered fentanyl choice. These results suggest that 5-HT_{2A}

receptor agonists do not enhance the reinforcing effects of opioids and, thus, will not likely enhance abuse potential. SIGNIFICANCE STATEMENT: Serotonin 2A subtype receptor agonists enhance some (e.g., antinociceptive) effects of opioids, suggesting they could be combined with opioids in some therapeutic contexts such as treating pain. However, it is unclear whether they also enhance adverse effects of opioids, including abuse. Results of this study indicate that serotonin 2A subtype receptor agonists do not reliably enhance opioid self-administration and, thus, are unlikely to enhance the abuse potential of opioids.

Effects Of Methadone, Buprenorphine, And Naltrexone On Actigraphy-Based Sleep-Like Parameters In Male Rhesus Monkeys Berro LF, Zamarripa CA, Talley JT, Freeman KB, Rowlett JK. *Addict Behav.* December 2022; 135: 107433.

Opioid use disorder (OUD) has been associated with the emergence of sleep disturbances. Although effective treatments for OUD exist, evidence suggests that these treatments also may be associated with sleep impairment. The extent to which these effects are an effect of OUD treatment or a result of chronic opioid use remains unknown. We investigated the acute effects of methadone, buprenorphine, and naltrexone on actigraphy-based sleep-like parameters in non-opioid-dependent male rhesus monkeys (*Macaca mulatta*, $n = 5$). Subjects were fitted with actigraphy monitors attached to primate collars to measure sleep-like parameters. Actigraphy recordings were conducted under baseline conditions, or following acute injections of vehicle, methadone (0.03-1.0 mg/kg, i.m.), buprenorphine (0.01-1.0 mg/kg, i.m.), or naltrexone (0.03-1.0 mg/kg, i.m.) in the morning (4 h after "lights on") or in the evening (1.5 h before "lights off"). Morning and evening treatments with methadone or buprenorphine significantly increased sleep latency and decreased sleep efficiency. The effects of buprenorphine on sleep-like measures resulted in a biphasic dose-response function, with the highest doses not disrupting actigraphy-based sleep. Buprenorphine induced a much more robust increase in sleep latency and decrease in sleep efficiency compared to methadone, particularly with evening administration, and detrimental effects of buprenorphine on sleep-like measures were observed up to 25.5 h after drug injection. Treatment with naltrexone, on the other hand, significantly improved sleep-like measures, with evening treatments improving both sleep latency and sleep efficiency. The currently available pharmacotherapies for OUD significantly alter sleep-like parameters in non-opioid-dependent monkeys, and opioid-dependent mechanisms may play a significant role in sleep-wake regulation.

Choice Between Food And Cocaine Reinforcers Under Fixed And Variable Schedules In Female And Male Rhesus Monkeys Zamarripa CA, Doyle WS, Freeman KB, Rowlett JK, Huskinson SL. *Exp Clin Psychopharmacol.* February 2023; 31(1): 204-218.

Illicit drugs like cocaine may be uncertain in terms of the time and effort required to obtain them. Behavior maintained by variable schedules resembles excessive drug-taking compared with fixed schedules. However, no prior research has examined fixed versus variable schedules in drug versus nondrug choice. The present study evaluated cocaine versus food choice under fixed- (FR) and variable-ratio (VR) schedules. The simpler food versus food and cocaine versus cocaine arrangements also were included. Adult female ($n = 6$) and male ($n = 7$) rhesus monkeys chose between cocaine (0.01-0.18 mg/kg/injection) and food (4 pellets/delivery), food and food (4 pellets/delivery), or cocaine and cocaine (0.018-0.03 mg/kg/injection) under FR and VR 100 and 200 schedules. In cocaine versus food choice, cocaine's potency to maintain choice was greatest when available under a VR 100 or 200 schedule and food under an FR schedule and was lowest when cocaine was available under an FR 200 schedule and food was available under a VR 200 schedule. In food versus food choice, males chose food associated with a VR schedule more than food associated with an FR schedule. In cocaine versus cocaine choice, females and males chose

cocaine associated with a VR schedule more than cocaine associated with an FR schedule, particularly under VR 200. These findings suggest that uncertainty in terms of time and effort required to obtain cocaine, or perhaps the occasional low-cost access that results from VR schedules, results in greater allocation of behavior toward drug reinforcers at the expense of more certain, nondrug alternatives.

[A Humanized Anti-Cocaine MAb Antagonizes The Cardiovascular Effects Of Cocaine In Rats](#)

Koch SE, Marckel JA, Rubinstein J, Norman AB. *Pharmacol Res Perspect*. February 2023; 11(1): e01045.

The recombinant monoclonal anti-cocaine antibody, h2E2, sequesters cocaine in plasma increasing concentrations more than 10-fold. The increased levels of cocaine in the plasma could have detrimental peripheral effects, particularly on the cardiovascular system. We investigated the duration and magnitude of the effect of cocaine on the rat heart, and if h2E2 could antagonize that effect. Echocardiography was used to evaluate cardiac function under isoflurane anesthesia, while a tail-cuff was used to measure blood pressure. Cocaine was delivered intravenously and the rats were continuously monitored for a total of 45 min. Echocardiography measurements were recorded every 5 min and blood pressure measurements were recorded throughout the duration of the experiment using 30-s cycles. ECG recordings were taken simultaneously with the echocardiography measurements. An increase in ejection fraction was seen after the cocaine push with the maximum change occurring at 25 min. Treatment with h2E2 1 h before the cocaine push did not have any effect on cardiac parameters. Subsequent cocaine treatment had no effect on the ejection fraction, indicating that the antibody-bound cocaine does not affect the heart. This antagonism of cocaine's effects was greatly decreased after 1 week and entirely absent after 1 month. Cocaine in the presence of h2E2 is pharmacologically inert and h2E2 may have additional clinical utility for reversing cocaine effects on the cardiovascular system.

[Catalytic Activities Of A Highly Efficient Cocaine Hydrolase For Hydrolysis Of Biologically Active Cocaine Metabolites Norcocaine And Benzoyllecgonine](#)

Shang L, Jin Z, Wei H, Park S, Zhan C-G, Zheng, F. *Sci Rep*. January 2023; 13(1): 640.

Cocaine is a widely abused, hepatotoxic drug without an FDA-approved pharmacotherapy specific for cocaine addiction or overdose. It is recognized as a promising therapeutic strategy to accelerate cocaine metabolism which can convert cocaine to pharmacologically inactive metabolite(s) using an efficient cocaine-metabolizing enzyme. Our previous studies have successfully designed and discovered a highly efficient cocaine hydrolase, denoted as Coch5-Fc(M6), capable of rapidly hydrolyzing cocaine at the benzoyl ester moiety. In the present study, we determined the kinetic parameters of Coch5-Fc(M6) against norcocaine ($k_{cat} = 9,210 \text{ min}^{-1}$, $K_M = 20.9 \text{ }\mu\text{M}$, and $k_{cat}/K_M = 1.87 \times 10^5 \text{ min}^{-1} \text{ M}^{-1}$) and benzoyllecgonine ($k_{cat} = 158 \text{ min}^{-1}$, $K_M = 286 \text{ }\mu\text{M}$, and $k_{cat}/K_M = 5.5 \times 10^5 \text{ min}^{-1} \text{ M}^{-1}$) for the first time. Further in vivo studies have demonstrated that Coch5-Fc(M6) can effectively accelerate clearance of not only cocaine, but also norcocaine (known as a cocaine metabolite which is more toxic than cocaine itself) and benzoyllecgonine (known as an unfavorable long-lasting metabolite with some long-term toxicity concerns) in rats. Due to the desired high catalytic activity against norcocaine, Coch5-Fc(M6) is capable of quickly detoxifying both cocaine and its more toxic metabolite norcocaine after intraperitoneally administering lethal dose of 60 or 180 mg/kg cocaine. In addition, the ability of Coch5-Fc(M6) to accelerate clearance of benzoyllecgonine should also be valuable for the use of Coch5-Fc(M6) in treatment of cocaine use disorder.

Characterization Of A Potential KOR/DOR Dual Agonist With No Apparent Abuse Liability Via A Complementary Structure-Activity Relationship Study On Nalfurafine Analogues

Li M, Stevens DL, Arriaga M, Townsend EA, Mendez RE, Blajkevch NA, Selley DE, Banks ML, Negus SS, Dewey WL, Zhang Y. ACS Chem Neurosci. December 2022; 13(24): 3608-3628.

Discovery of analgesics void of abuse liability is critical to battle the opioid crisis in the United States. Among many strategies to achieve this goal, targeting more than one opioid receptor seems promising to minimize this unwanted side effect while achieving a reasonable therapeutic profile. In the process of understanding the structure-activity relationship of nalfurafine, we identified a potential analgesic agent, NMF, as a dual kappa opioid receptor/delta opioid receptor agonist with minimum abuse liability. Further characterizations, including primary in vitro ADMET studies (hERG toxicity, plasma protein binding, permeability, and hepatic metabolism), and in vivo pharmacodynamic and toxicity profiling (time course, abuse liability, tolerance, withdrawal, respiratory depression, body weight, and locomotor activity) further confirmed NMF as a promising drug candidate for future development.

Wireless Electroencephalography (EEG) To Monitor Sleep Among Patients Being Withdrawn From Opioids: Evidence Of Feasibility And Utility

Dunn KE, Finan PH, Huhn AS, Gamaldo C, Bergeria CL, Strain EC. Exp Clin Psychopharmacol. December 2022; 30(6): 1016-1023.

Sleep impairment is a common comorbid and debilitating symptom for persons with opioid use disorder (OUD). Research into underlying mechanisms and efficacious treatment interventions for OUD-related sleep problems requires both precise and physiologic measurements of sleep-related outcomes and impairment. This pilot examined the feasibility of a wireless sleep electroencephalography (EEG) monitor (Sleep Profiler™) to measure sleep outcomes and architecture among participants undergoing supervised opioid withdrawal. Sleep outcomes were compared to a self-reported sleep diary and opioid withdrawal ratings. Participants (n = 8, 100% male) wore the wireless EEG 85.6% of scheduled nights. Wireless EEG detected measures of sleep architecture including changes in total, NREM and REM sleep time during study phases, whereas the diary detected changes in wakefulness only. Direct comparisons of five overlapping outcomes revealed lower sleep efficiency and sleep onset latency and higher awakenings and time spent awake from the wireless EEG versus sleep diary. Associations were evident between wireless EEG and increased withdrawal severity, lower sleep efficiency, less time in REM and non-REM stages 1 and 2, and more hydroxyzine treatment; sleep diary was associated with total sleep time and withdrawal only. Data provide initial evidence that a wireless EEG is a feasible and useful tool for objective monitoring of sleep in persons experiencing acute opioid withdrawal. Data are limited by the small and exclusively male sample, but provide a foundation for using wireless EEG sleep monitors for objective evaluation of sleep-related impairment in persons with OUD in support of mechanistic and treatment intervention research.

