DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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Director
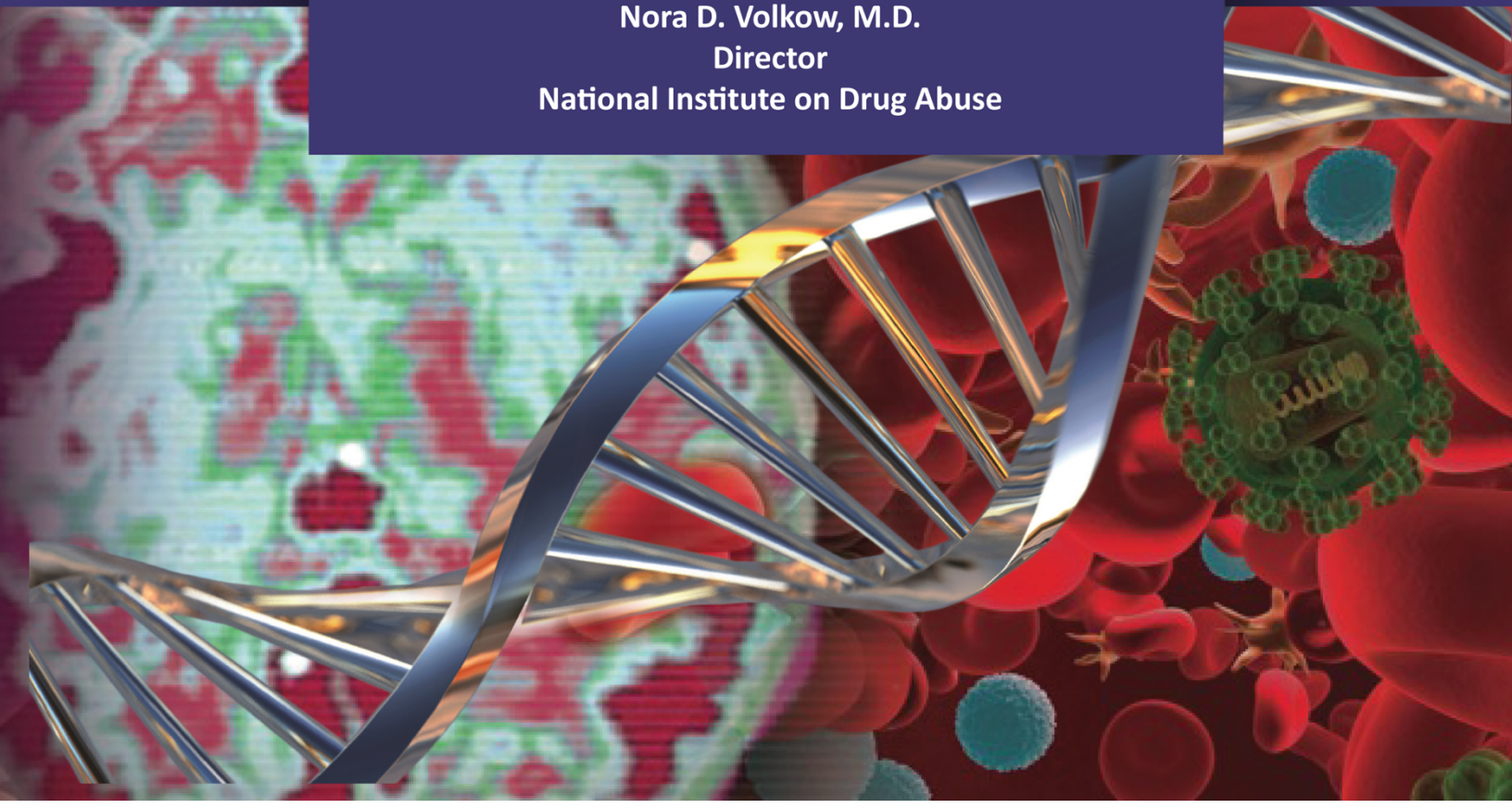**National Institute on Drug Abuse**

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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

An Endogenous Opioid Circuit Determines State-Dependent Reward Consumption Castro DC, Oswell CS, Zhang ET, Pedersen CE, Piantadosi SC, Rossi MA, Hunker AC, Guglin A, Moron JA, Zweifel LS, Stuber GD, Bruchas MR. Nature 13 October 2021; 598: 646-651.
μ-Opioid peptide receptor (MOPR) stimulation alters respiration, analgesia and reward behaviour, and can induce substance abuse and overdose. Despite its evident importance, the endogenous mechanisms for MOPR regulation of consummatory behaviour have remained unknown. Here we report that endogenous MOPR regulation of reward consumption in mice acts through a specific dorsal raphe to nucleus accumbens projection. MOPR-mediated inhibition of raphe terminals is necessary and sufficient to determine consummatory response, while select enkephalin-containing nucleus accumbens ensembles are engaged prior to reward consumption, suggesting that local enkephalin release is the source of the endogenous MOPR ligand. Selective modulation of nucleus accumbens enkephalin neurons and CRISPR–Cas9-mediated disruption of enkephalin substantiate this finding. These results isolate a fundamental endogenous opioid circuit for state-dependent consumptive behaviour and suggest alternative mechanisms for opiate modulation of reward.

Pharmacostorm Nanoscale Pharmacology Reveals Cariprazine Binding On Islands Of Calleja Granule Cells Prokop S, Ábrányi-Balogh P, Barti B, Vámosi M, Zöldi M, Barna L, Urbán GM, Tóth AD, Dudok B, Egyed A, Deng H, Leggio GM, Hunyady L, van der Stel M, Keserű GM, Katona I. Nat Commun 11 November 2021; 12(1): 6505.
Immunolabeling and autoradiography have traditionally been applied as the methods-of-choice to visualize and collect molecular information about physiological and pathological processes. Here, the authors introduce PharmacoSTORM super-resolution imaging that combines the complementary advantages of these approaches and enables cell-type- and compartment-specific nanoscale molecular measurements. They took advantage of PharmacoSTORM to provide in vivo evidence that cariprazine predominantly binds to D3 dopamine receptors on Islands of Calleja granule cell axons but avoids dopaminergic terminals. These findings show that PharmacoSTORM helps to quantify drug-target interaction sites at the nanoscale level in a cell-type- and subcellular context-dependent manner and within complex tissue preparations.

Chromatin-Mediated Alternative Splicing Regulates Cocaine-Reward Behavior Xu SJ, Lombroso SI, Fischer DK, Carpenter MD, Marchione DM, Hamilton PJ, Lim CJ, Neve RL, Garcia BA, Wimmer ME, Pierce RC, Heller EA. Neuron. 2021 Sep 15; 109(18): 2943-2966.e8.
Neuronal alternative splicing is a key gene regulatory mechanism in the brain. However, the spliceosome machinery is insufficient to fully specify splicing complexity. In considering the role of the epigenome in activity-dependent alternative splicing, we and others find the histone modification H3K36me3 to be a putative splicing regulator. In this study, we found that mouse cocaine self-administration caused widespread differential alternative splicing, concomitant with the enrichment of H3K36me3 at differentially spliced junctions. Importantly, only targeted epigenetic editing can distinguish between a direct role of H3K36me3 in splicing and an indirect role via regulation of splice factor expression elsewhere on the genome. We targeted Srsf11, which was both alternatively spliced and H3K36me3 enriched in the brain following cocaine self-

administration. Epigenetic editing of H3K36me3 at Srsf11 was sufficient to drive its alternative splicing and enhanced cocaine self-administration, establishing the direct causal relevance of H3K36me3 to alternative splicing of Srsf11 and to reward behavior.

[Closed-Loop Enhancement And Neural Decoding Of Cognitive Control In Humans](#) Basu I, Yousefi A, Crocker B, Zelmann R, Paulk AC, Peled N, Ellard KK, Weisholtz DS, Cosgrove GR, Deckersbach T, Eden UT, Eskandar EN, Dougherty DD, Cash SS, Widge AS. Nature Biomedical Engineering 01 November 2021, 1-13.
Deficits in cognitive control—that is, in the ability to withhold a default pre-potent response in favour of a more adaptive choice—are common in depression, anxiety, addiction, and other mental disorders. Here we report proof-of-concept evidence that, in participants undergoing intracranial epilepsy monitoring, closed-loop direct stimulation of the internal capsule or striatum, especially the dorsal sites, enhances the participants' cognitive control during a conflict task. We also show that closed-loop stimulation upon the detection of lapses in cognitive control produced larger behavioural changes than open-loop stimulation, and that task performance for single trials can be directly decoded from the activity of a small number of electrodes via neural features that are compatible with existing closed-loop brain implants. Closed-loop enhancement of cognitive control might remediate underlying cognitive deficits and aid the treatment of severe mental disorders.

[Synthon-Based Ligand Discovery In Virtual Libraries Of Over 11 Billion Compounds](#)
Sadybekov AA, Sadybekov AV, Liu Y, Iliopoulos-Tsoutsouvas C, Huang XP, Pickett J, Houser B, Patel N, Tran NK, Tong F, Zvonok N, Jain MK, Savych O, Radchenko DS, Nikas SP, Petasis NA, Moroz YS, Roth BL, Makriyannis A, Katritch V. Nature, 15 Dec 2021.
Structure-based virtual ligand screening is emerging as a key paradigm for early drug discovery owing to the availability of high-resolution target structures and ultra-large libraries of virtual compounds. However, to keep pace with the rapid growth of virtual libraries, such as readily available for synthesis (REAL) combinatorial libraries, new approaches to compound screening are needed. Here we introduce a modular synthon-based approach-V-SYNTHES-to perform hierarchical structure-based screening of a REAL Space library of more than 11 billion compounds. V-SYNTHES first identifies the best scaffold-synthon combinations as seeds suitable for further growth, and then iteratively elaborates these seeds to select complete molecules with the best docking scores. This hierarchical combinatorial approach enables the rapid detection of the best-scoring compounds in the gigascale chemical space while performing docking of only a small fraction (<0.1%) of the library compounds. Chemical synthesis and experimental testing of novel cannabinoid antagonists predicted by V-SYNTHES demonstrated a 33% hit rate, including 14 submicromolar ligands, substantially improving over a standard virtual screening of the Enamine REAL diversity subset, which required approximately 100 times more computational resources. Synthesis of selected analogues of the best hits further improved potencies and affinities (best inhibitory constant (K_i) = 0.9 nM) and CB_2/CB_1 selectivity (50-200-fold). V-SYNTHES was also tested on a kinase target, ROCK1, further supporting its use for lead discovery. The approach is easily scalable for the rapid growth of combinatorial libraries and potentially adaptable to any docking algorithm.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Patterns And Correlates Of Cannabidiol Product And Marijuana Co-Use In A Sample Of U.S. Young Adults Dunbar MS, Seelam R, Tucker JS, Firth CL, Pedersen ER, Klein DJ, Rodriguez A, D'Amico EJ. Addict Behav. 2021 Nov 20; 126: 107185.

