



DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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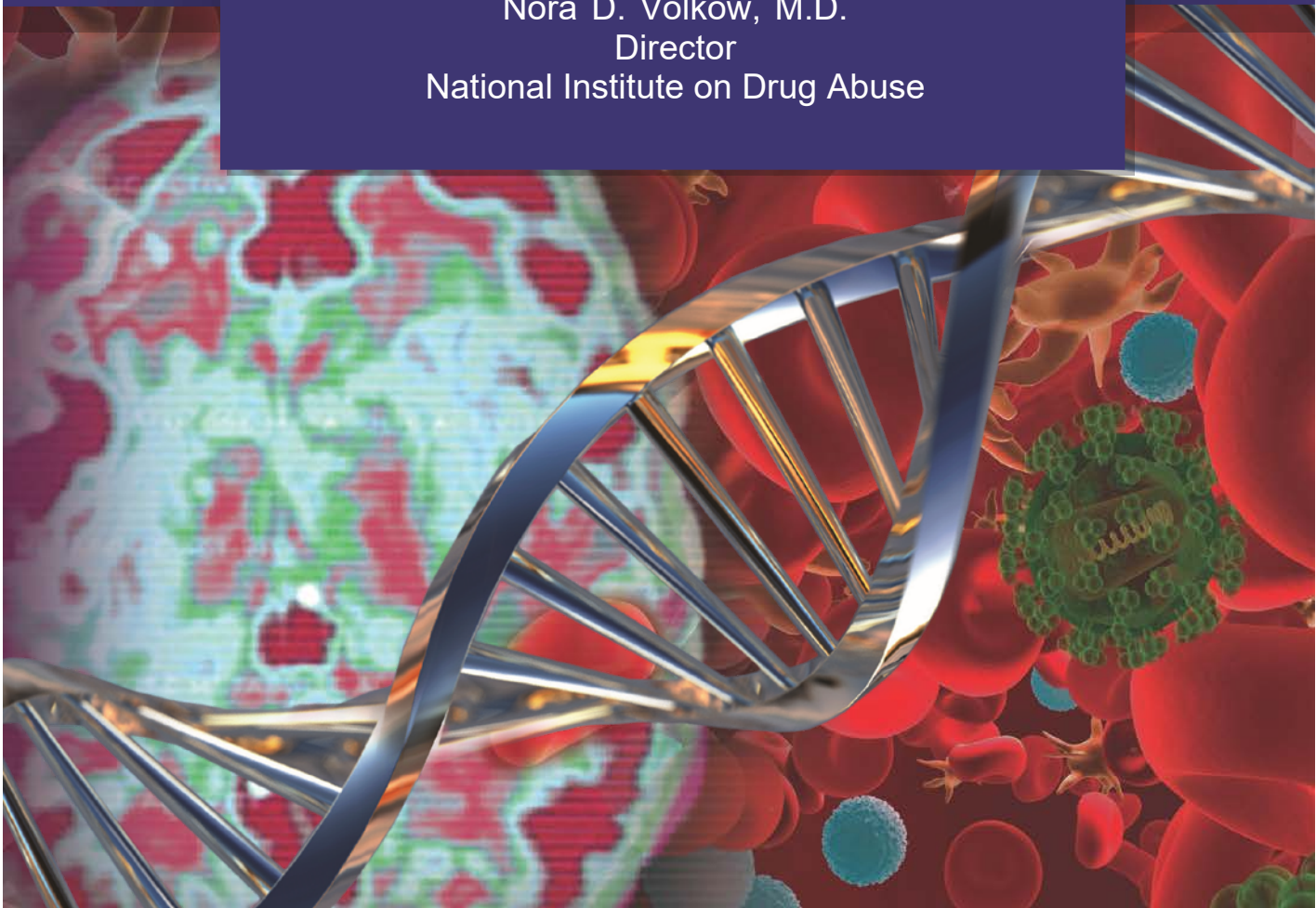


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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

[Structure Of The Neurotensin Receptor 1 In Complex With \$\beta\$ -arrestin 1](#) Huang W, Masureel M, Qianhui Q, Janetzko J, Asuka I, Kato HE, Robertson MJ, Nguyen KC, Glenn JS, Skiniotis G, Kobilka BK. Nature. March 2020. 579:303-308.