Neuroeconomic Predictors Of Smoking Cessation Outcomes: A Preliminary Study Of Delay Discounting In Treatment-Seeking Adult Smokers

Amlung M, Owens MM, Hargreaves T, Gray JC, Murphy CM, MacKillop J, Sweet LH. Psychiatry Res Neuroimaging. December 2022; 327: 111555.

Large proportions of smokers are unsuccessful in evidence-based smoking cessation treatment and identifying prognostic predictors may inform improvements in treatment. Steep discounting of delayed rewards (delay discounting) is a robust predictor of poor smoking cessation outcome, but the underlying neural predictors have not been investigated. Forty-one treatment-seeking adult smokers completed a functional magnetic resonance imaging (fMRI) delay discounting paradigm

prior to initiating a 9-week smoking cessation treatment protocol. Behavioral performance significantly predicted treatment outcomes (verified 7-day abstinence, $n = 18$; relapse, $n = 23$). Participants in the relapse group exhibited smaller area under the curve ($d = 1.10$) and smaller AUC was correlated with fewer days to smoking relapse ($r = 0.56$, $p < 0.001$) Neural correlates of discounting included medial and dorsolateral prefrontal cortex, posterior cingulate, precuneus and anterior insula, and interactions between choice type and relapse status were present for the dorsolateral prefrontal cortex, precuneus and the striatum. This initial investigation implicates differential neural activity in regions associated with frontal executive and default mode activity, as well as motivational circuits. Larger samples are needed to improve the resolution in identifying the neural underpinnings linking steep delay discounting to smoking cessation.

[A Phase 1b Study To Investigate The Potential Interactions Between ASP8062 And Buprenorphine/Naloxone In Patients With Opioid Use Disorder](#)

Ito M, Walzer M, Blauwet MB, Spence A, Heo N, Kelsh D, Blahunka P, Erdman J, Nour Alsharif M, Marek GJ. J Psychopharmacol. February 2023; 37(2): 144-154.

BACKGROUND: There is an unmet need for therapeutics with greater efficacy and tolerability for the treatment of opioid use disorder (OUD). ASP8062 is a novel compound with positive allosteric modulator activity on the γ -aminobutyric acid type B receptor under development for use with standard-of-care treatment for patients with OUD. **AIMS:** To investigate the safety, tolerability, interaction potential, and pharmacokinetics (PK) of ASP8062 in combination with buprenorphine/naloxone (B/N; Suboxone®) **METHODS:** In this phase 1, randomized, double-masked, placebo-controlled study, patients with OUD began B/N (titrated to 16/4 mg/day) treatment upon enrollment (induction, Days 1-4; maintenance, Days 5-18; downward titration, Days 19-26; and discharge, Day 27). On Day 12, patients received a single dose of ASP8062 60 mg or placebo with B/N and underwent safety and PK assessments. Primary endpoints included frequency and severity of treatment-emergent adverse events (TEAEs), clinical laboratory tests, respiratory depression, and suicidal ideation. Secondary endpoints investigated the impact of ASP8062 on B/N PK. **RESULTS:** Eighteen patients were randomized and completed the study (ASP8062, $n = 12$; placebo, $n = 6$). With this sample size typical for phase 1 drug-drug interaction studies, ASP8062 was well tolerated; most TEAEs were mild in severity, and none led to treatment withdrawal. ASP8062 did not enhance substance use-related TEAEs, respiratory depression, or suicidal ideation and did not have a clinically significant impact on the PK of B/N. **CONCLUSIONS:** In this phase 1 study, ASP8062 was safe, well tolerated, and did not enhance respiratory suppression induced by buprenorphine. **TRIAL REGISTRATION:** Clinicaltrials.gov identifier: NCT04447287.

[Objective Identification Of Cannabis Use Levels In Clinical Populations Is Critical For Detecting Pharmacological Outcomes](#)

Huang W, Czuba LC, Manuzak JA, Martin JN, Hunt PW, Klatt NR, Isoherranen N. Cannabis Cannabinoid Res. December 2022; 7(6): 852-864.

Introduction: Cannabis is widely used for recreational and medical purposes, but its therapeutic efficacy remains unresolved for many applications as data from retrospective studies show dramatic discrepancy. We hypothesized that false self-reporting of cannabis use and lack of differentiation of heavy users from light or occasional users contribute to the conflicting outcomes. **Objective:** The goal of this study was to develop an objective biomarker of cannabis use and test how application of such biomarker impacts clinical study outcomes and dose-response measures. **Methods and Analysis:** Population pharmacokinetic (PK) models of (-)-trans- Δ^9 -tetrahydrocannabinol (THC) and its metabolites 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (11-COOH-THC) were developed based on published studies reporting cannabinoid disposition in individual subjects following intravenous administration or smoking of

cannabis. Plasma 11-COOH-THC concentration distributions in different cannabis user groups smoking cannabis were generated via Monte Carlo simulations, and plasma concentration cutoff values of 11-COOH-THC were developed to differentiate light and heavy daily cannabis users in clinical studies. The developed cutoff value was then applied to a retrospective study that assessed the impact of cannabis use on T cell activation in subjects with HIV who self-reported as either nonuser or daily user of cannabis. Results: The developed population PK models established plasma 11-COOH-THC concentration of 73.1 µg/L as a cutoff value to identify heavy daily users, with a positive predictive value of 80% in a mixed population of equal proportions of once daily and three times a day users. The stratification allowed detection of changes in T cell activation in heavy users which was not detected based on self-reporting or detectability of plasma cannabinoids. A proof-of-concept power analysis demonstrated that implementation of such cutoff value greatly increases study power and sensitivity to detect pharmacological effects of cannabis use. Conclusions: This study shows that the use of plasma 11-COOH-THC concentration cutoff value as an objective measure to classify cannabis use in target populations is critical for study sensitivity and specificity and provides much needed clarity for addressing dose-response relationships and therapeutic effects of cannabis.

More Intensive Hepatitis C Virus Care Models Promote Adherence Among People Who Inject Drugs With Active Drug Use: The PREVAIL Study

Heo M, Pericot-Valverde I, Niu J, Norton BL, Akiyama MJ, Nahvi S, Arnsten JH, Litwin AH. *J Viral Hepat.* February 2023; 30(2): 172-175.

Adequate adherence to medications for hepatitis C infection (HCV) among people who inject drugs (PWID) is crucial for cure. However, active drug use may interfere with optimal adherence. Using data from the PREVAIL study that randomized three models of care with different levels of intensity—modified directly observed therapy (mDOT), groups therapy (GT), or standard individual therapy (SIT)—we examined whether more intensive care models such as mDOT or GT would also increase adherence among participants with active drug use compared to those without at baseline and during the entire treatment period. The daily adherence was measured using electronic blister packs available for analysis from N=147 participants. Drug use was ascertained by urine toxicology tests and defined in four ways: at baseline, and ever, frequent, and concurrent use during treatment period. Regardless of how drug use was defined, adherence of drug users was the greatest in mDOT, the lowest in SIT, and middle in GT. For instance, adjusted adherence was significantly higher for participants with baseline drug use than those without in mDOT (86.6±3.9(SE) vs. 76.8±4.3, p=.035) but significantly lower for those with baseline drug use in SIT (64.7±4.1 vs. 79.1±4.2, p=.003). Among non-drug users, there was no such clear dose-response relationship between intensity levels of care and adherence. In conclusion, more intensive care models should be implemented to promote adherence and mitigate the potential negative effect of drug use on adherence among PWID living with HCV.

Impact Of Multiple Substance Use On Circulating ST2, A Biomarker Of Adverse Cardiac Remodelling, In Women

Riley ED, Kazi DS, Coffin PO, Vittinghoff E, Wade AN, Bulfone TC, Lynch KL, Atai Z, Wu AHB. *Biomarkers.* December 2022; 27(8): 802-808.

CONTEXT: Cardiovascular disease (CVD) and heart failure (HF) are major causes of mortality in low-income populations and differ by sex. Risk assessment that incorporates cardiac biomarkers is common. However, research evaluating the utility of biomarkers rarely includes controlled substances, which may influence biomarker levels and thus influence CVD risk assessment. MATERIALS AND METHODS: We identified the effects of multiple substances on soluble "suppression of tumorigenicity 2" (sST2), a biomarker of adverse cardiac remodelling, in 245 low-

income women. Adjusting for CVD risk factors, we examined associations between substance use and sST2 over six monthly visits. RESULTS: Median age was 53 years and 74% of participants were ethnic minority women. An sST2 level > 35 ng/mL (suggesting cardiac remodelling) during ≥ 1 study visit was observed in 44% of participants. In adjusted analysis, higher sST2 levels were significantly and positively associated with the presence of cocaine (Adjusted Linear Effect [ALE]:1.10; 95% CI:1.03-1.19), alcohol (ALE:1.10; 95% CI:1.04-1.17), heroin (ALE:1.25; 95% CI:1.10-1.43), and the interaction between heroin and fentanyl use. CONCLUSION: Results suggest that the use of multiple substances influences the level of sST2, a biomarker often used to evaluate cardiovascular risk. Incorporating substance use alongside cardiac biomarkers may improve CVD risk assessment in vulnerable women.

Overdose Mortality Rates For Opioids Or Stimulants Are Higher In Males Than Females, Controlling For Rates Of Drug Misuse: State-Level Data

Butelman ER, Huang Y, Epstein DH, Shaham Y, Goldstein RZ, Volkow ND, Alia-Klein N. medRxiv. March 6, 2023. Preprint.