Objective: Cannabis-derived products containing cannabidiol with no or minimal levels of delta 9-tetrahydrocannabinol (CBD products) are widely available in the United States and use of these products is common among young adults and those who use marijuana. The purpose of this study was to examine patterns and correlates of CBD product use and co-use with marijuana in a sample of young adults. Method: The study used cross-sectional survey data collected in 2019-2020 from a cohort of young adults (n = 2534; mean age 23) based primarily in California. The survey assessed lifetime, past-year, and past-month frequency and type of CBD products used, frequency and amount of marijuana consumption and indicators of marijuana use-related problems. Linear, Poisson, and logistic regression models compared individuals reporting past month CBD-only use, marijuana-only use, concurrent CBD + marijuana use (co-use), and use of neither product. Among those reporting co-use, we examined associations between CBD use frequency and marijuana use frequency and heaviness of use (occasions per day) and indicators of problem marijuana use (e.g., Cannabis Use Disorder Identification Test Short-Form, solitary use, marijuana consequences). Results: Approximately 13% of respondents endorsed past-month CBD use; of these, over three-quarters (79%) indicated past-month co-use of marijuana. Among individuals reporting co-use, more frequent CBD use was associated with more frequent and heavier marijuana use but was not associated with marijuana use-related problems. Conclusions: CBD use was common and associated with higher levels of marijuana consumption in this sample. Routinely assessing CBD use may provide a more comprehensive understanding of individuals' cannabis product consumption.

Examining The Effects Of Implicit And Explicit Racial Identity On Psychological Distress And Substance Use Among Black Young Adults Clifton RL, Rowe AT, Banks DE, Ashburn-Nardo L, Zapolski TCB. Exp Clin Psychopharmacol. 2021 Oct; 29(5): 479-486.

Racial identity is an aspect of self-concept that is important to the mental and behavioral health of Black individuals. Yet, much of the current research on racial identity is based on self-report measures, which may impact findings due to reporting biases. One way to alleviate some of the measurement concerns is to use implicit measures to assess racial identity. The purpose of the present study was to examine whether an implicit assessment of racial identity, specifically racial centrality, provided a unique contribution to the understanding of risk for psychological distress and substance use among Black young adults above potential effects observed from an explicit measurement of racial identity. Additionally, the potential moderating effect of implicit racial identity, controlling for explicit racial identity, on the association between racial discrimination and these health outcomes was also examined. One hundred and forty-seven Black young adults participated in this study. Contrary to our hypothesis, there was no significant main effect of implicit racial centrality on depressive symptoms or substance use after accounting for explicit racial centrality. However, after controlling for explicit racial centrality, a significant moderating effect of implicit racial centrality on the relationship between racial discrimination and substance use was observed. Although support for all of our hypotheses was not definitively found, our findings can be added to this emerging area of study. Additionally, potential explanations for the findings are provided that can be used to inform future research in this area to better understand the utility of assessing for implicit racial identity among Black young adults.

Addressing Barriers To Primary Care Screening And Referral To Prevention For Youth Risky Health Behaviors: Evidence Regarding Potential Cost-Savings And Provider Concerns Ridenour TA, Murray DW, Hinde J, Glasheen C, Wilkinson A, Rackers H, Coyne-Beasley T Prev Sci 2021 Oct 29; 1-12.

Despite growing evidence and support for co-locating behavioral services in primary care to prevent risky health behaviors, implementation of these services has been limited due to a lack of reimbursement for services and negative perceptions among providers. The researchers investigated potential to overcome these barriers based on new developments in healthcare funding and screening and referral to prevention (SRP) in primary care based on the Consolidated Framework for Implementation Research (CFIR), which could guide future SRP implementation strategies. To investigate the economic need for healthcare-based SRP, the researchers quantified hospital charges to healthcare payors for services arising from adolescent risky behaviors (e.g., substance use, risky sex). Annual North Carolina (NC) hospital charges for these services exceeded $327 M (2019 dollars), suggesting high potential for cost savings if SRP can curb hospital services associated with risky behaviors. To investigate provider barriers and facilitators, 151 NC pediatricians and 230 NC family therapists were surveyed about their attitudes regarding a recently developed well-child visit SRP with family-based prevention. Both sets of professionals reported widespread need for and interest in the SRP but cited barriers of lack of reimbursement, training, and referrals to/from each other. Physicians, but not family therapists, reported concerns with poor patient or parent compliance. Many barriers could be resolved by co-locating family therapists in pediatric clinics to conduct well-child SRP. Results support further research to develop business models for payor-funded SRP and CFIR-guided research to develop implementation strategies for primary care SRP to prevent adolescent risky health behaviors.

Individual And Community Factors Associated With Naloxone Co-prescribing Among Long-term Opioid Patients: A Retrospective Analysis Stein BD, Smart R, Jones C M, Sheng F, Powell D, Sorbero M. Journal of General Internal Medicine, 2021; 36(10): 2952–2957.

Naloxone co-prescribing to individuals at increased opioid overdose risk is a key component of opioid overdose prevention efforts. This retrospective cross-sectional study of 2017-2018 pharmacy claims representing 90% of all prescriptions filled at retail pharmacies in 50 states and the District of Columbia to examine co-prescribing of naloxone for individuals on long-term opioid therapy for pain. Naloxone co-prescribing occurred in only 2.3% of long-term opioid therapy episodes. Odds of naloxone co-prescribing were higher for Medicaid and Medicare episodes, having high-dose opioid episodes, when concomitant benzodiazepines were prescribed, and in counties with higher fatal overdose rates. Co-prescription of naloxone represents a tangible clinical action that can be taken to help prevent opioid overdose deaths. However, despite recommendations to co-prescribe naloxone to patients at increased risk for opioid overdose, the investigators found that co-prescribing rates remain low overall. States, insurers, and health systems should consider implementing strategies to facilitate increased co-prescribing of naloxone to at-risk individuals.

Methadone And Buprenorphine Discontinuation Among Postpartum Women With Opioid Use Disorder Schiff DM, Nielsen TC, Hoeppner BB, Terplan M, Hadland SE, Bernson D, Greenfield S F, Bernstein J, Bharel M, Reddy J, Taveras EM, Kelly JF, Wilens TE. American Journal of Obstetrics and Gynecology, 2021; 225(4): 424.e1–424.e12.

The postpartum year is a vulnerable period for women with opioid use disorder, with increased rates of fatal and nonfatal overdose; however, data on the continuation of medications for opioid use

disorder on a population level are limited. This study aimed to determine the extent to which maternal and infant characteristics are associated with time to discontinuation of medications for opioid use disorder. This population-based retrospective cohort study used linked administrative data of 2,314 women who received medications for opioid use disorder at delivery in Massachusetts between 2011 and 2014 to examine the adherence to medications for opioid use disorder. Overall, 1,484 women (64.1%) continued receiving medications for opioid use disorder for a full 12 months following delivery. The rate of continued medication use varied from 34% if women started on medications for opioid use disorder the month before delivery to 80% if the medications were used throughout pregnancy. Duration of receipt of prenatal medications for opioid use disorder and incarceration were most strongly associated with the discontinuation of medications for opioid use disorder. Rates of medication continuation also varied significantly by race and ethnicity. Prioritizing medication continuation across the perinatal continuum and expanding access to medications for opioid use disorder for women who are incarcerated can help improve postpartum medication adherence.

TREATMENT RESEARCH

Engineering Quick- And Long-Acting Naloxone Delivery Systems For Treating Opioid Overdose Sharifi Farrokh, Meqbil Yazan J, Otte Andrew, Gutridge Anna M, Blaine Arryn T, van Rijn Richard M, Park Kinam. Pharm Res. 2021; 38(7): 1221-1234.
PURPOSE: Opioids have been the main factor for drug overdose deaths in the United States. Current naloxone delivery systems are effective in mitigating the opioid effects only for hours. Naloxone-loaded poly(lactide-co-glycolide) (PLGA) microparticles were prepared as quick- and long-acting naloxone delivery systems to extend the naloxone effect as an opioid antidote. METHODS: The naloxone-PLGA microparticles were made using an emulsification solvent extraction approach with different formulation and processing parameters. Two PLGA polymers with the lactide:glycolide (L:G) ratios of 50:50 and 75:25 were used, and the drug loading was varied from 21% to 51%. Two different microparticles of different sizes with the average diameters of 23 μm and 50 μm were produced using two homogenization-sieving conditions. All the microparticles were critically characterized, and three of them were evaluated with β-arrestin recruitment assays. RESULTS: The naloxone encapsulation efficiency (EE) was in the range of 70-85%. The EE was enhanced when the theoretical naloxone loading was increased from 30% to 60%, the L:G ratio was changed from 50:50 to 75:25, and the average size of the particles was reduced from 50 μm to 23 μm. The in vitro naloxone release duration ranged from 4 to 35 days. Reducing the average size of the microparticles from 50 μm to 23 μm helped eliminate the lag phase and obtain the steady-state drug release profile. The cellular pharmacodynamics of three selected formulations were evaluated by applying DAMGO, a synthetic opioid peptide agonist to a μ-opioid receptor, to recruit β-arrestin 2. CONCLUSIONS: Naloxone released from the three selected formulations could inhibit DAMGO-induced β-arrestin 2 recruitment. This indicates that the proposed naloxone delivery system is adequate for opioid reversal during the naloxone release duration.

Functional Profile Of Systemic And Intrathecal Cebranopadol In Nonhuman Primates Ding Huiping, Trapella Claudio, Kiguchi Norikazu, Hsu Fang-Chi, Caló Girolamo Ko, Mei-Chuan. Anesthesiology. 2021; 135(3): 482-493.

BACKGROUND: Cebranopadol, a mixed nociceptin/opioid receptor full agonist, can effectively relieve pain in rodents and humans. However, it is unclear to what degree different opioid receptor subtypes contribute to its antinociception and whether cebranopadol lacks acute opioid-associated side effects in primates. The authors hypothesized that coactivation of nociceptin receptors and μ receptors produces analgesia with reduced side effects in nonhuman primates. METHODS: The antinociceptive, reinforcing, respiratory-depressant, and pruritic effects of cebranopadol in adult rhesus monkeys (n = 22) were compared with μ receptor agonists fentanyl and morphine using assays, including acute thermal nociception, IV drug self-administration, telemetric measurement of respiratory function, and itch-scratching responses. RESULTS: Subcutaneous cebranopadol (ED50, 2.9 [95% CI, 1.8 to 4.6] μg/kg) potently produced antinociception compared to fentanyl (15.8 [14.6 to 17.1] μg/kg). Pretreatment with antagonists selective for nociceptin and μ receptors, but not δ and κ receptor antagonists, caused rightward shifts of the antinociceptive dose-response curve of cebranopadol with dose ratios of 2 and 9, respectively. Cebranopadol produced reinforcing effects comparable to fentanyl, but with decreased reinforcing strength, i.e., cebranopadol (mean ± SD, 7 ± 3 injections) versus fentanyl (12 ± 3 injections) determined by a progressive-ratio schedule of reinforcement. Unlike fentanyl (8 ± 2 breaths/min), systemic cebranopadol at higher doses did not decrease the respiratory rate (17 ± 2 breaths/min). Intrathecal cebranopadol (1 μg) exerted full antinociception with minimal scratching responses (231 ± 137 scratches) in contrast to intrathecal morphine (30 μg; 3,009 ± 1,474 scratches). CONCLUSIONS: In nonhuman primates, the μ receptor mainly contributed to cebranopadol-induced antinociception. Similar to nociceptin/μ receptor partial agonists, cebranopadol displayed reduced side effects, such as a lack of respiratory depression and pruritus. Although cebranopadol showed reduced reinforcing strength, its detectable reinforcing effects and strength warrant caution, which is critical for the development and clinical use of cebranopadol.