Arrestin proteins bind to active, phosphorylated G-protein-coupled receptors (GPCRs), thereby preventing G-protein coupling, triggering receptor internalization and affecting various downstream signalling pathways. Although there is a wealth of structural information detailing the interactions between GPCRs and G proteins, less is known about how arrestins engage GPCRs. Here we report a cryo-electron microscopy structure of full-length human neurotensin receptor 1 (NTSR1) in complex with truncated human β -arrestin 1 (β arr1(Δ CT)). We find that phosphorylation of NTSR1 is critical for the formation of a stable complex with β arr1(Δ CT), and identify phosphorylated sites in both the third intracellular loop and the C terminus that may promote this interaction. In addition, we observe a phosphatidylinositol-4,5-bisphosphate molecule forming a bridge between the membrane side of NTSR1 transmembrane segments 1 and 4 and the C-lobe of arrestin. Compared with a structure of a rhodopsin-arrestin-1 complex, in our structure arrestin is rotated by approximately 85° relative to the receptor. These findings highlight both conserved aspects and plasticity among arrestin-receptor interactions.

[A Dopamine-Induced Gene Expression Signature Regulates Neuronal Function And Cocaine Response](#) Savell KE, Tuscher JJ, Zipperly ME, Duke CG, Phillips III RA, Bauman AJ, Thukral S, Sultan FA, Goska NA, Ianov L, Day JJ. Science Advances. June 24, 2020, 6: eaba4221.

Drugs of abuse elevate dopamine levels in the nucleus accumbens (NAc) and alter transcriptional programs believed to promote long-lasting synaptic and behavioral adaptations. Here, we leveraged single-nucleus RNA-sequencing to generate a comprehensive molecular atlas of cell subtypes in the NAc, defining both sex-specific and cell type-specific responses to acute cocaine experience in a rat model system. Using this transcriptional map, we identified an immediate early gene expression program that is up-regulated following cocaine experience in vivo and dopamine receptor activation in vitro. Multiplexed induction of this gene program with a large-scale CRISPR-dCas9 activation strategy initiated a secondary synapse-centric transcriptional profile, altered striatal physiology in vitro, and enhanced cocaine sensitization in vivo. Together, these results define the transcriptional response to cocaine with cellular precision and demonstrate that drug-responsive gene programs can potentiate both physiological and behavioral adaptations to drugs of abuse.

[The Central Amygdala Recruits Mesocorticolimbic Circuitry For Pursuit Of Reward Or Pain](#) Warlow SM, Naffziger EE, Berridge KC. Nature. 11(1): 2716. June 1, 2020.

How do brain mechanisms create maladaptive attractions? Here intense maladaptive attractions are created in laboratory rats by pairing optogenetic channelrhodopsin (ChR2) stimulation of central nucleus of amygdala (CeA) in rats with encountering either sucrose, cocaine, or a painful shock-delivering object. We find that pairings make the respective rats pursue either sucrose exclusively, or cocaine exclusively, or repeatedly self-inflict shocks. CeA-induced maladaptive

attractions, even to the painful shock-rod, recruit mesocorticolimbic incentive-related circuitry. Shock-associated cues also gain positive incentive value and are pursued. Yet the motivational effects of paired CeA stimulation can be reversed to negative valence in a Pavlovian fear learning situation, where CeA ChR2 pairing increases defensive reactions. Finally, CeA ChR2 valence can be switched to neutral by pairing with innocuous stimuli. These results reveal valence plasticity and multiple modes for motivation via mesocorticolimbic circuitry under the control of CeA activation.