IMPORTANCE: Drug overdoses from opioids like fentanyl and heroin and stimulant drugs such as methamphetamine and cocaine are a major cause of mortality in the United States, with potential sex differences across the lifespan. OBJECTIVE: To determine overdose mortality for specific drug categories across the lifespan of males and females, using a nationally representative state-level sample. DESIGN: State-level analyses of nationally representative epidemiological data on overdose mortality for specific drug categories, across 10-year age bins (age range: 15-74).

SETTING: Population-based study of Multiple Cause of Death 2020-2021 data from the Centers of Disease Control and Prevention (CDC WONDER platform). PARTICIPANTS: Decedents in the United States in 2020-2021. MAIN OUTCOME MEASURES: The main outcome measure was sex-specific rates of overdose death (per 100,000) for: synthetic opioids excluding methadone (ICD-10 code: T40.4; predominantly fentanyl), heroin (T40.1), psychostimulants with potential for misuse, excluding cocaine (T43.6, predominantly methamphetamine; labeled "psychostimulants" hereafter), and cocaine (T40.5). Multiple regression analyses were used to control for ethnic-cultural background, household net worth, and sex-specific rate of misuse of the relevant substances (from the National Survey on Drug Use and Health, 2018-2019). RESULTS: For each of the drug categories assessed, males had greater overall overdose mortality than females, after controlling for rates of drug misuse. The mean male/female sex ratio of mortality rate for the separate drug categories was relatively stable across jurisdictions: synthetic opioids (2.5 [95%CI, 2.4-2.7]), heroin, (2.9 [95%CI, 2.7-3.1], psychostimulants (2.4 [95%CI, 2.3-2.5]), and cocaine (2.8 [95%CI, 2.6-2.9]). With data stratified in 10-year age bins, the sex difference generally survived adjustment for state-level ethnic-cultural and economic variables, and for sex-specific misuse of each drug type (especially for bins in the 25-64 age range). For synthetic opioids, the sex difference survived adjustment across the lifespan (i.e., 10-year age bins ranging from 15-74), including adolescence, adulthood and late adulthood. CONCLUSIONS AND RELEVANCE: The robustly greater overdose mortality in males versus females for synthetic opioids (predominantly fentanyl), heroin, and stimulant drugs including methamphetamine and cocaine indicate that males who misuse these drugs are significantly more vulnerable to overdose deaths. These results call for research into diverse biological, behavioral, and social factors that underlie sex differences in human vulnerability to drug overdose. KEY POINTS: Question: What are the current national trends in overdose mortality from opioids (synthetic opioids such as fentanyl, and heroin) and stimulant drugs (psychostimulants such as methamphetamine and cocaine) for males and females, over the lifespan (overall range 15-74 years)? Findings: State-level analyses of data from CDC for 2020-2021 indicate that after controlling for rates of drug misuse, males had significantly greater (2-3 fold)

overdose mortality rates than females for synthetic opioids, heroin, psychostimulants and cocaine. These findings were generally consistent across the lifespan, studied as 10-year age bins (especially in the 25-64 age range). Meaning: These data indicate that males who misuse opioids and stimulant drugs are considerably more vulnerable to overdose mortality, compared to females. This finding calls for research on the underlying biological, behavioral, and social factors. R01DA049547

Estimating The Impact Of Stimulant Use On Initiation Of Buprenorphine And Extended-Release Naltrexone In Two Clinical Trials And Real-World Populations

Cook RR, Foot C, Arah OA, Humphreys K, Rudolph KE, Luo SX, Tsui JI, Levander XA, Korthuis PT. *Addict Sci Clin Pract.* February 14, 2023; 18(1): 11.

BACKGROUND: Co-use of stimulants and opioids is rapidly increasing. Randomized clinical trials (RCTs) have established the efficacy of medications for opioid use disorder (MOUD), but stimulant use may decrease the likelihood of initiating MOUD treatment. Furthermore, trial participants may not represent "real-world" populations who would benefit from treatment. **METHODS:** We conducted a two-stage analysis. First, associations between stimulant use (time-varying urine drug screens for cocaine, methamphetamine, or amphetamines) and initiation of buprenorphine or extended-release naltrexone (XR-NTX) were estimated across two RCTs (CTN-0051 X:BOT and CTN-0067 CHOICES) using adjusted Cox regression models. Second, results were generalized to three target populations who would benefit from MOUD: Housed adults identifying the need for OUD treatment, as characterized by the National Survey on Drug Use and Health (NSDUH); adults entering OUD treatment, as characterized by Treatment Episodes Dataset (TEDS); and adults living in rural regions of the U.S. with high rates of injection drug use, as characterized by the Rural Opioids Initiative (ROI). Generalizability analyses adjusted for differences in demographic characteristics, substance use, housing status, and depression between RCT and target populations using inverse probability of selection weighting. **RESULTS:** Analyses included 673 clinical trial participants, 139 NSDUH respondents (weighted to represent 661,650 people), 71,751 TEDS treatment episodes, and 1,933 ROI participants. The majority were aged 30-49 years, male, and non-Hispanic White. In RCTs, stimulant use reduced the likelihood of MOUD initiation by 32% (adjusted HR [aHR] = 0.68, 95% CI 0.49-0.94, $p = 0.019$). Stimulant use associations were slightly attenuated and non-significant among housed adults needing treatment (25% reduction, aHR = 0.75, 0.48-1.18, $p = 0.215$) and adults entering OUD treatment (28% reduction, aHR = 0.72, 0.51-1.01, $p = 0.061$). The association was more pronounced, but still non-significant among rural people injecting drugs (39% reduction, aHR = 0.61, 0.35-1.06, $p = 0.081$). Stimulant use had a larger negative impact on XR-NTX initiation compared to buprenorphine, especially in the rural population (76% reduction, aHR = 0.24, 0.08-0.69, $p = 0.008$). **CONCLUSIONS:** Stimulant use is a barrier to buprenorphine or XR-NTX initiation in clinical trials and real-world populations that would benefit from OUD treatment. Interventions to address stimulant use among patients with OUD are urgently needed, especially among rural people injecting drugs, who already suffer from limited access to MOUD.

Findings From A Pilot Study Of Buprenorphine Population Pharmacokinetics: A Potential Effect Of HIV On Buprenorphine Bioavailability

Bart G, Jaber M, Giang LM, Brundage RC, Korthuis PT. *Drug Alcohol Depend.* December 1, 2022; 241: 109696.

BACKGROUND: Buprenorphine is widely used in the treatment of opioid use disorder (OUD). There are few pharmacokinetic models of buprenorphine across diverse populations. Population pharmacokinetics (POPPK) allows for covariates to be included in pharmacokinetic studies, thereby opening the potential to evaluate the effect of comorbidities, medications, and other factors on buprenorphine pharmacokinetics. This pilot study used POPPK to explore buprenorphine

pharmacokinetics in patients with and without HIV receiving buprenorphine for OUD. **METHODS:** Plasma buprenorphine levels were measured in 54 patients receiving buprenorphine for OUD just prior to and 2-5 h following regular buprenorphine dosing. A linear one-compartment POPPK model with first-order estimation was used to evaluate buprenorphine clearance (CL/F) and volume of distribution (V/F). Covariates included weight and HIV status. **RESULTS:** All HIV+ patients reported complete past-month adherence to taking antiretroviral therapy that included either efavirenz or nevirapine. Buprenorphine CL/F was 76% higher in HIV+ patients (n = 17) than HIV- patients (n = 37). Buprenorphine V/F was 41% higher in the HIV+ patients. **CONCLUSIONS:** POPPK can be used to model buprenorphine pharmacokinetics in a real-world clinical population. While interactions between ART and buprenorphine alter buprenorphine CL/F, we also found alteration in V/F. Proportionate changes in CL/F and V/F might indicate a primary effect on bioavailability (F) rather than two separate effects. These findings indicate reduced buprenorphine bioavailability in patients with HIV.

[Association Of Sex Work And Social-Structural Factors With Non-Fatal Overdose Among Women Who Use Drugs In Vancouver, Canada](#) Harris MT, Goldenberg S, Cui Z, Fairbairn N, Milloy M-JS, Hayashi K, Samet JH, Walley AY, Nolan S. *Int J Drug Policy*. February 2023; 112: 103950.

BACKGROUND: Women who use drugs (WWUD) and engage in sex work experience disproportionate sex- and drug-related harms, such as HIV, however comparatively little is known about their overdose risk. Therefore, we examined the association between sex work and overdose and secondarily explored the association of social-structural factors, such as policing and gendered violence, with overdose. **METHODS:** Data were derived from two community cohort studies based in Vancouver, Canada between 2005 to 2018. We used logistic regression with GEE to examine the associations between a) sex work and nonfatal overdose and b) social-structural and individual variables with overdose among WWUD who engaged in sex work during the study. Sex work, overdose, and other variables were time-updated, captured every six months. **RESULTS:** Among 857 WWUD included, 56% engaged in sex work during the study. Forty-three percent of WWUD engaged in sex work had at least one overdose compared to 26% of WWUD who did not. Sex work was not significantly associated with an increased odds of overdose (AOR = 1.14, 95% CI: 0.93-1.40). In the exploratory analysis amongst 476 WWUD engaged in sex work, social-structural variables associated with overdose in the multivariable model included exposure to: punitive policing (OR = 1.97, 95% CI: 1.30-2.96) and physical or sexual violence (OR = 2.55, 95% CI: 1.88-3.46). **CONCLUSIONS:** WWUD engaged in sex work had an increased overdose burden that may be driven by social-structural factors rather than sex work itself. Interventions that address policing and gendered violence represent potential targets for effective overdose prevention.

HIV RESEARCH

[Virally Suppressed People Living With HIV Who Use Opioids Have Diminished Latency Reversal](#) Basukala B, Rossi S, Bendiks S, Gnatienco N, Patts G, Krupitsky E, Lioznov D, So-Armah K, Sagar M, Cheng C, Henderson AJ. *Viruses*. February 2023; 15(2): 415.