Differential In Vitro Pharmacological Profiles Of Structurally Diverse Nociceptin Receptor Agonists In Activating G Protein And Beta-Arrestin Signaling At The Human Nociceptin Opioid Receptor Lu James J; Polgar Willma E, Mann Anika, Dasgupta Pooja, Schulz Stefan, Zaveri Nurulain T. Mol Pharmacol. 2021; 100(1): 7-18.

Agonists at the nociceptin opioid peptide receptor (NOP) are under investigation as therapeutics for nonaddicting analgesia, opioid use disorder, Parkinson's disease, and other indications. NOP full and partial agonists have both been of interest, particularly since NOP partial agonists show a reduced propensity for behavioral disruption than NOP full agonists. Here, we investigated the in vitro pharmacological properties of chemically diverse NOP receptor agonists in assays measuring functional activation of the NOP receptor such as guanosine 5'-O-[gamma-thio]triphosphate (GTPγS) binding, cAMP inhibition, G protein-coupled inwardly rectifying potassium (GIRK) channel activation, phosphorylation, β-arrestin recruitment and receptor internalization. When normalized to the efficacy of the natural agonist nociceptin/orphanin FQ (N/OFQ), we found that different functional assays that measure intrinsic activity produce inconsistent levels of agonist efficacy, particularly for ligands that were partial agonists. Agonist efficacy obtained in the GTPγS assay tended to be lower than that in the cAMP and GIRK assays. These structurally diverse NOP agonists also showed differential receptor phosphorylation profiles at the phosphosites we examined and induced varying levels of receptor internalization. Interestingly, although the rank order for β-arrestin recruitment by these NOP agonists was consistent with their ability to induce receptor internalization, their phosphorylation signatures at the time point we investigated were not indicative of the levels of β-arrestin recruitment or internalization induced by these agonists. It is

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possible that other phosphorylation sites, yet to be identified, drive the recruitment of NOP receptor ensembles and subsequent receptor trafficking by some nonpeptide NOP agonists. These findings potentially help understand NOP agonist pharmacology in the context of ligand-activated receptor trafficking. SIGNIFICANCE STATEMENT: Chemically diverse agonist ligands at the nociceptin opioid receptor G protein-coupled receptor showed differential efficacy for activating downstream events after receptor binding, in a suite of functional assays measuring guanosine 5'-O-[gamma-thio]triphosphate binding, cAMP inhibition, G protein-coupled inwardly rectifying protein channel activation, β-arrestin recruitment, receptor internalization and receptor phosphorylation. These analyses provide a context for understanding nociceptin opioid peptide receptor (NOP) agonist pharmacology driven by ligand-induced differential NOP receptor signaling.

[**Glucagon-Like Peptide-1 Receptor Agonist, Liraglutide, Reduces Heroin Self-Administration And Drug-Induced Reinstatement Of Heroin-Seeking Behaviour In Rats**](#) Douton Joaquin E, Horvath Nelli, Mills-Huffnagle Sara, Nyland Jennifer E, Hajnal Andras, Grigson Patricia S. Addict Biol. 2021; e13117.
Drug addiction is a chronic brain disease characterized by the uncontrolled use of a substance. Due to its relapsing nature, addiction is difficult to treat, as individuals can relapse following even long periods of abstinence and, it is during this time, that they are most vulnerable to overdose. In America, opioid overdose has been increasing for decades, making finding new treatments to help patients remain abstinent and prevent overdose deaths imperative. Recently, glucagon-like peptide-1 (GLP-1) receptor agonists have shown promise in reducing motivated behaviours for drugs of abuse. In this study, we test the effectiveness of the GLP-1 analogue, liraglutide (LIR), in reducing heroin addiction-like behaviour, and the potential side effects associated with the treatment. We show that daily treatment with LIR (0.1 mg/kg sc) increases the latency to take heroin, reduces heroin self-administration, prevents escalation of heroin self-administration and reduces drug-induced reinstatement of heroin-seeking behaviour in rats. A 1-h pretreatment time, however, was too short to reduce cue-induced seeking in our study. Moreover, we showed that, while LIR (0.1, 0.3, 0.6 and 1.0 mg/kg sc) supported conditioned taste avoidance of a LIR-paired saccharin cue, it did not elicit intake of the antiemetic kaolin in heroin-naïve or heroin-experienced rats. Further, 0.1 mg/kg LIR did not produce great disruptions in food intake or body weight. Overall, the data show that LIR is effective in reducing heroin taking and heroin seeking at doses that do not cause malaise and have a modest effect on food intake and body weight gain.

[**A Novel Maintenance Therapeutic For Opioid Use Disorder**](#) Youngblood Beth, Li Kevin, Gehlert Donald R, Medina Julio C, Schwartz Neil. J Pharmacol Exp Ther. 2021; 378(2): 133-145.
Opioid use disorder (OUD) is a major socioeconomic burden. An ideal OUD pharmacotherapy will mitigate the suffering associated with opioid-withdrawal, inhibit the effects of high efficacy opioids, and minimize opioid-cravings while being safe and accessible to a diverse patient population. Although current OUD pharmacotherapies inhibit the euphoric effects of opioids of abuse, the extent to which they safely alleviate withdrawal and opioid-cravings corresponds with their intrinsic μ opioid receptor (MOR) efficacy. In addition to inhibiting the euphoric effects of opioids of abuse, the medium efficacy MOR agonist buprenorphine alleviates withdrawal and opioid-cravings, but its intrinsic MOR efficacy is sufficient such that its utility is limited by abuse and safety liabilities. Although the MOR antagonist naltrexone minimizes euphoria and has no abuse liability, it exacerbates suffering associated with withdrawal and opioid cravings. Therefore, a therapeutic with intrinsic MOR activity between the partial agonist (buprenorphine) and the antagonist (naltrexone)

would strike a balance between the benefits and liabilities of these two therapeutics. To address this need, we derived RM1490, an MOR agonist based on a nonmorphinan scaffold that exhibits approximately half the intrinsic MOR efficacy of buprenorphine. In a series of preclinical assays, we compared RM1490 with buprenorphine and naltrexone at doses that achieve therapeutic levels of central nervous system MOR occupancy. RM1490 exhibited a behavioral profile consistent with reduced reward, dependence, and precipitated withdrawal liabilities. RM1490 was also more effective than buprenorphine at reversing the respiratory depressant effects of fentanyl and did not suppress respiration when combined with diazepam. SIGNIFICANCE STATEMENT: In preclinical studies, RM1490 has a physiological and behavioral profile suitable for opioid use disorder maintenance therapy.

Effects Of Cytidine-5'-Diphosphate Choline On Gray Matter Volumes In Methampheta-Mine-Dependent Patients: A Randomized, Double-Blind, Placebo-Controlled Study
Hyeonseok Jeong, Sujung Yoon, Young-Hoon Sung, Jungyoon Kim, In Kyoon Lyoo, Yurgelun-Todd Deborah A, Renshaw Perry F. J Psychiatr Res. 2021; 143: 215-221.
BACKGROUND: Cytidine-5'-diphosphate choline (CDP-choline) has been suggested to exert neuroprotective and neuroreparative effects and may be beneficial for patients with stimulant dependence. This randomized, double-blind, placebo-controlled study in methamphetamine (MA) dependence investigated effects of CDP-choline on the brain structures and their associations with craving and MA use. METHODS: MA users (n = 44) were randomized to receive 2 g/day of CDP-choline (n = 22) or placebo (n = 22) for 8 weeks. Patients underwent brain magnetic resonance imaging (MRI) at baseline and 8-week follow-up. Healthy individuals (n = 27) were also examined using brain MRI at the same interval. Voxel-based morphometry analysis was conducted to examine changes in gray matter (GM) volumes and their associations with craving and MA use. RESULTS: Craving for MA was significantly reduced after the 8 week-treatment with CDP-choline (p = 0.01), but not with the placebo treatment (p = 0.10). There was no significant difference in the total number of MA-negative urine samples between the two groups (p = 0.19). With CDP-choline treatment, GM volumes in the left middle frontal gyrus (p = 0.001), right hippocampus (p = 0.009), and left precuneus (p = 0.001) were the left middle frontal gyrus with CDP-choline treatment were associated with reduced craving for MA (Spearman's ρ = -0.56, p = 0.03). In addition, the right hippocampal volume increases were positively associated with the total number of MA-negative urine results in the CDP-choline group (Spearman's ρ = 0.67, p = 0.006). CONCLUSION: Our findings suggest that CDP-choline may increase GM volumes of MA-dependent patients, which may be related to decreases in MA use and craving.

HIV RESEARCH

Associations Of Prescription Stimulant Misuse With Subsequent Methamphetamine Use Among A U.S. Cohort Of HIV-Vulnerable Sexual And Gender Minorities Who Have Sex With Men Westmoreland DA, Goldshear JL, Carrico AW, Grov C. Drug Alcohol Depend 2021 Sep 1; 226.
Prescription stimulants and methamphetamine have similarities in chemical structure and impact on biological functioning. However, there is limited literature on prescription stimulant misuse among sexual and gender minorities as well as how prescription misuse may impact later methamphetamine use. Data collected from a HIV prevention cohort was used to describe (e.g.,

frequencies, percentages) prescription stimulant use/misuse and methamphetamine use at baseline and 12-month follow-up (n = 4857). Multivariable logistic regression models were used to determine the impact of baseline prescription stimulant misuse and methamphetamine use on 12-month prescription stimulant misuse and methamphetamine use. At baseline, 10.2 % of participants misused prescription stimulants and 12 % of participants used methamphetamine in the past 3 months, while at 12-month follow-up 11.6 % of participants misused prescription stimulants and 11.2 % of participants used methamphetamine in the past 3 months. Multivariable regression analyses indicated that participants who misused prescription stimulants (in the absence of methamphetamine) at baseline had 2.51 (95 % CI: 1.44-3.59, ref. no stimulant or methamphetamine use) times the odds of using methamphetamine at 12-month follow-up. Findings suggest that prescription stimulant use is a risk factor for continued meth use. Therefore, earlier and targeted public health interventions could reduce methamphetamine use by disrupting the progression from prescription stimulant misuse to methamphetamine use through early screening and interventions for prescription stimulant misuse.

Associations Between Fentanyl Use And Initiation, Persistence, And Retention On Medications For Opioid Use Disorder Among People Living With Uncontrolled HIV Disease
Cook RR, Torralva R, King C, Lum PJ, Tookes H, Foot C, Vergara-Rodriguez P, Rodriguez A, Fanucchi L, Lucas GM, Waddell EN, Korthuis PT. Drug and Alcohol Dependence, 2021; 228. Associations between fentanyl use and initiation and retention on medications for opioid use disorder (MOUD) are poorly understood. Data were from a multisite clinical trial comparing extended-release naltrexone (XR-NTX) with treatment as usual (TAU; buprenorphine or methadone) to achieve HIV viral suppression among 111 people with OUD and uncontrolled HIV disease. The exposure of interest was fentanyl use, as measured by urine drug screening. Outcomes were time to MOUD initiation, MOUD persistence, and MOUD retention. Sixty-four percent of participants tested positive for fentanyl at baseline. Participants with baseline fentanyl positivity were 11 times less likely to initiate XR-NTX than those negative for fentanyl, but there was no evidence that fentanyl use impacted the likelihood of TAU initiation. Baseline fentanyl use was not associated with persistence or retention on any MOUD. Fentanyl use was a substantial barrier to XR-NTX initiation for the treatment of OUD in persons with uncontrolled HIV infection. There was no evidence that fentanyl use impacted partial/full agonist initiation and, once initiated, retention on any MOUD.