Orchestrating Opiate-Associated Memories in Thalamic Circuits Keyes PC, Adams EL, Chen Z, Bi L, Nachtrab G, Wang VJ, Tessier-Lavigne M, Zhu Y, and Chen X. *Neuron*. 107, Sept 23, 2020.

Disrupting memories that associate environmental cues with drug experiences holds promise for treating addiction, yet accessing the distributed neural network that stores such memories is challenging. Here, we show that the paraventricular nucleus of the thalamus (PVT) orchestrates the acquisition and maintenance of opiate-associated memories via projections to the central nucleus of the amygdala (CeA) and nucleus accumbens (NAc). PVT/CeA activity associates morphine reward to the environment, whereas transient inhibition of the PVT/NAc pathway during retrieval causes enduring protection against opiate-primed relapse. Using brain-wide activity mapping, we revealed distributed network activities that are altered in non-relapsing mice, which enabled us to find that activating the downstream NAc/lateral hypothalamus (LH) pathway also prevents relapse. These findings establish the PVT as a key node in the opiate-associated memory network and demonstrate the potential of targeting the PVT/NAc/LH pathway for treating opioid addiction.

Characterization of a Knock-In Mouse Line Expressing a Fusion Protein of Kappa Opioid Receptor Conjugated With tdTomato: 3-Dimensional Brain Imaging Via CLARITY

Chen C, Willhouse AH, Huang P, Ko N, Wang Y, Xu B, Hsuan LHM, Huang M, Kieffer B, Barbe MF, Liu-Chen L-Y. *eNeuro*. July 23, 2020.

Activation of kappa opioid receptor (KOR) produces analgesia, antipruritic effect, sedation and dysphoria. To characterize neuroanatomy of KOR at high resolutions and circumvent issues of specificity of KOR antibodies, we generated a knock-in mouse line expressing KOR fused at the C-terminus with the fluorescent protein tdTomato (KtdT). The selective KOR agonist U50,488H caused anti-scratch effect and hypolocomotion, indicating intact KOR neuronal circuitries. Clearing of brains with CLARITY revealed 3-dimensional (3-D) images of distribution of KOR, and any G protein-coupled receptors, for the first time. 3-D brain images of KtdT and immunohistochemistry (IHC) on brain sections with antibodies against tdTomato show similar distribution to that of autoradiography of [³H]U69,593 binding to KOR in wildtype mice. KtdT was observed in regions involved in reward and aversion, pain modulation and neuroendocrine regulation. KOR is present in several areas with unknown roles, including the claustrum, dorsal endopiriform nucleus, paraventricular nucleus of the thalamus, lateral habenula and substantia nigra pars reticulata (SNr), which are discussed. Prominent KtdT45 containing fibers were observed to project from caudate putamen (CP) and nucleus accumbens (ACB) to substantia innominata (SI) and SNr. Double IHC revealed co-localization of KtdT with tyrosine hydroxylase (TH) in brain regions, including CP, ACB and ventral tegmental area (VTA). KOR was visualized at the cellular level, such as colocalization with TH and agonist-induced KOR translocation into intracellular space in some VTA neurons. These mice thus represent a

powerful and heretofore unparalleled tool for neuroanatomy of KOR at both the 3-D and cellular levels localization of KdtT with tyrosine hydroxylase (TH) in brain regions, including CP, ACB and ventral tegmental area (VTA). KOR was visualized at the cellular level, such as colocalization with TH and agonist-induced KOR translocation into intracellular space in some VTA neurons. These mice thus represent a powerful and heretofore unparalleled tool for neuroanatomy of KOR at both the 3-D and cellular levels.

Expectancy-Related Changes In Dopaminergic Error Signals Are Impaired By Cocaine Self-Administration

Takahashi YK, Stalnaker TA, Marrero-Garcia Y, Rada RM, Schoenbaum G. *Neuron*. 2019 Jan 16; 101(2): 294-306.