Of the 12 million people who inject drugs worldwide, 13% live with HIV. Whether opioid use impacts HIV pathogenesis and latency is an outstanding question. To gain insight into whether opioid use influences the proviral landscape and latent HIV reservoir, we performed intact proviral DNA assays (IPDA) on peripheral blood mononuclear cells (PBMCs) from antiretroviral therapy (ART)-suppressed people living with HIV (PWH) with or without current opioid use. No

differences were observed between PWH with and without opioid use in the frequency of HIV intact and defective proviral genomes. To evaluate the latent reservoir, we activated PBMCs from ART-suppressed PWH with or without opioid use and assessed the induction of HIV RNA. PWH using opioids had diminished responses to ex vivo HIV reactivation, suggesting a smaller reversible reservoir of HIV-1 latently infected cells. However, in vitro studies using primary CD4+ T cells treated with morphine showed no effect of opioids on HIV-1 infection, replication or latency establishment. The discrepancy in our results from in vitro and clinical samples suggests that while opioids may not directly impact HIV replication, latency and reactivation in CD4+ T cells, opioid use may indirectly shape the HIV reservoir in vivo by modulating general immune functions.

[A Modular CRISPR Screen Identifies Individual And Combination Pathways Contributing To HIV-1 Latency](#) Hsieh E, Janssen DH, Paddison PJ, Browne EP, Henikoff S, OhAinle M, and Emerman M. Plos Pathogens, January 27, 2023; 19(1):e1011101.

Transcriptional silencing of latent HIV-1 proviruses entails complex and overlapping mechanisms that pose a major barrier to in vivo elimination of HIV-1. We developed a new latency CRISPR screening strategy, called Latency HIV-CRISPR which uses the packaging of guideRNA-encoding lentiviral vector genomes into the supernatant of budding virions as a direct readout of factors involved in the maintenance of HIV-1 latency. We developed a custom guideRNA library targeting epigenetic regulatory genes and paired the screen with and without a latency reversal agent—AZD5582, an activator of the non-canonical NFκB pathway—to examine a combination of mechanisms controlling HIV-1 latency. A component of the Nucleosome Acetyltransferase of H4 histone acetylation (NuA4 HAT) complex, ING3, acts in concert with AZD5582 to activate proviruses in J-Lat cell lines and in a primary CD4+ T cell model of HIV-1 latency. We found that the knockout of ING3 reduces acetylation of the H4 histone tail and BRD4 occupancy on the HIV-1 LTR. However, the combination of ING3 knockout accompanied with the activation of the non-canonical NFκB pathway via AZD5582 resulted in a dramatic increase in initiation and elongation of RNA Polymerase II on the HIV-1 provirus in a manner that is nearly unique among all cellular promoters.

[Evaluating The Impact Of Naloxone Dispensation At Public Health Vending Machines In Clark County, Nevada](#) Allen ST, O'Rourke A, Johnson JA, Cheatom C, Zhang Y, Delise B, Watkins K, Reich K, Reich R, Lockett C. Ann Med. 2022; 54(1): 2692-2700.

Abstract: Introduction: Implementing public health vending machines (PHVMs) is an evidence-based strategy for mitigating substance use-associated morbidity and mortality via the dispensation of essential supplies to people who use drugs, including overdose prevention resources. PHVMs have been implemented throughout the world; however, their implementation in the United States (US) is a recent phenomenon. In 2017, Trac-B Exchange (a syringe services program in Clark County, Nevada) installed three PHVMs. In 2019, naloxone dispensation was launched at PHVMs in Clark County. The purpose of this research is to examine the extent to which naloxone dispensation at PHVMs was associated with changes in opioid-involved overdose fatalities. Methods: Monthly counts of opioid-involved overdose fatalities among Clark County residents that occurred from January 2015 to December 2020 were used to build an autoregressive integrated moving averages (ARIMA) model to measure the impact of naloxone dispensation at PHVMs. We forecasted the number of expected opioid-involved overdose fatalities had naloxone dispensation at PHVMs not occurred and compared to observed monthly counts. Interrupted time series analyses (ITSA) were used to evaluate the step (i.e. the immediate impact of naloxone dispensation at PHVMs on opioid-involved overdose fatalities) and slope change (i.e. changes in trend and directionality of monthly counts of opioid-involved overdose fatalities following naloxone

dispensation at PHVMs). Results: During the 12-months immediately following naloxone dispensation at PHVMs, our model forecasted 270 opioid-involved overdose fatalities, but death certificate data indicated only 229 occurred, suggesting an aversion of 41 deaths. ITSA identified a significant negative step change in opioid-involved overdose fatalities at the time naloxone dispensation at PHVMs was launched ($B = -8.52$, $p = .0022$) and a significant increasing slope change ($B = 1.01$, $p < .0001$). Forecasts that extended into the COVID-19 pandemic suggested worsening trends in overdose fatalities. Conclusion: Naloxone dispensation at PHVMs was associated with immediate reductions in opioid-involved overdose fatalities. Funding: National Institutes of Health (K01DA046234; Allen, 1st author); Johns Hopkins University Center for AIDS Research [P30AI094189] and the District of Columbia Center for AIDS Research [P30AI117970].

Differential Effects Of Patient Navigation Across Latent Profiles Of Barriers To Care Among People Living With HIV And Comorbid Conditions Traynor SM, Schmidt RD, Gooden LK, Matheson T, Haynes L, Rodriguez A, Mugavero M, Jacobs P, Mandler R, Del Rio C, Carrico AW, Horigian VE, Metsch LR, Feaster DJ. J Clin Med. December 23, 2022; 12(1): 114.

Engaging people living with HIV who report substance use (PLWH-SU) in care is essential to HIV medical management and prevention of new HIV infections. Factors associated with poor engagement in HIV care include a combination of syndemic psychosocial factors, mental and physical comorbidities, and structural barriers to healthcare utilization. Patient navigation (PN) is designed to reduce barriers to care, but its effectiveness among PLWH-SU remains unclear. We analyzed data from NIDA Clinical Trials Network's CTN-0049, a three-arm randomized controlled trial testing the effect of a 6-month PN with and without contingency management (CM), on engagement in HIV care and viral suppression among PLWH-SU ($n = 801$). Latent profile analysis was used to identify subgroups of individuals' experiences to 23 barriers to care. The effects of PN on engagement in care and viral suppression were compared across latent profiles. Three latent profiles of barriers to care were identified. The results revealed that PN interventions are likely to be most effective for PLWH-SU with fewer, less severe healthcare barriers. Special attention should be given to individuals with a history of abuse, intimate partner violence, and discrimination, as they may be less likely to benefit from PN alone and require additional interventions.

CLINICAL TRIALS NETWORK RESEARCH

Implementation Facilitation To Promote Emergency Department-Initiated Buprenorphine For Opioid Use Disorder D'Onofrio G, Edelman EJ, Hawk KF, Chawarski MC, Pantaloni MV, Owens PH, Martel SH, Rothman R, Saheed M, Schwartz RP, Cowan E, Richardson L, Salsitz E, Lyons MS, Freiermuth C, Wilder C, Whiteside L, Tsui JI, Klein JW, Coupet E, O'Connor PG, Matthews AG, Murphy SM, Huntley K, Fiellin DA. JAMA Netw Open. April 3, 2023; 6(4): e235439.

Importance: Emergency department (ED)-initiated buprenorphine for the treatment of opioid use disorder (OUD) is underused. **Objective:** To evaluate whether provision of ED-initiated buprenorphine with referral for OUD increased after implementation facilitation (IF), an educational and implementation strategy. **Design, setting, and participants:** This multisite hybrid type 3 effectiveness-implementation nonrandomized trial compared grand rounds with IF, with pre-post 12-month baseline and IF evaluation periods, at 4 academic EDs. The study was conducted from April 1, 2017, to November 30, 2020. Participants were ED and community clinicians treating patients with OUD and observational cohorts of ED patients with untreated OUD. Data were

analyzed from July 16, 2021, to July 14, 2022. **Exposure:** A 60-minute in-person grand rounds was compared with IF, a multicomponent facilitation strategy that engaged local champions, developed protocols, and provided learning collaboratives and performance feedback. **Main outcomes and measures:** The primary outcomes were the rate of patients in the observational cohorts who received ED-initiated buprenorphine with referral for OUD treatment (primary implementation outcome) and the rate of patients engaged in OUD treatment at 30 days after enrollment (effectiveness outcome). Additional implementation outcomes included the numbers of ED clinicians with an X-waiver to prescribe buprenorphine and ED visits with buprenorphine administered or prescribed and naloxone dispensed or prescribed. **Results:** A total of 394 patients were enrolled during the baseline evaluation period and 362 patients were enrolled during the IF evaluation period across all sites, for a total of 756 patients (540 [71.4%] male; mean [SD] age, 39.3 [11.7] years), with 223 Black patients (29.5%) and 394 White patients (52.1%). The cohort included 420 patients (55.6%) who were unemployed, and 431 patients (57.0%) reported unstable housing. Two patients (0.5%) received ED-initiated buprenorphine during the baseline period, compared with 53 patients (14.6%) during the IF evaluation period ($P < .001$). Forty patients (10.2%) were engaged with OUD treatment during the baseline period, compared with 59 patients (16.3%) during the IF evaluation period ($P = .01$). Patients in the IF evaluation period who received ED-initiated buprenorphine were more likely to be in treatment at 30 days (19 of 53 patients [35.8%]) than those who did not 40 of 309 patients (12.9%; $P < .001$). Additionally, there were increases in the numbers of ED clinicians with an X-waiver (from 11 to 196 clinicians) and ED visits with provision of buprenorphine (from 259 to 1256 visits) and naloxone (from 535 to 1091 visits). **Conclusions and relevance:** In this multicenter effectiveness-implementation nonrandomized trial, rates of ED-initiated buprenorphine and engagement in OUD treatment were higher in the IF period, especially among patients who received ED-initiated buprenorphine. **Trial registration:** ClinicalTrials.gov Identifier: [NCT03023930](https://clinicaltrials.gov/ct2/show/study/NCT03023930).

[Repurposing Ketamine To Treat Cocaine Use Disorder: Integration Of Artificial Intelligence-Based Prediction, Expert Evaluation, Clinical Corroboration And Mechanism Of Action](#)

[Analyses](#) Gao Z, Winhusen TJ, Gorenflo M, Ghitza UE, Davis PB, Kaelber DC, Xu R. *Addiction*. February 15, 2023. Online ahead of print.