Effect Of HIV, Antiretrovirals, And Genetics On Methadone Pharmacokinetics: Results From The Methadone Antiretroviral Pharmacokinetics Study Bart Gavin, Giang Le Minh, Yen Hoang, Hodges James S, Brundage Richard C. Drug Alcohol Depend. 2021; 227: 109025. BACKGROUND: Methadone treatment of opioid use disorder in HIV-infected individuals is complicated by drug-drug interactions. Genetic and other cofactors further contribute to interindividual variability in methadone pharmacokinetics. We used population pharmacokinetics to estimate the effect of drug-drug interactions, genetics, and other cofactors on methadone pharmacokinetics in a methadone maintained population in Vietnam. METHODS: Plasma R- and S-methadone levels were measured in 309 methadone maintained individuals just before and 2-5 h following methadone dosing. A linear one-compartment population pharmacokinetic model with first-order conditional estimation with interaction was used to evaluate methadone clearance (CL/F) and volume of distribution (V/F). The influence of covariates on parameter estimates was evaluated using stepwise covariate modeling. Covariates included HIV status, antiretroviral use (efavirenz or

nevirapine), weight, BMI, age, methadone dose, and 8 single nucleotide polymorphisms in across the CYP2B6, ABCB1, and NR1I3 genes. RESULTS: Taking either efavirenz or nevirapine increased R-methadone CL/F 220%. Nevirapine and efavirenz increased S-methadone CL/F by 404% and 273%, respectively. Variants in NR1I3 increased R- and S-methadone CL/F by approximately 20% only in patients taking efavirenz. Different alleles in ABCB1 rs2032582 either increased or decreased R-methadone CL/F by 10%. The CYP 2B6*4 variant decreased S-methadone CL/F by 18%. HIV-infection increased R- and S-methadone CL/F and V/F by 24%-39%. CONCLUSIONS: The HIV antiretrovirals nevirapine and efavirenz significantly increase methadone clearance. Variants in NR1I3 increased the effect of efavirenz on methadone clearance. Other variants affecting methadone CL/F were also confirmed. To our knowledge, this is the first report of HIV itself affecting methadone pharmacokinetics.

[Cocaine Augments Neuro-Inflammation Via Modulating Extracellular Vesicle Release In HIV-1 Infected Immune Cells](#) Narayanan M, Kulkarni R, Jiang S, Kashanchi F, Prasad A. Retrovirology. 16 Septemeber 2021, 18(1): 26.
Extracellular Vesicles (EV) recently have been implicated in the pathogenesis of HIV-1 syndromes, including neuroinflammation and HIV-1 associated neurological disorder (HAND). Cocaine, an illicit stimulant drug used worldwide is known to exacerbate these HIV-1 associated neurological syndromes. However, the effects of cocaine on EV biogenesis and roles of EVs in enhancing HIV-1 pathogenesis are not yet well defined. Here, we investigated the effects of cocaine on EV biogenesis and release in HIV-1 infected immune cells and explored their roles in elicitation of neuroinflammation. We found that cocaine significantly augmented the release of EVs from uninfected and HIV-1 infected T-cells, DCs and macrophages. Further analysis of the molecular components of EVs revealed enhanced expression of adhesion molecules integrin β1 and LFA-1 in those EVs derived from cocaine treated cells. Intriguingly, in EVs derived from HIV-1 infected cells, cocaine treatment significantly increased the levels of viral genes in EVs released from macrophages and DCs, but not in T-cells. Exploring the molecular mechanism to account for this, we found that DCs and macrophages showed enhanced expression of the cocaine receptor Sigma 1-Receptor compared to T-cells. In addition, we found that cocaine significantly altered the integrity of the RNA-induced silencing complex (RISC) in HIV-1 infected macrophages and DCs compared to untreated HIV-1 infected cells. Characterizing further the molecular mechanisms involved in how cocaine increased EV release, we found that cocaine decreased the expression of the interferon-inducible protein BST-2; this resulted in altered trafficking of intracellular virus containing vesicles and EV biogenesis and release. We also observed EVs released from cocaine treated HIV-1 infected macrophages and DCs enhanced HIV-1 trans-infection to T-cells compared to those from untreated and HIV-1 infected cells. These EVs triggered release of proinflammatory cytokines in human brain microvascular endothelial cells (HBMECs) and altered monolayer integrity. Taken together, our results provide a novel mechanism which helps to elucidate the enhanced prevalence of neurological disorders in cocaine using HIV-1 infected individuals and offers insights into developing novel therapeutic strategies against HAND in these hosts.

[Plasma Virome And The Risk Of Blood-Borne Infection In Persons With Substance Use Disorder](#) Kandathil AJ, Cox AL, Page K, Mohr D, Razaghi R, Ghanem KG, Tuddenham SA, Hsieh Y-H, Evans JL, Coller KE, Timp W, Celentano DD, Ray SC, Thomas DL. Nature Communications 25 November 2021; 12(1): 6909.

There is an urgent need for innovative methods to reduce transmission of bloodborne pathogens like HIV and HCV among people who inject drugs (PWID). We investigate if PWID who acquire non-pathogenic bloodborne viruses like anelloviruses and pegiviruses might be at greater risk of acquiring a bloodborne pathogen. PWID who later acquire HCV accumulate more non-pathogenic viruses in plasma than matched controls who do not acquire HCV infection. Additionally, phylogenetic analysis of those non-pathogenic virus sequences reveals drug use networks. Here we find first in Baltimore and confirm in San Francisco that the accumulation of non-pathogenic viruses in PWID is a harbinger for subsequent acquisition of pathogenic viruses, knowledge that may guide the prioritization of the public health resources to combat HIV and HCV.

[Perspectives On Extended-Release Naltrexone Induction Among Patients Living With HIV And Opioid Use Disorder: A Qualitative Analysis](). Hoffman KA, Baker R, Fanucchi LC, Lum PJ, Kunkel LE, Ponce Terashima J, McCarty D, Jacobs P, Korthuis PT. Addict Sci Clin Pract. 2021 Nov 10; 16(1): 67.
Background: The CHOICES study randomized participants with HIV and opioid use disorder (OUD) to HIV clinic-based extended-release naltrexone (XR-NTX), which requires complete cessation of opioid use, versus treatment-as-usual (i.e., buprenorphine, methadone). Study participants randomized to XR-NTX were interviewed to assess their experiences with successful and unsuccessful XR-NTX induction. **Methods:** Semi-structured qualitative interviews were completed with a convenience sample of study participants with HIV and OUD (n = 37) randomized to XR-NTX in five HIV clinics between 2018 and 2019. All participants approached agreed to be interviewed. Interviews were digitally recorded, professionally transcribed, and analyzed using thematic analysis. **Results:** Participants included women (43%), African Americans (62%) and Hispanics (16%), between 27 to 69 years of age. Individuals who completed XR-NTX induction (n = 20) reported experiencing (1) readiness for change, (2) a supportive environment during withdrawal including comfort medications, and (3) caring interactions with staff. Four contrasting themes emerged among participants (n = 17) who did not complete induction: (1) concern and anxiety about withdrawal including past negative experiences, (2) ambivalence about or reluctance to stop opioids, (3) concerns about XR-NTX effects, and (4) preferences for other medications. **Conclusions:** The results highlight opportunities to improve initiation of XR-NTX in high-need groups. Addressing expectations regarding induction may enhance XR-NTX initiation rates.

CLINICAL TRIALS NETWORK RESEARCH

[Baseline- And Treatment-Associated Pain In The X:BOT Comparative Effectiveness Study Of Extended-Release Naltrexone Versus Buprenorphine-Naloxone For OUD]() Wang AL, Shulman M, Choo TH, Pavlicova M, Langleben DD, Nunes EV, Rotrosen J. Addict Biol. 2021 Dec 7:e13112. Online ahead of print.
Chronic pain is highly prevalent among patients with opioid use disorder (OUD). However, little is known about how pharmacological treatments for OUD, for example, extended-release naltrexone (XR-NTX) and buprenorphine-naloxone (BUP-NX), affect pain. To begin addressing this question, we performed a secondary analysis of pain data on a large prospective 24-week, open-label, randomized-controlled comparative effectiveness trial of XR-NTX versus BUP-NX (X:BOT trial). Participants' pain status was measured by the EuroQol (EQ-5D). Based on their responses to the

pain question at baseline, participants were dichotomized into "Pain" versus "No Pain" categories. Participant's pain status was evaluated every 4 weeks. A mixed effects longitudinal logistic regression model was fitted to examine the differential effect of XR-NTX versus BUP-NX on pain, modelling pain at all available follow-up assessments, adjusted for age, sex, and baseline pain. A total of 474 individuals who were successfully inducted onto their assigned medications were included in this analysis. Among participants endorsing pain at baseline, substantial reductions in pain were observed over the course of the study in both treatment groups. However, reduction in pain was slightly greater in the group treated with XR-NTX than the one treated with BUP-NX (OR = 1.60 [95% CI: 1.07-2.40], P = 0.023). Future research using instruments and design specifically focused on pain could extend the present observations and evaluate their clinical significance.

[Is Extended Release Naltrexone Superior To Buprenorphine-Naloxone To Reduce Drinking Among Outpatients Receiving Treatment For Opioid Use Disorder? A Secondary Analysis Of The CTN X:BOT Trial](#) Roache JD, Pavlicova M, Campbell A, Choo TH, Peavy M, Kermack AS, Nunes EV Jr, Rotrosen J. Alcohol Clin Exp Res. 2021 Dec; 45(12): 2569-2578. Epub 2021 Nov 23.
Background: The comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT) trial showed that following induction, treatment with the sublingual agonist (buprenorphine-naloxone, BUP-NX) or injected antagonist (extended release naltrexone, XR-NTX) produced similar reductions in opioid relapse in injection users with opioid use disorder (OUD). Because XR-NTX reduces drinking in alcohol use disorder (AUD), we conducted a secondary analysis of the X:BOT sample of patients successfully inducted onto treatment to determine whether XR-NTX (n = 204) was superior to BUP-NX (n = 270) in reducing drinking or heavy drinking in patients with OUD. **Methods:** Standard drink units consumed were measured using the Timeline Follow-back method. Mixed-models regression was used to examine the monthly frequency of any drinking and heavy drinking over 6 months of treatment. We used a proportional hazard survival analysis to examine the time to first drink. **Results:** Both treatment groups reduced drinking from baseline to posttreatment (small to medium effect), but no differences between groups were detected. However, only 29% (n = 136) of the sample had AUD and 19% (n = 26/136) of those were abstinent before treatment. Analysis of a subsample enriched for possible drinking included 136 individuals with an AUD diagnosis plus 43 who did not have AUD, but reported at least one day of heavy drinking prior to the study. However, this subsample reported only 32% of days of any drinking with a median of only 13% of days designated as "heavy." Within this subsample, at baseline, the BUP-NX group reported more mean drinks per drinking day than the XR-NTX group (p = 0.03); however, there were no other significant group differences on drinking observed before, during, or at the end of treatment. **Conclusions:** There was an overall reduction in drinking during treatment of OUD using both agonist and antagonist medications, so that the hypothesis that XR-NTX would be superior to BUP-NX was not supported. The study is limited by low levels of comorbid AUD or heavy drinking observed in X:BOT trial participants seeking treatment for OUD.