Addiction is a disorder of behavioral control and learning. While this may reflect pre-existing propensities, drug use also clearly contributes by causing changes in outcome processing in prefrontal and striatal regions. This altered processing is associated with behavioral deficits, including changes in learning. These areas provide critical input to midbrain dopamine neurons regarding expected outcomes, suggesting that effects on learning may result from changes in dopaminergic error signaling. Here, the authors show that dopamine neurons recorded in rats that had self-administered cocaine failed to suppress firing on omission of an expected reward and exhibited lower amplitude and imprecisely timed increases in firing to an unexpected reward. Learning also appeared to have less of an effect on reward-evoked and cue-evoked firing in the cocaine-experienced rats. Overall, the changes are consistent with reduced fidelity of input regarding the expected outcomes, such as their size, timing, and overall value, because of cocaine.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Outcomes Of Childhood Preventive Intervention Across 2 Generations: A Nonrandomized Controlled Trial

Hill KG, Bailey JA, Steeger CM, Hawkins JD, Catalano RF, Kosterman R, Epstein M, Abbott RD. *JAMA Pediatr*. 2020 June 8; e201310.

OBJECTIVE To examine possible intervention outcomes on the offspring of individuals (now parents) who participated in the Raising Healthy Children preventive intervention as children in the elementary grades. **DESIGN, SETTING, AND PARTICIPANTS** This nonrandomized controlled trial was conducted in public elementary schools serving high-crime areas in Seattle, Washington. The panel originated in Seattle but was followed up locally and in out-of-state locations over time. Data analyzed in this study were collected from September 1980 to June 2011, with follow-up of the firstborn offspring (aged 1 through 22 years) of 182 parents who had been in the full intervention vs control conditions in childhood. Their children were assessed across 7 waves in 2 blocks (2002-2006 and 2009-2011). Data were analyzed for this article from September 2018 through January 2019. **INTERVENTIONS** In grades 1 through 6, the Raising Healthy Children intervention provided elementary school teachers with methods of classroom management and instruction, first-generation (G1) parents with skills to promote opportunities for children's active involvement in the classroom and family, and second-generation (G2) child with social and emotional skills training. **MAIN OUTCOMES AND MEASURES** Outcomes examined in the third-generation (G3) offspring were self-regulation (emotion, attention, and behavioral regulation), cognitive capabilities, and social capabilities. Risk behaviors, including substance use and delinquency, were examined from age 6 years to study completion. Early onset of sexual activity was examined from age 13 years to study completion. Intent-to-treat

analyses controlled for potential confounding factors. RESULTS A total of 182 G3 children were included in this analysis (72 in the full intervention and 110 in the control condition; mean age at first wave of data collection, 7 [range, 1-13] years). Significant differences in the offspring of intervention parents were observed across 4 domains: improved early child developmental functioning (ages 1-5 years; significant standardized β range, 0.45-0.56), lower teacher-rated behavioral problems (ages 6-18 years; significant standardized β range, -0.39 to -0.46), higher teacher-rated academic skills and performance (ages 6-18 years; significant standardized β range, 0.34-0.49), and lower child-reported risk behavior (ages 6-18 years; odds ratio for any drug use [alcohol, cigarettes, or marijuana], 0.27 [95% CI, 0.10-0.73]). CONCLUSIONS AND RELEVANCE To our knowledge, this is the first study to report significant intervention differences in the offspring of participants in a universal childhood preventive intervention. Cost-benefit analyses have examined the benefits of childhood intervention in the target generation. The present study suggests that additional benefits can be realized in the next generation as well.

[Buprenorphine Waiver Uptake Among Nurse Practitioners and Physician Assistants: The Role Of Existing Waivered Prescriber Supply](#) Auty SG, Stein MG, Walley AY, Drainoni, ML. J Subst Abuse Treat. 2020; 115: 108032.