Background and aims: Cocaine use disorder (CUD) is a significant public health issue for which there is no Food and Drug Administration (FDA) approved medication. Drug repurposing looks for new cost-effective uses of approved drugs. This study presents an integrated strategy to identify repurposed FDA-approved drugs for CUD treatment. **Design:** Our drug repurposing strategy combines artificial intelligence (AI)-based drug prediction, expert panel review, clinical corroboration and mechanisms of action analysis being implemented in the National Drug Abuse Treatment Clinical Trials Network (CTN). Based on AI-based prediction and expert knowledge, ketamine was ranked as the top candidate for clinical corroboration via electronic health record (EHR) evaluation of CUD patient cohorts prescribed ketamine for anesthesia or depression compared with matched controls who received non-ketamine anesthesia or antidepressants/midazolam. Genetic and pathway enrichment analyses were performed to understand ketamine's potential mechanisms of action in the context of CUD. **Setting:** The study utilized TriNetX to access EHRs from more than 90 million patients world-wide. Genetic- and functional-level analyses used DisGeNet, Search Tool for Interactions of Chemicals and Kyoto Encyclopedia of Genes and Genomes databases. **Participants:** A total of 7742 CUD patients who received anesthesia (3871 ketamine-exposed and 3871 anesthetic-controlled) and 7910 CUD patients with depression (3955 ketamine-exposed and 3955 antidepressant-controlled) were identified after propensity score-matching. **Measurements:** EHR analysis outcome was a CUD remission diagnosis within 1 year of

drug prescription. **Findings:** Patients with CUD prescribed ketamine for anesthesia displayed a significantly higher rate of CUD remission compared with matched individuals prescribed other anesthetics [hazard ratio (HR) = 1.98, 95% confidence interval (CI) = 1.42-2.78]. Similarly, CUD patients prescribed ketamine for depression evidenced a significantly higher CUD remission ratio compared with matched patients prescribed antidepressants or midazolam (HR = 4.39, 95% CI = 2.89-6.68). The mechanism of action analysis revealed that ketamine directly targets multiple CUD-associated genes (BDNF, CNR1, DRD2, GABRA2, GABRB3, GAD1, OPRK1, OPRM1, SLC6A3, SLC6A4) and pathways implicated in neuroactive ligand-receptor interaction, cAMP signaling and cocaine abuse/dependence. **Conclusions:** Ketamine appears to be a potential repurposed drug for treatment of cocaine use disorder. **Keywords:** Artificial intelligence; clinical corroboration; cocaine use disorder; drug repurposing; expert evaluation; ketamine; mechanism of action analyses.

[Incidence Of Precipitated Withdrawal During A Multisite Emergency Department-Initiated Buprenorphine Clinical Trial In The Era Of Fentanyl](#) D'Onofrio G, Hawk KF, Perrone J, Walsh SL, Lofwall MR, Fiellin DA, Herring A. JAMA Netw Open. March 1, 2023; 6(3): e236108.

Introduction: Buprenorphine treatment is associated with decreased mortality and morbidity,¹ yet the treatment gap remains wide. Emergency departments (EDs) offer an effective, low-barrier setting in which to initiate buprenorphine.² Retrospective case series³ have raised concerns about increased incidence of precipitated withdrawal (PW) when buprenorphine is initiated in persons using fentanyl, a high-potency μ -opioid agonist with high affinity and slow dissociation from the μ receptor. With long-term use, its high lipophilicity leads to bioaccumulation and prolonged metabolite excretion. As confidence in standard buprenorphine inductions has eroded, alternative strategies, such as low-dose buprenorphine, have emerged, often prompting continued use of illicit opioids. Thus, there is a need for high-quality evidence from prospective studies using uniform surveillance and operational definitions of PW. We report the incidence of PW as part of an ongoing randomized clinical trial⁴ comparing traditional sublingual buprenorphine with CAM2038, a 7-day extended-release injectable form of buprenorphine, conducted in sites with high prevalence of fentanyl. **Methods:** This observational cohort study using data from an ongoing clinical trial⁴ included patients aged 18 years or older with moderate-to-severe opioid use disorder, opioid-positive and methadone-negative urine tests, and a Clinical Opiate Withdrawal Scale (COWS) score of 4 or higher. Pregnant or admitted patients were excluded. Twenty-eight geographically diverse EDs participated from June 30, 2020, to October 26, 2022. Patients were randomized to standard sublingual buprenorphine inductions or extended-release buprenorphine and were observed for 2 hours. PW was defined⁵ a priori and was considered when a marked escalation in objective COWS scores (score ≥ 5) occurred, requiring additional buprenorphine and ancillary medications, often within 2 hours of buprenorphine administration. Suspected PW cases were documented prospectively and adjudicated by expert consultants (S.L.W. and M.R.L.). This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (**STROBE**) reporting guideline for cohort studies and was approved by the WCG institutional review board. Participants provided written consent. Patients with a COWS score of 8 or higher received 8 mg of sublingual buprenorphine in the ED and were discharged with a prescription for 16 mg/day. Individuals with COWS scores of 4 to 7 received uniform instructions for unobserved induction, up to 12 mg the first day, and then 16 mg/day. In the extended-release buprenorphine group, on the basis of dose equivalency to 16 mg of sublingual buprenorphine, patients received 24 mg of injectable CAM2038 in the ED during the index visit and follow-up.³ Data analysis was performed with SAS statistical software version 9.4 (SAS Institute). **Results:** Among 1200 enrolled patients (800 men [66.7%]; mean [SD] age, 38.4 [12.0] years), there were 9 cases of PW, or 0.76% (95% CI, 0.35%-1.43%) of the overall sample. Patient characteristics (total and PW) are presented in **Table 1**.

The PW cases were enrolled from diverse locations; 5 received sublingual buprenorphine and 4 received extended-release buprenorphine. Detailed data from the PW cases are reported in **Table 2**. All patients had urine tests positive for fentanyl, 7 with multiple drugs. Routes of use, changes in baseline and peak COWS scores, and time elapsed from buprenorphine administration to PW varied. Time since last use ranged from 8 to more than 24 hours. All patients experiencing PW were discharged after symptoms resolved, with 1 self-directed discharge. Follow-up rates at 7 days after the ED visit were 86%. **Discussion:** This cohort study used data from the first, to our knowledge, prospective trial⁴ using uniform surveillance, operational definitions, and adjudicated outcomes to document buprenorphine-induced PW in persons using fentanyl. Despite high fentanyl prevalence, the incidence of PW in this multisite trial⁴ of ED-initiated buprenorphine was less than 1%, similar to reported rates among persons using heroin or prescription opioids.⁶ All 9 patients with PW used fentanyl, most without PW also used fentanyl, and no factors suggest a specific phenotype for PW. The discordance between our findings and those of retrospective studies is striking. Limitations include possible undetected fentanyl analogues or nitazenes leading to PW. We may have missed PW after discharge, although follow-up rates at 7 days after the ED visit were 86% and likely would be captured as adverse events. In this geographically diverse observational cohort, buprenorphine induction in the ED remained safe and effective, even with fentanyl present. Continued access to buprenorphine for opioid use disorder treatment is essential given the ongoing overdose crisis.

Risk Of Experiencing An Overdose Event For Patients Undergoing Treatment With Medication For Opioid Use Disorder

Brandt L, Hu MC, Liu Y, Castillo F, Odom GJ, Balise RR, Feaster DJ, Nunes EV, Luo SX. Am J Psychiatry. March 9, 2023; appiajp20220312.

Objective: Overdose risk during a course of treatment with medication for opioid use disorder (MOUD) has not been clearly delineated. The authors sought to address this gap by leveraging a new data set from three large pragmatic clinical trials of MOUD. **Methods:** Adverse event logs, including overdose events, from the three trials (N=2,199) were harmonized, and the overall risk of having an overdose event in the 24 weeks after randomization was compared for each study arm (one methadone, one naltrexone, and three buprenorphine groups), using survival analysis with time-dependent Cox proportional hazard models. **Results:** By week 24, 39 participants had ≥ 1 overdose event. The observed frequency of having an overdose event was 15 (5.30%) among 283 patients assigned to naltrexone, eight (1.51%) among 529 patients assigned to methadone, and 16 (1.15%) among 1,387 patients assigned to buprenorphine. Notably, 27.9% of patients assigned to extended-release naltrexone never initiated the medication, and their overdose rate was 8.9% (7/79), compared with 3.9% (8/204) among those who initiated naltrexone. Controlling for sociodemographic and time-varying medication adherence variables and baseline substance use, a proportional hazard model did not show a significant effect of naltrexone assignment. Significantly higher probabilities of experiencing an overdose event were observed among patients with baseline benzodiazepine use (hazard ratio=3.36, 95% CI=1.76, 6.42) and those who either were never inducted on their assigned study medication (hazard ratio=6.64, 95% CI=2.12, 19.54) or stopped their medication after initial induction (hazard ratio=4.04, 95% CI=1.54, 10.65).

Conclusions: Among patients with opioid use disorder seeking medication treatment, the risk of overdose events over the next 24 weeks is elevated among those who fail to initiate or discontinue medication and those who report benzodiazepine use at baseline. **Keywords:** Addiction Psychiatry; Medication-Assisted Treatment; Opioids; Substance-Related and Addictive Disorders.

Homelessness And Treatment Outcomes Among Black Adults With Opioid Use Disorder: A Secondary Analysis Of X:BOT Justen M, Scodes J, Pavlicova M, Choo TH, Gopaldas M, Haeny A, Opara O, Rhee TG, Rotrosen J, Nunes EV Jr, Hawk K, Edelman EJ. *J Addict Med.* January 6, 2023; Online ahead of print.