[Validation And Threshold Identification Of A Prescription Drug Monitoring Program Clinical Opioid Risk Metric With The WHO Alcohol, Smoking, And Substance Involvement Screening Test](#) Cochran G, Brown J, Yu Z, Frede S, Bryan MA, Ferguson A, Bayyari N, Taylor B, Snyder ME, Charron E, Adeoye-Olatunde OA, Ghitza UE, Winhusen T. Drug Alcohol Depend. 2021 Nov 1; 228: 109067. Epub 2021 Sep 24.

Background: Prescription drug monitoring programs (PDMPs) are critical for pharmacists to identify risky opioid medication use. We performed an independent evaluation of the PDMP-based Narcotic Score (NS) metric. **Methods:** This study was a one-time, cross-sectional health assessment within 19 pharmacies from a national chain among adults picking-up opioid medications. The NS metric is a 3-digit composite indicator. The WHO Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) was the gold-standard to which the NS metric was compared. Machine learning determined optimal risk thresholds; Receiver Operating Characteristic curves and Spearman (P) and Kappa (K) coefficients analyzed concurrent validity. Regression analyses evaluated participant characteristics associated with misclassification. **Results:** The NS metric showed fair concurrent validity (area under the curve$\geq$0.70; K=0.35; P = 0.37, p < 0.001). The ASSIST and NS metric categorized 37% of participants as low-risk (i.e., not needing screening/intervention) and 32.3% as moderate/high-risk (i.e., needing screening/intervention). Further, 17.2% were categorized as low ASSIST risk but moderate/high NS metric risk, termed false positives. These reported disability (OR=3.12), poor general health (OR=0.66), and/or greater pain severity/interference (OR=1.12/1.09; all p < 0.05; i.e., needing unmanaged-pain screening/intervention). A total of 13.4% were categorized as moderate/high ASSIST risk but low NS metric risk, termed false negatives. These reported greater overdose history (OR=1.24) and/or substance use (OR=1.81-12.66; all p < 0.05). **Conclusions:** The NS metric could serve as a useful initial universal prescription opioid-risk screener given its: 1) low-burden (i.e., no direct assessment); 2) high accuracy (86.5%) of actionable data identifying low-risk patients and those needing opioid use/unmanaged pain screening/intervention; and 3) broad availability.

[Reductions In Tobacco Use In Naltrexone, Relative To Buprenorphine-Maintained Individuals With Opioid Use Disorder: Secondary Analysis From The National Drug Abuse Treatment Clinical Trials Network](#) Montgomery L, Winhusen T, Scodes J, Pavlicova M, Twitty D, Campbell ANC, Wang AL, Nunes EV, Rotrosen J. J Subst Abuse Treat. 2021 Nov; 130: 108489. Epub 2021 May 21.

Background: Smoking prevalence in individuals with opioid use disorder (OUD) is over 80%. Research suggests that opioid use significantly increases smoking, which could account for the strikingly low smoking-cessation rates observed in both methadone- and buprenorphine-maintained patients, even with the use of first-line smoking-cessation interventions. If opioids present a barrier to smoking-cessation, then better smoking outcomes should be observed in OUD patients treated with extended-release naltrexone (XR-NTX, an opioid antagonist) compared to those receiving buprenorphine (BUP-NX, a partial opioid agonist). **Methods:** The current study is a secondary analysis of a 24-week, multi-site, open-label, randomized clinical trial conducted within the National Drug Abuse Treatment Clinical Trials Network comparing the effectiveness of XR-NTX vs. BUP-NX for adults with OUD. Longitudinal mixed effects models were used to determine if there was a significant reduction in cigarette use among daily smokers successfully inducted to treatment (n = 373) and a subset of those who completed treatment (n = 169). **Results:** Among daily smokers inducted onto OUD medication, those in the XR-NTX group smoked fewer cigarettes per day (M = 11.36, SE = 0.62) relative to smokers in the BUP-NX group (M = 13.33, SE = 0.58) across all study visits, (b (SE) = -1.97 (0.55), p < .01). Results were similar for the treatment completers. **Conclusions:** OUD patients treated with XR-NTX reduced cigarette use more than those treated with BUP-NX, suggesting that XR-NTX in combination with other smoking cessation interventions might be a better choice for OUD smokers interested in reducing their tobacco use.

[Concomitant Cannabis Misuse And Associations With Depression, Pain And Substance Misuse Among Patients Prescribed Opioids](#) Bryan MA, Charron E, Adeoye-Olatunde O, Brown J, Ghitza U, Winhusen TJ, Cochran G. Pharmacy (Basel). 2021 Aug 4; 9(3): 134.
Background: Cannabis use is common among individuals with pain who are prescribed opioids, occurring in approximately 10% of this population. This study aims to explore the relationship between non-medical cannabis use and other health risks among individuals filling opioids at community pharmacies. **Methods:** This study was an exploratory secondary data analysis of a National Drug Abuse Treatment Clinical Trials Network (CTN)-sponsored study, Validation of a Community Pharmacy-Based Prescription Drug Monitoring Program Risk Screening, examining the relationship between risky cannabis use and depressive symptoms, pain, overdose, and other substance misuse among individuals filling opioid prescriptions in community pharmacies (N = 1440). **Results:** Participants reporting moderate- to high-risk compared to low-risk cannabis use were more likely to report depressive symptoms (adjusted OR = 1.67, 95% CI = 1.11-2.56), history of overdose (adjusted OR = 2.15, 95% CI = 1.34-3.44), and moderate- to high-risk use of alcohol (adjusted OR = 2.10, 95% CI = 1.28-3.45), opioids (adjusted OR = 2.50, 95% CI = 1.67-3.76), sedatives (adjusted OR = 2.58, 95% CI = 1.72-3.86), stimulants (adjusted OR = 4.79, 95% CI = 2.83-8.01), and tobacco (adjusted OR = 3.60, 95% CI = 2.47-5.24). **Conclusions:** Community pharmacies may be valuable sites for identifying, studying, and intervening with substance use problems.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

[Association Between Discrimination Stress And Suicidality In Preadolescent Children](#) Argabright ST, Visoki E, Moore TM, Ryan DT, DiDomenico GE, Njoroge WFM, Taylor JH, Guloksuz S, Gur RC, Gur RE, Benton TD, Barzilay R. J Am Acad Child Adolesc Psychiatry 2021 Aug 20; S0890-8567(21)01355-1. Online ahead of print.
Objective: Youth suicide rates in the United States have been increasing in recent years, especially in Black Americans, the reasons for which are unclear. Environmental adversity is key in youth suicidality; hence there is a need to study stressors that have a disproportionate impact on Black youths. We aimed to disentangle the unique contribution of racial/ethnic discrimination from other adversities associated with childhood suicidal ideation and attempts (suicidality). **Method:** We analyzed data from the Adolescent Brain Cognitive Development (ABCD) Study, which included a large, diverse sample of US children (N = 11,235, mean age 10.9 years, 20.2% Black), assessed for multiple environmental adversities including discrimination. Multivariate regression models tested the association of self-reported racial/ethnic discrimination with suicidality, covarying for multiple confounders including other discrimination types (toward non-US-born individuals, sexual orientation-based, and weight-based). Matched analyses contrasted effects of racial/ethnic discrimination and racial identity on suicidality. **Results:** Black youths reported more discrimination and higher suicidality rates than non-Black youths. High racial/ethnic discrimination was positively and significantly associated with suicidality, adjusting for other discrimination types (odds ratio = 2.6, 95% CI = 2.1-3.2). Findings remained significant after adjusting for multiple suicidality risk factors. Once experienced, racial/ethnic discrimination was similarly associated with suicidality in White, Black, and Hispanic youths. Matched analyses revealed that racial/ethnic discrimination was associated with suicidality (relative risk = 2.7, 95% CI = 2-3.5), whereas Black race was not (relative risk = 0.9, 95% CI = 0.7-1.2). **Conclusion:** Racial/ethnic discrimination is

disproportionately experienced by Black children, and is associated with preadolescent suicidality, over and above other adversities. Findings highlight the need to address discrimination as part of suicide prevention strategies. Cross-sectional design hampers causal inferences.

Shared Genetic Etiology Between Cortical Brain Morphology And Tobacco, Alcohol, And Cannabis Use Rabinowitz JA, Campos AI, Ong JS, García-Marín LM, Alcauter S, Mitchell BL, Grasby KL, Cuéllar-Partida G, Gillespie NA, Huhn AS, Martin NG, Thompson PM, Medland SE, Maher BS, Rentería ME. Cereb Cortex 2021 Aug 11; bhab243. Online ahead of print. Genome-wide association studies (GWAS) have identified genetic variants associated with brain morphology and substance use behaviors (SUB). However, the genetic overlap between brain structure and SUB has not been well characterized. We leveraged GWAS summary data of 71 brain imaging measures and alcohol, tobacco, and cannabis use to investigate their genetic overlap using linkage disequilibrium score regression. We used genomic structural equation modeling to model a "common SUB genetic factor" and investigated its genetic overlap with brain structure. Furthermore, we estimated SUB polygenic risk scores (PRS) and examined whether they predicted brain imaging traits using the Adolescent Behavior and Cognitive Development (ABCD) study. We identified 8 significant negative genetic correlations, including between (1) alcoholic drinks per week and average cortical thickness, and (2) intracranial volume with age of smoking initiation. We observed 5 positive genetic correlations, including those between (1) insula surface area and lifetime cannabis use, and (2) the common SUB genetic factor and pericalcarine surface area. SUB PRS were associated with brain structure variation in ABCD. Our findings highlight a shared genetic etiology between cortical brain morphology and SUB and suggest that genetic variants associated with SUB may be causally related to brain structure differences.

Adolescent Civic Engagement: Lessons From Black Lives Matter Baskin-Sommers A, Simmons C, Conley M, Chang S-A, Estrada S, Collins M, Pelham W, Beckford E, Mitchell-Adams H, Berrian N, Tapert SF, Gee DG, Casey BJ Proc Natl Acad Sci U S A. 2021 Oct 12; 118(41): e2109860118.
In 2020, individuals of all ages engaged in demonstrations condemning police brutality and supporting the Black Lives Matter (BLM) movement. Research that used parent reports and trends commented on in popular media suggested that adolescents under 18 had become increasingly involved in this movement. In the first large-scale quantitative survey of adolescents' exposure to BLM demonstrations, 4,970 youth (mean$_{age}$ = 12.88 y) across the United States highlighted that they were highly engaged, particularly with media, and experienced positive emotions when exposed to the BLM movement. In addition to reporting strong engagement and positive emotions related to BLM demonstrations, Black adolescents in particular reported higher negative emotions when engaging with different types of media and more exposure to violence during in-person BLM demonstrations. Appreciating youth civic engagement, while also providing support for processing complex experiences and feelings, is important for the health and welfare of young people and society.

Longitudinal Impact Of Childhood Adversity On Early Adolescent Mental Health During The COVID-19 Pandemic In The ABCD Study® Cohort: Does Race Or Ethnicity Moderate Findings? Stinson EA, Sullivan RM, Peteet BJ, Tapert SF, Baker FC, Breslin FJ, Dick AS, Gonzalez MR, Guillaume M, Marshall AT, McCabe CJ, Pelham WE, Van Rinsveld AM, Sheth CS,

Sowell ER, Wade NE, Wallace AL, Lisdahl KM Biol Psychiatry Glob Open Sci. 2021 Dec; 1(4): 324-335. Epub 2021 Sep 29.