Buprenorphine is an effective pharmacotherapy for the treatment of opioid use disorder (OUD), but recent increases in the rate of OUD in the U.S. have outpaced the supply of clinicians waived to prescribe buprenorphine. To increase the supply of buprenorphine prescribers, the Comprehensive Addiction and Recovery Act expanded buprenorphine prescribing waiver eligibility beyond physicians to nurse practitioners (NP) and physician assistants (PA) in 2017. Little is known about patterns of waiver uptake among NPs and PAs. This study examined associations between the existing supply of waived prescribers and waiver uptake among NPs and PAs in U.S. states. NP and PA waiver uptake was evaluated as the number of NPs or PAs obtaining an initial buprenorphine prescribing waiver per 10,000 state residents from January 2017 to December 2018 using data from the Buprenorphine Waiver Notification System. NP and PA waiver uptake was estimated as a function of existing waived prescriber supply, OUD treatment capacity, and other state characteristics using generalized least squares (GLS) regression. 28,010 NPs and PAs have become waived to prescribe buprenorphine since January 2017. GLS regressions indicated that waived prescriber supply was significantly, positively associated with both NP ($b = 0.101$ $p < 0.001$) and PA ($b = 0.030$, $p < 0.001$) waiver uptake. Results suggest an addition of ten waived prescribers to existing supply was associated with an increase of one waived NP, and an addition of thirty-three waived prescribers to existing supply was associated with an increase of one waived PA. NP and PA waiver uptake is strongly associated with the existing supply of waived prescribers in a state, suggesting NPs and PAs may be more likely to acquire waivers in states with a high existing supply of buprenorphine prescribers. Additional policy solutions are needed to scale up the supply of buprenorphine prescribers in underserved states

[Adolescent Menthol Cigarette Use And Risk Of Nicotine Dependence: Findings From The National Population Assessment On Tobacco And Health \(PATH\) Study](#) Cwalina SN, Majmundar A, Unger JB, Barrington-Trimis JL, Pentz MA. Drug Alcohol Depend. 2020 Jan 1; 206: 107715.

Menthol cigarettes appeal to adolescents because they mask the harsh taste and sensation of tobacco smoke thereby making it easier to inhale the smoke. As a result, menthol cigarette users

expose themselves to higher levels of nicotine relative to non-menthol cigarettes and increase their risk for developing nicotine dependence. We examined whether adolescent menthol smokers (vs. non-menthol smokers) reported higher nicotine dependence. Methods: Data were from adolescent past 30-day cigarette smokers participating in Wave 2 of the Population Assessment of Tobacco and Health survey (n = 434). Nicotine dependence was assessed using eight items from the Wisconsin Inventory of Smoking Dependence Motives corresponding to individual subscale constructs. Linear regression models evaluated the association of past 30-day menthol (vs. non-menthol) cigarette use with each dependence outcome in separate models, adjusting for age, gender, race, and other tobacco product use. Results: 49.5% of past 30-day youth cigarette smokers reported smoking menthol cigarettes. In adjusted models, menthol smokers (vs. non-menthol smokers) reported significantly higher nicotine dependence for three constructs: craving (p = 0.005), affiliative attachment (p = 0.005), and tolerance (p = 0.003). No differences for menthol vs. non-menthol smokers were observed for loss of control, negative reinforcement, cognitive enhancement, automaticity, or social environment after correction for multiple comparisons. Conclusions: Findings suggest that menthol cigarette smokers are not just more physically dependent on nicotine but also experience increased emotional attachments to cigarettes compared to their non-menthol smoking peers. Because adolescents are vulnerable to developing nicotine dependence, tobacco control policies that restrict youth access to menthol cigarettes are urgently needed.

[Associations Between Stopping Prescriptions For Opioids, Length Of Opioid Treatment, And Overdose or Suicide Deaths In US Veterans: Observational Evaluation](#) Oliva EM, Bowe T, Manhapra A, Kertesz S, Hah JM, Henderson P, Robinson A, Paik M, Sandbrink F, Gordon AJ, Trafton JA. *BMJ*. 2020 Mar 4; 368: m283.