Objective: We sought to identify the sociodemographic and clinical characteristics associated with homelessness, and explore the relationship between homelessness and treatment outcomes among Black individuals. **Methods:** This is a secondary analysis of the subgroup of Black participants (n = 73) enrolled in "X:BOT," a 24-week multisite randomized clinical trial comparing the effectiveness of extended-release naltrexone versus sublingual buprenorphine-naloxone (n = 570). Outcomes included medication initiation, return to extramedical use of opioids assessed by both self-report and urine toxicology, and engagement in medications for opioid use disorder (MOUD) treatment at 28 weeks postrandomization. Descriptive statistics were performed. **Results:** Black participants were mostly unmarried and male, and about a third were aged 21-30 years. Among people experiencing homelessness, more were uninsured (45.5% [10/22] vs 19.6% [10/51]), unemployed (77.3% [17/22] vs 64.7% [33/51]), and reported alcohol (40.9% [9/22] vs 23.5% [12/51]) and sedative use (54.5% [12/22] vs 17.6% [9/51]) within the previous 30 days. Compared with housed Black individuals, a slightly higher proportion of Black individuals experiencing homelessness successfully initiated study medication (81.1% [18/22] vs 72.6% [37/51]); similar proportions returned to opioid use during the trial (68.2% [15/22] vs 68.6% [35/51]) and were engaged in MOUD at 28 weeks after trial entry (72.2% [13/18] vs 69.7% [23/33]) among participants located for follow-up. **Conclusions:** These descriptive results among Black patients participating in a trial of MOUD suggest that efficacious MOUD is possible despite homelessness with additional clinical supports such as those provided by a clinical trial.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

Task fMRI Paradigms May Capture More Behaviorally Relevant Information Than Resting-State Functional Connectivity Zhao W, Makowski C, Hagler DJ, Garavan HP, Thompson WK, Greene DJ, Jernigan TL, Dale AM. *Neuroimage.* February 17, 2023; 270: 119946.

Characterizing the optimal fMRI paradigms for detecting behaviorally relevant functional connectivity (FC) patterns is a critical step to furthering our knowledge of the neural basis of behavior. Previous studies suggested that FC patterns derived from task fMRI paradigms, which we refer to as task-based FC, are better correlated with individual differences in behavior than resting-state FC, but the consistency and generalizability of this advantage across task conditions was not fully explored. Using data from resting-state fMRI and three fMRI tasks from the Adolescent Brain Cognitive Development Study® (ABCD), we tested whether the observed improvement in behavioral prediction power of task-based FC can be attributed to changes in brain activity induced by the task design. We decomposed the task fMRI time course of each task into the task model fit (the fitted time course of the task condition regressors from the single-subject general linear model) and the task model residuals, calculated their respective FC, and compared the behavioral prediction performance of these FC estimates to resting-state FC and the original task-based FC. The FC of the task model fit was better than the FC of the task model residual and resting-state FC at predicting a measure of general cognitive ability or two measures of performance on the fMRI tasks. The superior behavioral prediction performance of the FC of the task model fit was content-specific insofar as it was only observed for fMRI tasks that probed similar cognitive constructs to the predicted behavior of interest. To our surprise, the task model parameters, the beta estimates of the

task condition regressors, were equally if not more predictive of behavioral differences than all FC measures. These results showed that the observed improvement of behavioral prediction afforded by task-based FC was largely driven by the FC patterns associated with the task design. Together with previous studies, our findings highlighted the importance of task design in eliciting behaviorally meaningful brain activation and FC patterns.

[Racial/Ethnic Disparities In Mental Healthcare In Youth With Incarcerated Parents](#) Ryan JE, McCabe SE, DiDonato S, Boyd CJ, Voepel-Lewis T, Ploutz-Snyder RJ, Veliz P. Am J Prev Med. March 12, 2023; S0749-3797(23)00133-2.

Introduction: Youth with incarcerated parents (YIP) experience more Adverse Childhood Experiences (ACEs) than other youth, placing them at higher risk for mental health and substance use disorders. Despite their increased risk, these youth may be less likely to access mental health services, particularly given their racial and ethnic makeup. Therefore, this study aimed to assess racial and ethnic disparities in access to mental health services for YIP. **Methods:** This secondary data analysis used longitudinal data from 2016 to 2019 from the Adolescent Brain Cognitive Development Study. Logistic regression models assessed the relationships among incarceration, cumulative ACEs, DSM-5 diagnoses and mental health services. Additional analyses stratified these models by race and ethnicity. All analyses were performed in 2022. **Results:** YIP were more likely to report 4 or more ACEs (51% vs 14%, aOR 3.92, 95% CI 3.3-4.65, $p < 0.001$) and to have received mental health services (25% vs 15%, 1.89 aOR, 1.6-2.21, $p < 0.001$) compared to unexposed youth. However, Black YIP (19% vs 34%, aOR 0.38, 95% CI .27-.52, $p < 0.001$) and Latinx YIP (10% vs 17%, aOR 0.5, 95% CI .33-.76, $p < 0.001$) were significantly less likely to report receiving mental health services compared to White YIP and non-Latinx YIP, respectively. **Conclusions:** YIP were more likely to report utilization of mental health services, but significant racial and ethnic disparities exist between Black and Latinx YIP compared to White and non-Latinx YIP. There is a continued need to expand mental health services to YIP and to address racial and ethnic disparities in access to care.

[Racial Disparities In Adversity During Childhood And The False Appearance Of Race-Related Differences In Brain Structure](#) Dumornay NM, Lebois LAM, Ressler KJ, Harnett NG. Am J Psychiatry. February 1, 2023; 180(2): 127-138.

Objective: Black Americans in the United States are disproportionately exposed to childhood adversity compared with White Americans. Such disparities may contribute to race-related differences in brain structures involved in regulating the emotional response to stress, such as the amygdala, hippocampus, and prefrontal cortex (PFC). The authors investigated neuroanatomical consequences of racial disparities in adversity. **Methods:** The sample included 7,350 White American and 1,786 Black American children (ages 9-10) from the Adolescent Brain Cognitive Development Study (public data release 2.0). Structural MRI data, parent and child self-reports of adversity-related measures, and U.S. Census neighborhood data were used to investigate the relationship between racial disparities in adversity exposure and race-related differences in brain structure. **Results:** Black children experienced more traumatic events, family conflict, and material hardship on average compared with White children, and their parents or caregivers had lower educational attainment, lower income, and more unemployment compared with those of White children. Black children showed lower amygdala, hippocampus, and PFC gray matter volumes compared with White children. The volumes of the PFC and amygdala, but not the hippocampus, also varied with metrics of childhood adversity, with income being the most common predictor of brain volume differences. Accounting for differences in childhood adversity attenuated the magnitude of some race-related differences in gray matter volume. **Conclusions:** The results

suggest that disparities in childhood adversity contribute to race-related differences in gray matter volume in key brain regions associated with threat-related processes. Structural alterations of these regions are linked to cognitive-affective dysfunction observed in disorders such as posttraumatic stress disorder. More granular assessments of structural inequities across racial/ethnic identities are needed for a thorough understanding of their impact on the brain. Together, the present findings may provide insight into potential systemic contributors to disparate rates of psychiatric disease among Black and White individuals in the United States.

[Adverse Childhood Experiences And Sipping Alcohol In U.S. Children: Findings From The Adolescent Brain Cognitive Development Study](#) Nagata JM, Smith N, Sajjid OM, Zamora G, Raney JH, Ganson KT, Testa A, Vittinghoff E, Jackson DB. *Prev Med Rep.* February 17, 2023; 32: 102153.

The objective of this study was to explore the relationship between accumulating adverse childhood experiences (ACEs) and sipping alcohol in a large, nationwide sample of 9-to-10-year-old U.S. children. We analyzed data from the Adolescent Brain Cognitive Development (ABCD) Study (2016-2018). Of 10,853 children (49.1 % female), 23.4 % reported ever sipping alcohol. A greater ACE score was associated with a higher risk of sipping alcohol. Having 4 or more ACEs placed children at 1.27 times the risk (95 % CI 1.11-1.45) of sipping alcohol compared to children with no ACEs. Among the nine distinct ACEs examined, household violence (Risk Ratio [RR] = 1.13, 95 % CI 1.04-1.22) and household alcohol abuse (RR = 1.14, 95 % CI 1.05-1.22) were associated with sipping alcohol during childhood. Our findings indicate a need for increased clinical attention to alcohol sipping among ACE-exposed children.

[Characterizing Alcohol Expectancies In The ABCD Study: Associations With Sociodemographic Factors, The Immediate Social Environment, And Genetic Propensities](#)

Johnson EC, Paul SE, Baranger DAA, Hatoum AS, Colbert SMC, Lin S, Wolff R, Gorelik AJ, Hansen I, Karcher NR, Bogdan R, Agrawal A. *Behav Genet.* January 20, 2023. Online ahead of print.

Alcohol expectancies (AEs) are associated with likelihood of alcohol initiation and subsequent alcohol use disorders. It is unclear whether genetic predisposition to alcohol use and/or related traits contributes to shaping how one expects to feel when drinking alcohol. We used the Adolescent Brain Cognitive Development study to examine associations between genetic propensities (i.e., polygenic risk for problematic alcohol use, depression, risk-taking), sociodemographic factors (i.e., parent income), and the immediate social environment (i.e., peer use and disapproval toward alcohol) and positive and negative AEs in alcohol-naïve children (max analytic N = 5,352). Mixed-effect regression models showed that age, parental education, importance of the child's religious beliefs, adverse childhood experiences, and peer disapproval of alcohol use were associated with positive and/or negative AEs, to varying degrees. Overall, our results suggest several familial and psychosocial predictors of AEs but little evidence of contributions from polygenic liability to problematic alcohol use or related phenotypes.

INTRAMURAL RESEARCH

[The Role Of The Lateral Orbitofrontal Cortex In Creating Cognitive Maps](#) Costa KM, Scholz R, Lloyd K, Moreno-Castilla P, Gardner MPH, Dayan P, Schoenbaum G. Nat Neurosci. January 2023; 26(1): 107-115.

We use mental models of the world-cognitive maps-to guide behavior. The lateral orbitofrontal cortex (IOFC) is typically thought to support behavior by deploying these maps to simulate outcomes, but recent evidence suggests that it may instead support behavior by underlying map creation. We tested between these two alternatives using outcome-specific devaluation and a high-potency chemogenetic approach. Selectively inactivating IOFC principal neurons when male rats learned distinct cue-outcome associations, but before outcome devaluation, disrupted subsequent inference, confirming a role for the IOFC in creating new maps. However, IOFC inactivation surprisingly led to generalized devaluation, a result that is inconsistent with a complete mapping failure. Using a reinforcement learning framework, we show that this effect is best explained by a circumscribed deficit in credit assignment precision during map construction, suggesting that the IOFC has a selective role in defining the specificity of associations that comprise cognitive maps.