Background: During the COVID-19 pandemic in the United States, mental health among youth has been negatively affected. Youth with a history of adverse childhood experiences (ACEs), as well as youth from minoritized racial-ethnic backgrounds, may be especially vulnerable to experiencing COVID-19-related distress. The aims of this study are to examine whether exposure to pre-pandemic ACEs predicts mental health during the COVID-19 pandemic in youth and whether racial-ethnic background moderates these effects. **Methods:** From May to August 2020, 7983 youths (mean age, 12.5 years; range, 10.6-14.6 years) in the Adolescent Brain Cognitive Development (ABCD) Study completed at least one of three online surveys measuring the impact of the pandemic on their mental health. Data were evaluated in relation to youths' pre-pandemic mental health and ACEs. **Results:** Pre-pandemic ACE history significantly predicted poorer mental health across all outcomes and greater COVID-19-related stress and impact of fears on well-being. Youths reported improved mental health during the pandemic (from May to August 2020). While reporting similar levels of mental health, youths from minoritized racial-ethnic backgrounds had elevated COVID-19-related worry, stress, and impact on well-being. Race and ethnicity generally did not moderate ACE effects. Older youths, girls, and those with greater pre-pandemic internalizing symptoms also reported greater mental health symptoms. **Conclusions:** Youths who experienced greater childhood adversity reported greater negative affect and COVID-19-related distress during the pandemic. Although they reported generally better mood, Asian American, Black, and multiracial youths reported greater COVID-19-related distress and experienced COVID-19-related discrimination compared with non-Hispanic White youths, highlighting potential health disparities.

COVID-RELATED| RESEARCH

[COVID-Related Victimization, Racial Bias And Employment And Housing Disruption Increase Mental Health Risk Among U.S. Asian, Black And Latinx Adults](#) Fisher CB, Tao X, Liu T, Giorgi S, Curtis B. Front Public Health. 2021 Oct 29; 9: 772236.

Background: The mental health of racial/ethnic minorities in the U.S. has been disproportionately impacted by the COVID-19 pandemic. This study examined the extent to which disruptions in employment and housing, coronavirus-specific forms of victimization and racial bias independently and conjointly contributed to mental health risk among Asian, Black, and Latinx adults in the United States during the pandemic. **Methods:** This study reports on data from 401 Asian, Black, and Latinx adults (age 18-72) who participated in a larger national online survey conducted from October 2020-June 2021, Measures included financial and health information, housing disruptions and distress in response to employment changes, coronavirus related victimization distress and perceived increases in racial bias, depression and anxiety. **Results:** Asian participants had significantly higher levels of COVID-related victimization distress and perceived increases in racial bias than Black and Latinx. Young adults (<26 years old) were more vulnerable to depression, anxiety, and coronavirus victimization distress than older respondents. Having at least one COVID-related health risk, distress in response to changes in employment and housing disruptions, pandemic related victimization distress and perceived increases in racial bias were positively and significantly related to depression and anxiety. Structural equation modeling indicated COVID-related increases in racial bias mediated the effect of COVID-19 related victimization distress on depression and anxiety. **Conclusions:** COVID-19 has created new pathways to mental health

disparities among racial/ethnic minorities in the U.S. by exacerbating existing structural and societal inequities linked to race. Findings highlight the necessity of mental health services sensitive to specific challenges in employment and housing and social bias experienced by people of color during the current and future health crises.

[Loneliness And Daily Alcohol Consumption During The COVID-19 Pandemic](#) Bragard E, Giorgi S, Juneau P, Curtis BL. Alcohol Alcohol. 2021 Aug 20.
Aims: This pilot study aimed to identify associations of loneliness and daily alcohol consumption among US adults during the Coronavirus Disease-2019 pandemic. **Method:** Participants completed daily assessments for 30 days. **Results:** Results suggest people who feel lonelier on average drink more alcohol, however, people who feel lonelier than usual drink less. **Conclusion:** Findings highlight the need to disaggregate within- and between-person components of alcohol use. Published by Oxford University Press on behalf of the Medical Council on Alcohol Society 2021.

INTRAMURAL RESEARCH

[Orbitofrontal Cortex And Dorsal Striatum Functional Connectivity Predicts Incubation Of Opioid Craving After Voluntary Abstinence](#) Fredriksson I, Tsai PJ, Shekara A, Duan Y, Applebey SV, Lu H, Bossert JM, Shaham Y, Yang Y. Proc Natl Acad Sci U S A. 2021 Oct 26; 118(43).
We recently introduced a rat model of incubation of opioid craving after voluntary abstinence induced by negative consequences of drug seeking. Here, we used resting-state functional MRI to determine whether longitudinal functional connectivity changes in orbitofrontal cortex (OFC) circuits predict incubation of opioid craving after voluntary abstinence. We trained rats to self-administer for 14 d either intravenous oxycodone or palatable food. After 3 d, we introduced an electric barrier for 12 d that caused cessation of reward self-administration. We tested the rats for oxycodone or food seeking under extinction conditions immediately after self-administration training (early abstinence) and after electric barrier exposure (late abstinence). We imaged their brains before self-administration and during early and late abstinence. We analyzed changes in OFC functional connectivity induced by reward self-administration and electric barrier-induced abstinence. Oxycodone seeking was greater during late than early abstinence (incubation of oxycodone craving). Oxycodone self-administration experience increased OFC functional connectivity with dorsal striatum and related circuits that was positively correlated with incubated oxycodone seeking. In contrast, electric barrier-induced abstinence decreased OFC functional connectivity with dorsal striatum and related circuits that was negatively correlated with incubated oxycodone seeking. Food seeking was greater during early than late abstinence (abatement of food craving). Food self-administration experience and electric barrier-induced abstinence decreased or maintained functional connectivity in these circuits that were not correlated with abated food seeking. Opposing functional connectivity changes in OFC with dorsal striatum and related circuits induced by opioid self-administration versus voluntary abstinence predicted individual differences in incubation of opioid craving.

[Lateral Hypothalamic LEPR Neurons Drive Appetitive But Not Consummatory Behaviors](#) Siemian JN, Arenivar MA, Sarsfield S, Borja CB, Russell CN, Aponte Y. Cell Rep. 2021 Aug 24; 36(8): 109615.

Assigning behavioral roles to genetically defined neurons within the lateral hypothalamus (LH) is an ongoing challenge. We demonstrate that a subpopulation of LH GABAergic neurons expressing leptin receptors (LH^{LEPR}) specifically drives appetitive behaviors in mice. Ablation of LH GABAergic neurons (LH^{VGAT}) decreases weight gain and food intake, whereas LH^{LEPR} ablation does not. Appetitive learning in a Pavlovian conditioning paradigm is delayed in LH^{VGAT}-ablated mice but prevented entirely in LH^{LEPR}-ablated mice. Both LH^{VGAT} and LH^{LEPR} neurons bidirectionally modulate reward-related behaviors, but only LH^{VGAT} neurons affect feeding. In the Pavlovian paradigm, only LH^{LEPR} activity discriminates between conditioned cues. Optogenetic activation or inhibition of either population in this task disrupts discrimination. However, manipulations of LH^{LEPR}→VTA projections evoke divergent effects on responding. Unlike food-oriented learning, chemogenetic inhibition of LH^{LEPR} neurons does not alter cocaine-conditioned place preference but attenuates cocaine sensitization. Thus, LH^{LEPR} neurons may specifically regulate appetitive behaviors toward non-drug reinforcers.

Gut Microbiome And Metabolome In A Non-Human Primate Model Of Chronic Excessive Alcohol Drinking Piacentino D, Grant-Beurmann S, Vizioli C, Li X, Moore CF, Ruiz-Rodado V, Lee MR, Joseph PV, Fraser CM, Weerts EM, Leggio L. Transl Psychiatry. 2021 Dec 1; 11(1): 609. A relationship between the gut microbiome and alcohol use disorder has been suggested. Excessive alcohol use produces changes in the fecal microbiome and metabolome in both rodents and humans. Yet, these changes can be observed only in a subgroup of the studied populations, and reversal does not always occur after abstinence. We aimed to analyze fecal microbial composition and function in a translationally relevant baboon model of chronic heavy drinking that also meets binge criteria (drinking too much, too fast, and too often), i.e., alcohol ~1 g/kg and blood alcohol levels (BALs) ≥ 0.08 g/dL in a 2-hour period, daily, for years. We compared three groups of male baboons (Papio anubis): L = Long-term alcohol drinking group (12.1 years); S = Short-term alcohol drinking group (2.7 years); and C = Control group, drinking a non-alcoholic reinforcer (Tang®) (8.2 years). Fecal collection took place during 3 days of Drinking (D), followed by a short period (3 days) of Abstinence (A). Fecal microbial alpha- and beta-diversity were significantly lower in L vs. S and C (p's < 0.05). Members of the commensal families Lachnospiraceae and Prevotellaceae showed a relative decrease, whereas the opportunistic pathogen Streptococcus genus showed a relative increase in L vs. S and C (p's < 0.05). Microbiota-related metabolites of aromatic amino acids, tricarboxylic acid cycle, and pentose increased in L vs. S and C (FDR-corrected p < 0.01), with the latter two suggesting high energy metabolism and enhanced glycolysis in the gut lumen in response to alcohol. Consistent with the long-term alcohol exposure, mucosal damage and oxidative stress markers (N-acetylated amino acids, 2-hydroxybutyrate, and metabolites of the methionine cycle) increased in L vs. S and C (FDR-corrected p < 0.01). Overall, S showed few differences vs. C, possibly due to the long-term, chronic alcohol exposure needed to alter the normal gut microbiota. In the three groups, the fecal microbiome barely differed between conditions D and A, whereas the metabolome shifted in the transition from condition D to A. In conclusion, changes in the fecal microbiome and metabolome occur after significant long-term excessive drinking and are only partially affected by acute forced abstinence from alcohol. These results provide novel information on the relationship between the fecal microbiome and metabolome in a controlled experimental setting and using a unique non-human primate model of chronic excessive alcohol drinking.

Laterality Hotspots In The Striatum Korponay C, Stein EA, Ross TJ. Cereb Cortex. 2021 Nov 2. pii: bhab392. Online ahead of print.

Striatal loci are connected to both the ipsilateral and contralateral frontal cortex. Normative quantitation of the dissimilarity between striatal loci's hemispheric connection profiles and its spatial variance across the striatum, and assessment of how interindividual differences relate to function, stands to further the understaning of the role of corticostriatal circuits in lateralized functions and the role of abnormal corticostriatal laterality in neurodevelopmental and other neuropsychiatric disorders. A resting-state functional connectivity fingerprinting approach (n = 261) identified "laterality hotspots"-loci whose profiles of connectivity with ipsilateral and contralateral frontal cortex were disproportionately dissimilar-in the right rostral ventral putamen, left rostral central caudate, and bilateral caudal ventral caudate. Findings were replicated in an independent sample and were robust to both preprocessing choices and the choice of cortical atlas used for parcellation definitions. Across subjects, greater rightward connectional laterality at the right ventral putamen hotspot and greater leftward connectional laterality at the left rostral caudate hotspot were associated with higher performance on tasks engaging lateralized functions (i.e., response inhibition and language, respectively). In sum, we find robust and reproducible evidence for striatal loci with disproportionately lateralized connectivity profiles where interindividual differences in laterality magnitude are associated with behavioral capacities on lateralized functions.