To examine the associations between stopping treatment with opioids, length of treatment, and death from overdose or suicide in the Veterans Health Administration. Observational evaluation. Veterans Health Administration. 1,394,102 patients in the Veterans Health Administration with an outpatient prescription for an opioid analgesic from fiscal year 2013 to the end of fiscal year 2014 (1 October 2012 to 30 September 2014). A multivariable Cox non-proportional hazards regression model examined death from overdose or suicide, with the interaction of time varying opioid cessation by length of treatment (≤ 30 , 31-90, 91-400, and >400 days) as the main covariates. Stopping treatment with opioids was measured as the time when a patient was estimated to have no prescription for opioids, up to the end of the next fiscal year (2014) or the patient's death. 2887 deaths from overdose or suicide were found. The incidence of stopping opioid treatment was 57.4% (n=799 668) overall and based on length of opioid treatment was 32.0% (≤ 30 days), 8.7% (31-90 days), 22.7% (91-400 days), and 36.6% (>400 days). The interaction between stopping treatment with opioids and length of treatment was significant (P <0.001); stopping treatment was associated with an increased risk of death from overdose or suicide regardless of the length of treatment, with the risk increasing the longer patients were treated. Hazard ratios for patients who stopped opioid treatment (with reference values for all other covariates) were 1.67 (≤ 30 days), 2.80 (31-90 days), 3.95 (91-400 days), and 6.77 (>400 days). Descriptive life table data suggested that death rates for overdose or suicide increased immediately after starting or stopping treatment with opioids, with the incidence decreasing over about three to 12 months. Patients were at greater risk of death from overdose or suicide after stopping opioid treatment, with an increase in the risk the longer patients had been treated before stopping. Descriptive data suggested that starting treatment with opioids was also a risk period.

Strategies to mitigate the risk in these periods are not currently a focus of guidelines for long term use of opioids. The associations observed cannot be assumed to be causal; the context in which opioid prescriptions were started and stopped might contribute to risk and was not investigated. Safer prescribing of opioids should take a broader view on patient safety and mitigate the risk from the patient's perspective. Factors to address are those that place patients at risk for overdose or suicide after beginning and stopping opioid treatment, especially in the first three months.

[Screening, Counseling, And Health Care Utilization Among A National Sample Of Adolescent Smokers](#) Merianos AL, Mahabee-Gittens EM. Clin Pediatr (Phila). 2020 May; 59(4-5): 467-475.

Our objective was to assess the association between cigarette smoking and tobacco use screening and advising to quit use by a clinician among adolescents nationwide. We also examined the relationships between smoking and health-related indicators and health care utilization. A secondary analysis of the 2017 National Survey on Drug Use and Health was conducted (N = 11 884). Ever smokers were less likely to be screened for tobacco use. Current smokers and those who were nicotine dependent were more likely to have been advised to quit use. Ever and current smokers were significantly more likely to report good/fair/poor health status, illness-related school absenteeism in the past 30 days and were more likely to have had an emergency department visit or an overnight hospital stay. Standardized tobacco control efforts are needed in health care settings to support clinicians to screen all adolescents for tobacco use and advise every smoker irrespective of smoking frequency to quit use. Importance: The study highlights the need for more research to improve the implementation of clinical guidelines related screening for smoking for adolescents. The rates of adolescent smoking and service utilization also underscore the need to establish the evidence base for primary care-based tobacco cessation interventions. At present, the U.S. Preventive Services Task Force has concluded that the current evidence is insufficient to assess the balance of benefits and harms of primary care--feasible interventions for the cessation of tobacco use among school-aged children and adolescents. The lack of endorsement by the USPSTF may limit payment for these services by insurance companies, which could contribute to the low rate of screening and referral to intervention.

TREATMENT RESEARCH

[Two Weeks Of Image-Guided Left Dorsolateral Prefrontal Cortex Repetitive Transcranial Magnetic Stimulation Improves Smoking Cessation: A Double-Blind, Sham-Controlled, Randomized Clinical Trial](#) Xingbao L, Hartwell KJ, Henderson S, Badran BW, Brady KT, George MS. Brain Stimulation. September 1, 2020; 13(5): P1271-1279.