[Role Of Ventral Subiculum Neuronal Ensembles In Incubation Of Oxycodone Craving After Electric Barrier-Induced Voluntary Abstinence](#) Fredriksson I, Tsai PJ, Shekara A, Duan Y, Applebey SV, Minier-Toribio A, Batista A, Chow JJ, Altidor L, Barbier E, Cifani C, Li X, Reiner DJ, Rubio FJ, Hope BT, Yang Y, Bossert JM, Shaham Y. Sci Adv. January 13, 2023; 9(2): eadd8687.

High relapse rate is a key feature of opioid addiction. In humans, abstinence is often voluntary due to negative consequences of opioid seeking. To mimic this human condition, we recently introduced a rat model of incubation of oxycodone craving after electric barrier-induced voluntary abstinence. Incubation of drug craving refers to time-dependent increases in drug seeking after cessation of drug self-administration. Here, we used the activity marker Fos, muscimol-baclofen (GABA_A + GABA_B receptor agonists) global inactivation, Daun02-selective inactivation of putative relapse-associated neuronal ensembles, and fluorescence-activated cell sorting of Fos-positive cells and quantitative polymerase chain reaction to demonstrate a key role of vSub neuronal ensembles in incubation of oxycodone craving after voluntary abstinence, but not homecage forced abstinence. We also used a longitudinal functional magnetic resonance imaging method and showed that functional connectivity changes in vSub-related circuits predict opioid relapse after abstinence induced by adverse consequences of opioid seeking.

[Effect Of Selective Lesions of Nucleus Accumbens \$\mu\$ -Opioid Receptor-Expressing Cells On Heroin Self-Administration In Male And Female Rats: A Study With Novel Oprm1-Cre Knock-In Rats](#) Bossert JM, Mejias-Aponte CA, Saunders T, Altidor L, Emery M, Fredriksson I, Batista A, Claypool SM, Caldwell KE, Reiner DJ, Chow JJ, Foltz M, Kumar V, Seasholtz A, Hughes E, Filipiak W, Harvey BK, Richie CT, Vautier F, Gomez JL, Michaelides M, Kieffer BL, et al. J Neurosci. March 8, 2023; 43(10): 1692-1713.

The brain μ -opioid receptor (MOR) is critical for the analgesic, rewarding, and addictive effects of opioid drugs. However, in rat models of opioid-related behaviors, the circuit mechanisms of MOR-expressing cells are less known because of a lack of genetic tools to selectively manipulate them. We introduce a CRISPR-based Oprm1-Cre knock-in transgenic rat that provides cell type-specific genetic access to MOR-expressing cells. After performing anatomic and behavioral validation experiments, we used the Oprm1-Cre knock-in rats to study the involvement of NAc MOR-expressing cells in heroin self-administration in male and female rats. Using RNAscope,

autoradiography, and FISH chain reaction (HCR-FISH), we found no differences in Oprm1 expression in NAc, dorsal striatum, and dorsal hippocampus, or MOR receptor density (except dorsal striatum) or function between Oprm1-Cre knock-in rats and wildtype littermates. HCR-FISH assay showed that iCre is highly coexpressed with Oprm1 (95%-98%). There were no genotype differences in pain responses, morphine analgesia and tolerance, heroin self-administration, and relapse-related behaviors. We used the Cre-dependent vector AAV1-EF1a-Flex-taCasp3-TEVP to lesion NAc MOR-expressing cells. We found that the lesions decreased acquisition of heroin self-administration in male Oprm1-Cre rats and had a stronger inhibitory effect on the effort to self-administer heroin in female Oprm1-Cre rats. The validation of an Oprm1-Cre knock-in rat enables new strategies for understanding the role of MOR-expressing cells in rat models of opioid addiction, pain-related behaviors, and other opioid-mediated functions. Our initial mechanistic study indicates that lesioning NAc MOR-expressing cells had different effects on heroin self-administration in male and female rats. **SIGNIFICANCE STATEMENT** The brain μ -opioid receptor (MOR) is critical for the analgesic, rewarding, and addictive effects of opioid drugs. However, in rat models of opioid-related behaviors, the circuit mechanisms of MOR-expressing cells are less known because of a lack of genetic tools to selectively manipulate them. We introduce a CRISPR-based Oprm1-Cre knock-in transgenic rat that provides cell type-specific genetic access to brain MOR-expressing cells. After performing anatomical and behavioral validation experiments, we used the Oprm1-Cre knock-in rats to show that lesioning NAc MOR-expressing cells had different effects on heroin self-administration in males and females. The new Oprm1-Cre rats can be used to study the role of brain MOR-expressing cells in animal models of opioid addiction, pain-related behaviors, and other opioid-mediated functions.

[Persistent Binding At Dopamine Transporters Determines Sustained Psychostimulant Effects](#)

Niello M, Sideromenos S, Gradisch R, O Shea R, Schwazer J, Maier J, Kastner N, Sandtner W, Jäntschi K, Lupica CR, Hoffman AF, Lubec G, Loland CJ, Stockner T, Pollak DD, Baumann MH, Sitte HH. Proc Natl Acad Sci U S A. February 7, 2023; 120(6): e2114204120.

Psychostimulants interacting with the dopamine transporter (DAT) can be used illicitly or for the treatment of specific neuropsychiatric disorders. However, they can also produce severe and persistent adverse events. Often, their pharmacological properties in vitro do not fully correlate to their pharmacological profile in vivo. Here, we investigated the pharmacological effects of enantiomers of pyrovalerone, α -pyrrolidinovalerophenone, and 3,4-methylenedioxypyrovalerone as compared to the traditional psychostimulants cocaine and methylphenidate, using a variety of in vitro, computational, and in vivo approaches. We found that in vitro drug-binding kinetics at DAT correlate with the time-course of in vivo psychostimulant action in mice. In particular, a slow dissociation (i.e., slow k_{off}) of *S*-enantiomers of pyrovalerone analogs from DAT predicts their more persistent in vivo effects when compared to cocaine and methylphenidate. Overall, our findings highlight the critical importance of drug-binding kinetics at DAT for determining the in vivo profile of effects produced by psychostimulant drugs.

[Mu Opioid Receptor Activation Mediates \(S\)-Ketamine Reinforcement In Rats: Implications For Abuse Liability](#)

Levinstein MR, Carlton ML, Di Ianni T, Ventriglia EN, Rizzo A, Gomez JL, Budinich RC, Shaham Y, Airan RD, Zarate CA Jr, Bonaventura J, Michaelides M. Biol Psychiatry. December 24, 2022; S0006-3223(22)01854-6.

Background: (S)-ketamine is an NMDA receptor antagonist, but it also binds to and activates mu opioid receptors (MORs) and kappa opioid receptors in vitro. However, the extent to which these receptors contribute to (S)-ketamine's in vivo pharmacology is unknown. **Methods:** We investigated the extent to which (S)-ketamine interacts with opioid receptors in rats by combining in

vitro and in vivo pharmacological approaches, in vivo molecular and functional imaging, and behavioral procedures relevant to human abuse liability. **Results:** We found that the preferential opioid receptor antagonist naltrexone decreased (S)-ketamine self-administration and (S)-ketamine-induced activation of the nucleus accumbens, a key brain reward region. A single reinforcing dose of (S)-ketamine occupied brain MORs in vivo, and repeated doses decreased MOR density and activity and decreased heroin reinforcement without producing changes in NMDA receptor or kappa opioid receptor density. **Conclusions:** These results suggest that (S)-ketamine's abuse liability in humans is mediated in part by brain MORs.

GRANTEE HONORS AND AWARDS

Lynette C. Daws, Ph.D., Professor, University of Texas Health Science Center at San Antonio, was awarded the David Lehr Research Award from the American College of Pharmacology and Experimental Therapeutics for her trailblazing research on biogenic amine transporters and their relevance to psychiatric disease.

Lakshmi A. Devi, Ph.D., Professor, Department of Pharmacological Sciences, Nash Family Department of Neuroscience and Department of Psychiatry at the Icahn School of Medicine at Mount Sinai and **Marta Filizola, Ph.D.**, Dean, Graduate School of Biomedical Sciences and Professor, Department of Pharmacological Sciences, Nash Family Department of Neuroscience, and Windreich Department of Artificial Intelligence and Human Health, Icahn School of Medicine at Mount Sinai were awarded the 2023 Jacobi Medallion for distinguished achievement in the field of medicine or for extraordinary service to the alumni.

Gail D’Onofrio, M.D., M.S., of the NIDA Clinical Trials Network (CTN) New England Consortium Node, received the “Recognizing Excellence Among Us: HEAL Director’s Award for Excellence in Research.”

Howard Edenberg, Ph.D., Distinguished Professor at the University of Indiana, was awarded the 2023 Henri Begleiter Award for Excellence in Research from the Research Society on Alcohol.

Carrie Ferrario, Ph.D., Associate Professor at the University of Michigan, was awarded the John Jacob Abel Award from the American College of Pharmacology and Experimental Therapeutics in recognition of her groundbreaking studies on the neural mechanisms underlying drug addiction and obesity.

David Fiellin, M.D., of the CTN New England Consortium Node, received the 2023 James H. Tharp Award from the American Society of Addiction Medicine for his contributions to finding a solution to the problem of alcohol use disorder.

Howard Gendelman, M.D., Professor and Chair of the Department of Pharmacology and Experimental Neuroscience, is the recipient of the 2023 University of Nebraska Faculty Intellectual Property Innovation and Commercialization Award.

Shelly Greenfield, M.D., M.P.H., of the CTN New England Consortium Node, received the 2022 American Academy of Addiction Psychiatry’s Founders’ Award for being an outstanding member of the community who has contributed significantly to the science, teaching, treatment, or public policy in the addictions.

Josee Guindon, D.V.M., Ph.D., Associate Professor, Department of Pharmacology and Neuroscience Texas Tech University Health Sciences Center, was named as the recipient of the 2023 International Cannabinoid Research Society William A. Devane Young Investigator Award. This award recognizes dedication, perseverance, and skill in studying and researching the endocannabinoid system.