Synaptic Zn(2+) Potentiates The Effects Of Cocaine On Striatal Dopamine Neurotransmission And Behavior Gomez JL, Bonaventura J, Keighron J, Wright KM, Marable DL, Rodriguez LA, Lam S, Carlton ML, Ellis RJ, Jordan CJ, Bi GH, Solis O, Pignatelli M, Bannon MJ, Xi ZX, Tanda G, Michaelides M. Transl Psychiatry. 2021 Nov 8; 11(1): 570.

Cocaine binds to the dopamine (DA) transporter (DAT) to regulate cocaine reward and seeking behavior. Zinc (Zn^{2+}) also binds to the DAT, but the in vivo relevance of this interaction is unknown. We found that Zn^{2+} concentrations in postmortem brain (caudate) tissue from humans who died of cocaine overdose were significantly lower than in control subjects. Moreover, the level of striatal Zn^{2+} content in these subjects negatively correlated with plasma levels of benzoylecgonine, a cocaine metabolite indicative of recent use. In mice, repeated cocaine exposure increased synaptic Zn^{2+} concentrations in the caudate putamen (CPu) and nucleus accumbens (NAc). Cocaine-induced increases in Zn^{2+} were dependent on the Zn^{2+} transporter 3 (ZnT3), a neuronal Zn^{2+} transporter localized to synaptic vesicle membranes, as ZnT3 knockout (KO) mice were insensitive to cocaine-induced increases in striatal Zn^{2+}. ZnT3 KO mice showed significantly lower electrically evoked DA release and greater DA clearance when exposed to cocaine compared to controls. ZnT3 KO mice also displayed significant reductions in cocaine locomotor sensitization, conditioned place preference (CPP), self-administration, and reinstatement compared to control mice and were insensitive to cocaine-induced increases in striatal DAT binding. Finally, dietary Zn^{2+} deficiency in mice resulted in decreased striatal Zn^{2+} content, cocaine locomotor sensitization, CPP, and striatal DAT binding. These results indicate that cocaine increases synaptic Zn^{2+} release and turnover/metabolism in the striatum, and that synaptically released Zn^{2+} potentiates the effects of cocaine on striatal DA neurotransmission and behavior and is required for cocaine-primed reinstatement. In sum, these findings reveal new insights into cocaine's pharmacological mechanism of action and suggest that Zn^{2+} may serve as an environmentally derived regulator of DA neurotransmission, cocaine pharmacodynamics, and vulnerability to cocaine use disorders.

GRANTEE HONORS AND AWARDS

Nii Addy, Ph.D., who was recently appointed the Albert E. Kent Professor of Psychiatry, received the American College of Neuropsychopharmacology Dolores Shockley Diversity and Inclusion Advancement Award for 2021.

Mary Brunette, M.D., Geisel School of Medicine at Dartmouth, was named the Mental Health Professional of the Year (2021) by the New Hampshire chapter of the National Alliance on Mental Illness (NAMI).

Benjamin F. Cravatt, Ph.D., Scripps Research Institute, was awarded the 2022 Alfred Bader Award in Bioinorganic/Bioorganic Chemistry sponsored by the Alfred R. Bader Fund and administered by the American Chemical Society for the "development of protein-mapping technologies to find new ways to address drivers of disease which may have previously been considered 'undruggable'."

Jennifer Cremins, Ph.D., University of Pennsylvania, was awarded an NIH Director's Pioneer Award for research on the role of chromatin folding in the encoding of neural circuits and synaptic properties. She also received the International Society for Stem Cell Research (ISSCR) Susan Lim Outstanding New Investigator Award.

Karl Deisseroth, M.D., Ph.D., Stanford University, is a co-recipient of the 2021 Lasker Basic Medical Research Award "for the discovery of light-sensitive microbial proteins that can activate or deactivate individual brain cells, leading to the development of optogenetics and revolutionizing neuroscience."

Danielle Dick, Ph.D., has accepted a new position at Rutgers University to hold the Greg Brown Endowed Chair in Neuroscience and serve as the founding director of a new Addiction Research Center, which will grow addiction research across its four campuses and two medical schools.

Yasmin Hurd, Ph.D., Director Addiction Institute, Mount Sinai was awarded the 2021 Sarah Gund Prize Child Mind Institute Distinguished Scientist Award for her studies on the neurobiology underlying addiction disorders and related psychiatric illness.

Shawn Lockery, Ph.D., University of Oregon, was inducted as senior member of National Academy of Inventors. Shawn's research on C. elegans led to innovations in storage and experimental testing of C. elegans including microfluidic devices for the handling and testing of roundworms as tools in drug discovery.

Ryan Logan, Ph.D., Boston University, received the International Behavioural and Neural Genetics Society 2021 - Young Scientist Award.

Colleen McClung, Ph.D., University of Pittsburgh, was awarded the Colvin Prize from the Brain and Behavior Foundation for outstanding achievements in mood disorder research.

Eric Nestler, M.D., Ph.D., Icahn School of Medicine, Mount Sinai, received the Barbara Fish Memorial Award from the American College of Neuropsychopharmacology, which is awarded to a member who has made an outstanding contribution to basic, translational, or clinical neuroscience.

Cynthia Rudin, Ph.D., Duke University, became the second recipient of the Association for the Advancement of Artificial Intelligence Squirrel Award for pioneering socially responsible Artificial Intelligence.

Jill Turner, Ph.D., University of Kentucky, was awarded the American Society for Pharmacology and Experimental Therapeutics 2021 Early Career Award.

2021 NIH DIRECTOR'S AWARDS to NIDA Staff

Scientific—Medications Development for Opioid Use Disorders Team, in recognition of successfully advancing the development of medications and biologics to treat Opioid Use Disorder.

Jane B. Acri	*David J. McCann*
Ann L. Anderson	*Ivan D. Montoya*
Nathan M. Appel	*Tatiana S. Ramey*
Marta L. De Santis	*Kurt Rasmussen*
Katrina L. Foster	*Jason C. Sousa*
Shwe M. Gyaw	*Robert L. Walsh*
Aidan J. Hampson	*Kevin M. Walton*
Carol B. Hubner Katz	*David A. White*
Richard H. Kline	

Scientific, for extraordinary scientific leadership and vision that has driven basic neuroscience research toward elucidating mechanisms underlying addiction.
Rita J. Valentino

Administrative, for extraordinary contributions in improving budget planning and implementation, including oversight of NIH/NIDA The Helping to End Addiction Long-term® Initiative budget processes and interagency collaborations with Food and Drug Administration's Center for Tobacco Products.
Nathaniel M. Davis

RADX Underserved Populations (RADX-UP) Working Group, for outstanding contribution, coordination, and implementation of the RADxUP initiative to better understand and address health disparities associated with COVID-19.

Minki Chatterji	*Keisher Highsmith*
Wilson Compton	*Jennifer Hobin*
Gayathri Dowling	*Richard Jenkins*
Kathleen Etz	*Carrie Mulford*
Pamela Fleming	*Jeffrey Schulden*

TRANS-NIH Strategic Plan for COVID-19 Research Team, for the rapid development of a road map for the NIH strategic research response to the COVID-19 pandemic.

David Bochner	*Julie Frost Bellgowan*

Presidential Transition Preparation Team, for outstanding dedication to the preparation of transition materials ahead of the 2020 general election.
Jennifer Hobin

Recognition Across NIH - The following NIDA staff are recognized as part of groups hosted by another Institute and Centers.

National Center for Advancing Translational Sciences

Scott A. Bredow

Kimberly A. Espinosa

Stuart G. Kern

Mark E. McNally

Rieka N. Plugge

Suzanne K. Stinson

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Michelle P. Freund

Elliot A. Stein

Office of the Director

Leonardo M. Angelone

David N. Bochner

Minki Chatterji

Wilson M. Compton

Gayathri J. Dowling

Kathleen E. Etz

Pamela G. Fleming

Julie A. Frost Bellgowan

Keisher S. Highsmith

Jennifer A. Hobin

John C. Hubbard

Richard A. Jenkins

Chloe J. Jordan

Elena V. Koustova

Carrie F. Mulford

Karran A. Phillips

Jeffrey D. Schulden

Susan N. Wright

2021 NIDA DIRECTOR'S AWARDS

Individual Award: In recognition of your leadership, creativity and resourcefulness that were key to the success of the Neuroscience Workgroup and NIDA Mini-Convention.
Anne Tsai

Individual Award: In recognition for the totality of your outstanding scientific and service-related accomplishments benefitting the NIDA community.
Brandon Harvey

Individual Award: In recognition of resolving unique ethics cases and advising NIDA Senior NIDA Leadership on complex legal and ethical matters.
Anna Wheeler

Individual Award: In recognition of your professionalism, dedication, and resourcefulness in coordinating multiple NIH Helping to End Addiction Long-term Initiative teams at NIDA, advancing NIDA's efforts to address the opioid crisis.
Michele Rankin

NIDA Director's Rising Star Award (Individual): In recognition of your accomplishments, creativity, energy, and ability to inspire others at NIDA

Yvonne Walker	*Deon Harvey*
Keisher Highsmith	*Christopher Halstead*
Holly Moore	*Manuel Rodriguez*
Jason Sousa	

Group Award: In recognition of your leadership in creating and maintaining up-to date information in snapshot format on treatments in active development for substance use disorders.
Division of Therapeutics and Medical Consequences Pipeline Managers:

Will Aklin	*Aidan Hampson*
Marta De Santis	*Evan Hermann*
Katrina Foster	*Jennifer Wong*

Group Award: In recognition of your exceptional planning, vision, and implementation in providing experienced contract support to all NIH Institutes.
The Scientific, Operations, and Administrative Resources (SOAR) Team, Office of Management / Office of Acquisitions:
NIDA:

Christine Frate	*Jeffrey Moore*
Christopher Halstead	*Brian O'Laughlin*
Kyle Miller	

National Institute of Mental Health:

Kim Black	*Rachel Doherty*
Stephen Puckett	*George Birdsong*
Jason Fox	

Group Award: In recognition of NIDA Information Resource Management Branch's Desktop and Infrastructure Support Team for their work issuing, supporting, and maintaining our Information Technology assets in a safe and effective manner during the COVID-19 pandemic.
Information Resource Management Branch Information Technology Service Desk, Office of Management / Information Resource Management Branch:

Zoe Shieh	*Berhane Yitbarek*
Jamar Ali	*Jonathan Ingold*
Brian Chau	*Malik Lucas*
Nahom Gebray	*Marcus McIlwaian*
Jeff Grodine	

In recognition of your strategic coordination to amplify NIDA messaging on the issue of stigma, and its role as a pervasive barrier to treatment and care.
Office of Science Policy and Communications on Stigma Team:

Josie Anderson	*Judith Lavelle*
Michelle Corbin	*Janet Linton*
Jessica Cotto	*Stacy Lu*
Emily Einstein	*Brian Marquis*
Rachel Evans	*Anne Rancourt*
Mark Fleming	*Juwon Song*
Molly Freimuth	*Eric Wargo*

NIDA Director's Award for Collaboration: In recognition of your exemplary contributions over the past year+ to the successful scientific and programmatic stewardship of the HEALthy Brain and Child Development Study and Phase II launch.
HEALthy Brain and Child Development Study Team:

Carol Alderson	*Vani Pariyadath*
Michelle Freund	*Janani Prabhakar*
Jessica McKlveen	

NIDA Director's Award for Diversity (Individual): In recognition of being a true champion for diversity and inclusion at every level of NIDA and at the NIH.
Marisela Morales

NIDA Director's Award for Diversity: In recognition of your creative and dedicated efforts to increase and improve opportunities for diversity and inclusion within, and in initiatives overseen by, the Division of Neuroscience and Behavior.
Diversity Inclusion Group, Division of Neuroscience and Behavior:

Beth Babecki	*Amy Lossie*
Nic Johnston	*Holly Moore*
Mary Kautz	*Lizette Nkogongo*
Flair Lindsey	*Shang (Anne) Tsai*

NIDA Director's Award for Diversity: In recognition of your outreach to Historically Black Colleges and Universities and other minority-serving institutions in an effort to increase diversity and inclusion in the scientific workforce.
Historically Black Colleges and Universities Workgroup:

Will Aklin	*Michelle Jobes*
Yeka Aponte	*Nic Johnston*
Albert Avila	*Elena Koustova*
Beth Babecki	*Lorenzo Leggio*
Aria Crump	*Roger Little*
Gaya Dowling	*Amy Newman*
Emily Einstein	*Jonathan Pollock*
Katrina Foster	*Vasundhara Varthakavi*
Angela Holmes	

NIDA Director's Award for Diversity: In recognition of your outstanding contributions toward advancing racial equity in the NIDA workplace, workforce, and research portfolio through the NIDA Racial Equity Initiative.
*NIDA Racial Equity Initiative Volunteers***:**
80 NIDA Staff recognized

NIDA Director's Award for Quality of Worklife: In recognition of excellent leadership in developing and providing a wide array of administrative services to support the quality of work-life in the Division of Epidemiology, Services and Prevention Research, NIDA.
Division of Epidemiology, Services and Prevention Research Operations Team:

Brandin Dechabert	*Jorge Vizcaino-Riveros*
Bethany Deeds	*Karen Walls*

NIDA Director's Award for Quality of Worklife: In recognition of your dedication in maintaining and providing stability to ongoing Return to Physical Workspace efforts in 2021.
Stability and Maintenance of Intramural Research Program Return to Physical Workspace Efforts in 2021 Team:

Margaret Kroen	*Michelle Leff*
Janette Lebron	*Leslie Premo*

NIDA Director's Innovator Award (Individual): NIDA Director's Innovator Award, in recognition of your developing a new innovative Common Fund Program, The Somatic Mosaicism across Human Tissues.
Amy Lossie

NIDA Director's Innovator Award (Group): In recognition of creating an innovative computational platform to facilitate compound discovery against various therapeutic protein targets relevant to NIDA's mission.
Computational Chemistry and Molecular Biophysics Section, Intramural Research Program:

Andy Fant	*Michelle Leff*
Kuo-Hao Lee	

Length of Service Award - 30 years

Michael Baumann	*Cheryl Nathaniel*
Monglan Le	*Carol Alderson*
Thomas Haines	*Jurij Mojsiak*
Liza Zeinert	*Lanette Palmquist*

Length of Service Award - 40 years

Jane Acri	*Elaine Solano*

OTHER NIDA STAFF AWARDS

Rita Valentino, Ph.D., Director of the Division of Neuroscience and Behavior**,** was selected to the 2021 class of Fellows of the American Society of Pharmacology and Experimental Therapeutics.

Eliot Gardner, Ph.D., Intramural Research Program, received **the Inaugural Honorary Speaker** for the "Ward and Ryan Donovan Lectureship on Drug Abuse/Addiction Toxicology" of the American College of Medical Toxicology.

Lorenzo Leggio, M.D., Ph.D., Intramural Research Program, was promoted to American College of Neuropsychopharmacology Fellow effective January 2022.

Brenda Curtis, Ph.D., and **Michael Michaelides, Ph.D.,** Intramural Research Program, were selected as American College of Neuropsychopharmacology Associate Members, effective January 2022.

2022 Fellows Award for Research Excellence

Albert Burgess-Hull	*Justin Siemian*
Zak Brodnik	*Nicholas Beacher*
Kauê Costa	*Chase Francis*
Briana Hempel	*Tingting Liu*

STAFF CHANGES

New Appointments

Jennifer A. Hobin, Ph.D., was appointed as the Director of the Office of Science Policy and Communications in December 2021. Jennifer joined NIDA in October 2018 as Office of Science Policy and Communication's Deputy Director and Legislative Advisor. Prior to joining NIDA, she served as Chief of the Science Policy Branch at the National Institute on Alcohol Abuse and Alcoholism, and as Director of Science Policy for the American Association for Cancer Research and the Federation of American Societies for Experimental Biology. She earned her Ph.D. in biopsychology at the University of Michigan.

Lorenzo Leggio, M.D., Ph.D., has been appointed as the Acting Clinical Director of NIDA's Intramural Research Program. Lorenzo is an M.D./Ph.D. physician-scientist with broad clinical and research expertise that ranges from addiction, internal medicine, and liver diseases, to neuropsychopharmacology and neuroendocrinology. Lorenzo has a joint Principal Investigators appointment with NIDA/National Institute on Alcohol Abuse and Alcoholism, serves as the Chief of the NIDA Translational Addiction Medicine Branch, and is the NIDA Deputy Scientific Director.

New Staff

Elizabeth Barfield, Ph.D., joined Office of Science Policy and Communications in October 2021 as a Health Science Policy Analyst in the Science Policy Branch. Elizabeth participated in the American Association for the Advancement of Science fellowship program with a placement at the Department of Defense, where she led a project that created a comprehensive data book on women's health using medical billing data. She received her Ph.D. in neuroscience from Emory University, where she trained under NIDA grantee Shannon Gourley.

Garcia Elliott joined NIDA's Office of Management's Management Analysis Branch as a Program Analyst on November 7, 2021. Garcia comes to NIDA from a position with the Food and Drug Administration.

Li Rebekah Feng, Ph.D., joined Division of Extramural Research's Scientific Review Branch as a Health Scientist Administrator on September 12, 2021. Li comes to NIDA from a position with National Institute of Nursing Research.

Chase Francis, Ph.D., began working as a Research Fellow in the Intramural Research Program's Neuronal Networks Section in November 2021.

Michael Horn joined NIDA's Office of Acquisitions as a Contract Specialist on December 19, 2021. Michael comes to NIDA from a position with the National Heart, Lung, and Blood Institute.

David Houppert joined Division of Extramural Research's Grants Management Branch as a Grants Management Specialist on December 19, 2021. David comes to NIDA from a position with the Office of the Director, NIH.

Amy Janes, Ph.D., joined the NIDA Intramural Research Program as a new investigator within the Neuroimaging Research Branch where she will lead the newly created Cognitive and Pharmacological Neuroimaging Unit. Amy joins us from Harvard Medical School, where she served as an Associate Professor of Psychiatry as well as the Director of the Functional Integration of Addiction Research Laboratory at McLean Hospital.

Keva Collier Kidemu, M.D., joined Division of Epidemiology, Services and Prevention Research as a Medical Officer in September 2021. Keva is a Preventive Medicine and Public Health physician with a keen interest in leveraging interdisciplinary expertise to improve population health.

Yordan Kostov, Ph.D., joined NIDA's Office of Translational Initiatives & Program Innovations as a Health Scientist Administrator on October 10, 2021. Yordan comes to NIDA from a position with the Center for Advanced Sensor Technology.

Juliette Lee joined the Division of Extramural Research's Grants Management Branch as a Grants Management Specialist on January 18, 2022.

Renata Marchette, Ph.D., began working as a Research Fellow in the Intramural Research Program's Neurobiology of Addiction Lab in November 2021.

Cam Nguyen joined the Division of Extramural Research's Grants Management Branch as a Grants Management Specialist on January 18, 2022. Cam comes to NIDA from a position with the National Science Foundation.

Tam Nguyen, M.D., joined NIDA's Office of Translational Initiatives & Program Innovations as a Health Scientist Administrator on September 26, 2021. Tam comes to NIDA from a position with National Cancer Institute.

Cai Ning Sheng, Ph.D., began working as a Staff Scientist in the Intramural Research Program's Integrative Neurobiology Lab in October 2021.

Juwon Song joined the Office of Science Policy and Communications in October 2021 as a Technical Writer/Editor in the Communications Branch. Juwon comes to NIDA from the press team at the American Association for the Advancement of Science, the publisher of *Science Magazine*.

Daniel Stimson, J.D., Ph.D., joined Office of Science Policy and Communications in December 2021 as a Health Science Policy Analyst in the Science Policy Branch. Daniel was previously the chief of the Science Policy, Outreach, and Reporting Branch within Office of Science Policy, Engagement, Education, and Communications at the National Heart, Lung, and Blood Institute.

Stephanie Weiss, M.D., began working as a Staff Clinician II in the NIDA Intramural Research Program's Translational Addiction Medicine Branch in October 2021.

Kwesi Wright joined Division of Extramural Research's Grants Management Branch as a Grants Management Specialist on September 26, 2021. Kwesi comes to NIDA from a position with the National Institute of Biomedical Imaging and Bioengineering.

Staff Departures

Yvonne Ferguson, Ph.D., a Health Scientist Administrator in the Division of Extramural Research's Grants Management Branch, left NIDA on October 3, 2021.

Penny Greene, a Grants Management Specialist in the Division of Extramural Research's Grants Management Branch, left NIDA on November 6, 2021.

Lennin Greenwood, a Grants Management Specialist in the Division of Extramural Research's Grants Management Branch, left NIDA on September 25, 2021.

Jagdeep Kathuria, an Information Technology Specialist in NIDA's Information & Resource Management Branch, left NIDA on January 29, 2022.

Michelle Leff, M.D., Intramural Research Program Chief of Staff, resigned from her position in October 2021.

Karran Phillips, M.D., NIDA Clinical Director, left her position in January 2022 to assume the role of Deputy Director for the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration. Karran served for nearly 15 years at NIDA, first as a Staff Clinician in the Clinical Pharmacology Research Branch and for the last six years as the Clinical Director and Senior Clinician.

Natisha Rowe, an Extramural Support Assistant in the Division of Extramural Research's Office of Extramural Policy & Review, left NIDA on January 29, 2021.

Retirements

Montrue Crawford, Administrative Officer in NIDA's Administrative Management Branch, retired from Federal Service on October 31, 2021.

Edith Davis, a Grants Management Specialist in Division of Extramural Research's Grants Management Branch, retired from Federal Service on October 31, 2021.

Meyer Glantz, Ph.D., Health Scientist Administrator in Division of Epidemiology, Services and Prevention Research, retired from Federal Service on December 31, 2021.

Kathleen E. Giuliano, Contract Specialist, retired from Federal Service in September 2021.

Kenneth E. Goodling, NIDA Chief Contracting Officer, retired from Federal Service on December 31, 2021.

Steven Gust, Ph.D., Director of NIDA's International Program, retired from Federal Service on December 31, 2021.

Jack Stein, Ph.D., NIDA Chief of Staff and Director for NIDA's Office of Science Policy and Communications, retired from NIH at the end of December 2021, after 25 years of Federal Service.

Amina Woods, Ph.D., retired from Federal Service in September 2021.