Background: Previous studies have found that repetitive transcranial magnetic stimulation (rTMS) to the left dorsal lateral prefrontal cortex (LDLPFC) transiently reduces smoking craving, decreases cigarette consumption, and increases abstinence rates. Objective: We investigated whether 10 daily MRI-guided rTMS sessions over two weeks to the LDLPFC paired with craving cues could reduce cigarette consumption and induce smoking cessation. Methods: We enrolled 42 treatment-seeking nicotine-dependent smokers (10 cigarettes per day) in a randomized, double-blind, sham-controlled trial. Participants received 10 daily sessions over 2 weeks of either active or sham MRI-guided rTMS (10Hz, 3000 pulses each session) to the

LDLPFC concurrently with video smoking cues. The primary outcome was a reduction in biochemically confirmed cigarette consumption with a secondary outcome of abstinence on the target quit date. We also recorded cue induced craving and withdrawal symptoms. Results: Compared to sham (n=17), participants receiving active rTMS (n = 21) smoked significantly fewer cigarettes per day during the 2-week treatment (mean [SD], 13.73[9.18] vs. 11.06[9.29], $P < .005$) and at 1-month follow-up (12.78[9.53] vs. 7.93[7.24], $P < .001$). Active rTMS participants were also more likely to quit by their target quit rate (23.81%vs. 0%, OR 11.67, 90% CL, 0.96e141.32, $x^2 = 4.66$, $P = .031$). Furthermore, rTMS significantly reduced mean craving throughout the treatments and at follow-up (29.93[13.12] vs. 25.01[14.45], $P < .001$). Interestingly across the active treatment sample, more lateral coil location was associated with more success in quitting (43.43[0.40] vs. 41.79[2.24], $P < .013$). Conclusions: Daily MRI-guided rTMS to the LDLPFC for 10 days reduces cigarette consumption and cued craving for up to one month and also increases the likelihood of smoking cessation. Trial registration: ClinicalTrials.gov identifier: NCT02401672.

TAAR1 Agonists Attenuate Extended-Access Cocaine Self-Administration And Yohimbine-Induced Reinstatement Of Cocaine-Seeking Liu J, Johnson B, Wu R, Seaman R Jr, Vu J, Zhu Q, Zhang Y, Li JX. *Br J Pharmacol.* 2020.

The trace amine-associated receptor 1 (TAAR1) negatively modulates dopamine transmission. Our previous studies demonstrated that TAAR1 agonists attenuated cue- and drug-induced cocaine-seeking and increased the elasticity of the cocaine demand curve, in the short-access cocaine self-administration model. Compulsive use of cocaine, which is an essential criterion of cocaine use disorder, can be induced by extended access to cocaine self-administration. To characterize the role of TAAR1 in compulsive cocaine use, we evaluated the effects of activation of TAAR1 on cocaine intake, cocaine binge and cue-induced cocaine-seeking using the extended-access cocaine self-administration model in adult male Sprague-Dawley rats. We also investigated the role of TAAR1 in stress-triggered cocaine relapse by using the $\alpha 2$ -adrenoceptor antagonist yohimbine-induced reinstatement of cocaine-seeking. The selective TAAR1 partial agonist RO5263397 attenuated cocaine intake and did not develop tolerance during the 10-day extended-access cocaine self-administration. RO5263397 reduced a 12-h binge intake of cocaine after forced abstinence. RO5263397 also decreased cue-induced cocaine-seeking after prolonged abstinence from extended-access cocaine self-administration. Furthermore, RO5263397 and the selective TAAR1 full agonist RO5166017 reduced yohimbine-induced reinstatement of cocaine-seeking behaviour. Activation of TAAR1 attenuated extended-access cocaine self-administration and stress-induced cocaine reinstatement. These results suggest that TAAR1 agonists are promising pharmacological interventions to treat cocaine use disorder and relapse.

Protracted Renal Clearance Of Fentanyl In Persons With Opioid Use Disorder Huhn AS, Hobelmann JG, Oyler GA, Strain EC. *Drug Alcohol Depend.* 2020; 214: 108147.