Gabriel G. Haddad, M.D., Professor and Chair of Pediatrics, University of California, San Diego, has been elected as the Vice Chair of the Board of Governors of the St. Jude Research Hospital starting in July (2023-2025) and Chair of the Board subsequently.

Adam M. Leventhal, Ph.D., Professor of Population and Public Health Sciences, Director of the Institute for Addiction Science, at the Keck School of Medicine of the University of Southern California was awarded the 2023 MED Associates Brady-Schuster Award, which is given to an individual with a sustained record (at least 15 years after the doctoral degree) of conducting and publishing high-quality scientific research, with particular emphasis on a body of work that has had a lasting impact.

Scott Vrieze, Ph.D., Professor, University of Minnesota, was named the Scholar of the College in the College of Liberal Arts at the University of Minnesota.

STAFF HONORS AND AWARDS

A video produced by **Judith Lavelle, M.S.**, Supervisory Public Affairs Specialist; **Josie Anderson**, Digital Media Manager/Visual Production Specialist; and colleagues in the **Communications Branch**, titled “At the Intersection: Sex, Meth and HIV,” was awarded a National Association of Government Communicators Gold Screen Award of Excellence. This award program recognizes superior government communication products and those who produce them.

Marisela Morales, Ph.D., NIDA Intramural Research Program (IRP), was chosen to receive a 2023 Winter Conference on Brain Research Pioneer Award for her distinguished career as chief of the Integrative Neuroscience Research Branch and Neuronal Networks Section at the NIDA IRP.

Jonathan D. Pollock, Ph.D., Chief of the Genetics, Epigenetics, and Developmental Neuroscience Branch in the Division of Neuroscience and Behavior, received the Society for Neuroimmunology and Pharmacology award in the “Outstanding Service and Support” category.

STAFF CHANGES

New Appointments

Will Aklin, Ph.D., has been promoted to Chief, Clinical Research Grants Branch (CRGB) in the Division of Therapeutics and Medical Consequences (DTMC). Will earned his doctorate in Clinical Psychology from the University of Maryland, completed an internship in Clinical Psychology at the Yale University School of Medicine and a postdoctoral fellowship at Johns Hopkins School of Medicine. In his capacity as the Director of the Behavioral Therapy Development Program, DTMC, Will developed a robust behavioral therapy program and portfolio, along with strategic plans and research directions for clinical behavioral treatments and digital therapeutics.

New Staff

Stacy Coppess, M.L.I.S., joined the Office of Science Policy and Communications in March 2023 as a Technical Writer-Editor where she writes and edits webpages and publications for NIDA's Communications Branch. Prior to joining NIDA, Stacy was a medical librarian for the National Library of Medicine, where she developed consumer health information for MedlinePlus.gov, including on substance use topics. Stacy also developed and mapped MedlinePlus content to clinical health care terminology for inclusion in electronic health records.

Julia Solarczyk Donnelly, M.S., R.A.C., joined NIDA in April 2023 as the Chief, Regulatory Affairs Branch of DTMC. Before joining NIDA, Julia was a Senior Regulatory Affairs Associate at GenVec, Incorporated and MedImmune, LLC. She also served as a Regulatory Affairs Scientist and Regulatory Science Branch Chief (Acting) in the Division of Regulated Activities and Compliance of United States Army, and Director of Regulatory Affairs at Westat, Incorporated, where she was responsible for managing all aspects of the Regulatory Affairs Unit of the Clinical Trials Practice.

Shareen Iqbal, Ph.D., M.P.H., joined the Scientific Review Branch as a Scientific Review Officer. Shareen comes to NIDA from the Centers for Disease Control and Prevention's National Center for HIV, Viral Hepatitis, STD and TB prevention. She received a doctorate in Neuroscience, and master's in public health in Epidemiology from Emory University. She has significant biomedical and public health research experience—including the applied epidemiology of substance use, tuberculosis, and malaria. Shareen is also knowledgeable about the methods of laboratory neuroscience, systematic research synthesis, and national tuberculosis surveillance.

Chloe Jordan, Ph.D., recently re-joined the Division of Extramural Research (DER) as a scientific program manager for the HEALthy Brain and Child Development Study (HBCD) Study. Before returning to the HBCD Study, Chloe was a project director in the Division of Alcohol, Drugs and Addiction at McLean Hospital and an instructor in the Department of Psychiatry at Harvard Medical School, where she coordinated a NIDA CTN study evaluating opioid use disorder pharmacotherapy. Chloe completed her postdoctoral work in the Addiction Biology Unit at the NIDA IRP, where she studied neural mechanism-based medication development for drug use, and in the Basic Neuroscience Division at McLean Hospital, where she studied sex differences in neurodevelopmental risk factors for cocaine use.

Laila Khan joined NIDA's Financial Management Branch, Office of Management, in April 2023 as a Budget Analyst. Prior to joining NIDA, Laila worked as a Budget Analyst at Towson University's College of Fine Arts, where she used her financial management skills to enable students and staff to obtain grant funding to pursue their creative projects. She has worked for the City of Baltimore, gaining unique perspectives on municipal government finance and budgeting. Laila graduated from the Thomas Edison State College in 2008 with a bachelor's degree in Business Administration.

Hoang Le, Ph.D., joined NIDA as a Program Officer in the Chemistry, Pharmacology and Physiology Branch at DNB. Hoang has an extensive background in organic and medicinal chemistry. Before joining NIDA in 2023, he was an Assistant Professor of Medicinal Chemistry in the Department of BioMolecular Sciences in the School of Pharmacy at the University of Mississippi. Hoang's recent work is focused on ligands of the kappa opioid receptor. At NIDA, he will initially focus on developing and expanding a portfolio of grants on the chemistry and pharmacology of opioid receptors with special emphasis on novel ligands and molecular probes derived from natural product scaffolds.

Jessica Lukacs, M.D., M.B.A., joined the Office of Translational Initiatives and Program Innovations (OTIPI) from the Division of Scientific Categorization and Analysis in the NIH Office of the Director. She earned her bachelor's (Summa Cum Laude) with a double major in Economics and Cell Biology & Neuroscience from Rutgers University, her M.D. from the University of Virginia School of Medicine, and her M.B.A. from the University of Virginia Darden School of Business. She currently serves as the President of the Rutgers Alumni Club of DC.

Boris Sabirzhanov, Ph.D., M.A., joined OTIPI as a Health Scientist Administrator in March 2023. Prior to coming to NIDA, Boris served as a Research Biologist at the Armed Forces Radiobiology Research Institute at the Uniformed Services University of the Health Sciences and as a Postdoctoral Fellow, Faculty Research Associate, and Research Assistant Professor at the Shock, Trauma and Anesthesiology Research Center, Department of Anesthesiology, School of Medicine, University of Maryland, Baltimore. Boris was also a Postdoctoral Fellow, Neuroscience Group, Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota. He earned a Ph.D. in Molecular Biology from the Institute of Biochemistry and Genetics, Ufa Research Center, Russian Academy of Sciences.

Jaclyn Smith, Ph.D., M.A., joined NIDA's Division of Epidemiology, Prevention and Services Research on the newly established **Native Collective Research Effort to Enhance Wellness (N CREW) Program**. Through collaboration and training and technical assistance, Jaclyn will support Tribes and Native Serving Organizations as they enhance their research capacity and infrastructure to develop and conduct locally prioritized research projects and collect surveillance data to characterize substance use/misuse and related factors for their communities and Tribal/Native populations.

Jia Bei Wang, M.D., Ph.D., joined the Clinical Research Grants Branch at DTMC as a Health Scientist Administrator in February 2023. She has rich experience in drug abuse research as the pioneer in identifying the mu-opioid receptor and the nociceptin opioid receptor genes and the development of new medications for substance use disorders. Jia was one of the first recipients of NIDA's Avant-Garde Awards (2010) for Innovative Medication Development Research and had

successfully conducted preclinical and human safety and efficacy studies of the compound 1-tetrahydropalmatine—a molecule initially discovered in the extract of Chinese herbs—as a treatment for cocaine use disorder.

Sudhirkumar Yanpallewar, M.D., joined the Scientific Review Branch as a Scientific Review Officer. Sudhir is a trained neuroscientist with over two decades of behavioral neuroscience and pharmacology research experience. He is a medical doctor with specialization in pharmacology. Sudhir joined the National Cancer Institute (NCI) in 2005 and was promoted to a Staff Scientist position in 2013. At NCI, he has played an instrumental role in developing an animal model for behavioral neuroscience studies. His research focused on developing animal models of stress disorders, adult neuroplasticity, stroke, neurodegenerative disorders, pain, and neuropathic factor signaling.

Staff Departures

Garcia Elliott separated from NIDA in February 2023 to accept a position as a Medical Education Program Specialist at Walter Reed. Garcia had joined NIDA in November 2021 as a Management Analyst in the Management Analysis Branch, Office of Management. Her portfolio at NIDA included supporting the onboarding; Diversity, Equity, Inclusion, and Accessibility inventory; and risk management programs.

Arun Mather separated from NIDA in March 2023 to accept a position with the Substance Abuse and Mental Health Services Administration. Arun had joined NIDA in May 2020 as a Contract Specialist supporting the National Institute of Neurological Disorders and Stroke Section.

Josh Robbins, Social Media Strategist in NIDA’s Office of Science Policy and Communications, departed NIDA in March 2023.

Marian Wachtel, Ph.D., Director, Office of Extramural Policy at DER, is returning to the National Institute of Allergy and Infectious Diseases as a Scientific Initiatives Manager at the Office of Initiative Development.

Retirements

Kevin Walton Ph.D., Chief, Clinical Research Grants Branch (CRGB), DTMC, retired in March 2023 after 13 years of Federal service. His previous experience included 15 years in biopharmaceutical preclinical research for neurodegenerative and psychotherapeutic indications, followed by joining NIH as a Scientific Review Officer in the Center for Scientific Review. Kevin subsequently joined the NIDA Extramural Program in 2013 as a Health Scientist Administrator in DTMC, where he also served as Acting Chief for the Medical Consequences Branch. As Chief of the CRGB, Kevin was responsible for identifying strategic medications development clinical initiatives and worked closely with others in the Branch to pioneer neuromodulation, device-based and integrative interventions. He also worked on smoking cessation/harm reduction programs, including research tools to evaluate the safety and efficacy of electronic cigarettes.



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