The illicit opioid supply in the U.S. is increasingly adulterated with fentanyl. As such, persons with opioid use disorder (OUD) may be regularly exposed to fentanyl, however, the pharmacokinetics of repeated fentanyl exposure are not well understood. The current study aimed to quantify renal clearance of fentanyl in OUD patients presenting to residential treatment. Participants (N = 12) who presented to a 28-day residential treatment program were enrolled if they tested positive for fentanyl at intake. Urine samples were collected every 2-3 days and were quantitatively tested for fentanyl, norfentanyl, and creatinine via liquid chromatography mass

spectrometry (LC-MS). Fentanyl clearance was defined as the time since last illicit opioid use and the median time between last positive and first negative fentanyl urine screen. Participants had a mean and standard deviation (SD) age of 28.9 (11.0), were 67 % male, and 83 % white. The mean (SD) time for fentanyl and norfentanyl clearance was 7.3 (4.9) and 13.3 (6.9) days, respectively. One participant continued to test positive for fentanyl for 19 days and norfentanyl for 26 days following their last use, and left treatment without testing negative for norfentanyl. Fentanyl clearance in persons with OUD is considerably longer than the typical 2-4-day clearance of other short-acting opioids. The findings of this study might explain recent reports of difficulty in buprenorphine inductions for persons who use fentanyl and point to a need to better understand the pharmacokinetics of fentanyl in the context of opioid withdrawal in persons who regularly use fentanyl.

Associations Between Prescribed Benzodiazepines, Overdose Death And Buprenorphine Discontinuation Among People Receiving Buprenorphine Park TW, Laroche MR, Saitz R, Wang N, Bernson D, Walley AY. *Addiction*. 2020; 115(5): 924-932.

Benzodiazepines are commonly prescribed to patients with opioid use disorder receiving buprenorphine treatment yet may increase overdose risk. However, prescribed benzodiazepines may improve retention in care by reducing buprenorphine discontinuation and thus may prevent relapse to illicit opioid use. We aimed to test the association between benzodiazepine prescription and fatal opioid overdose, non-fatal opioid overdose, all-cause mortality and buprenorphine discontinuation. This was a retrospective cohort study using five individually linked data sets from Massachusetts, United States government agencies. We studied 63,389 Massachusetts residents aged 18 years or older who received buprenorphine treatment between January 2012 and December 2015. Filled benzodiazepine prescription during buprenorphine treatment was the main independent variable. The primary outcome was time to fatal opioid overdose. Secondary outcomes were time to non-fatal opioid overdose, all-cause mortality and buprenorphine discontinuation. We defined buprenorphine discontinuation as having a 30-day gap without another prescription following the end date of the previous prescription. We used Cox proportional hazards models to calculate hazards ratios that tested the association between receipt of benzodiazepines and all outcomes, restricted to periods during buprenorphine treatment. Of the 63,345 individuals who received buprenorphine, 24% filled at least one benzodiazepine prescription during buprenorphine treatment. Thirty-one per cent of the 183 deaths from opioid overdose occurred when individuals received benzodiazepines during buprenorphine treatment. Benzodiazepine receipt during buprenorphine treatment was associated with an increased risk of fatal opioid overdose adjusted hazard ratio (HR) = 2.92, 95% confidence interval (CI) = 2.10-4.06, non-fatal opioid overdose, adjusted HR = 2.05, 95% CI, 1.68-2.50, all-cause mortality, adjusted HR = 1.90, 95% CI, 1.48-2.44 and a decreased risk of buprenorphine discontinuation, adjusted HR = 0.87, 95% CI, 0.85-0.89. Benzodiazepine receipt appears to be associated with both increased risk of opioid overdose and all-cause mortality and decreased risk of buprenorphine discontinuation among people receiving buprenorphine.

Perceptions And Preferences For Long-acting Injectable And Implantable Medications In Comparison To Short-acting Medications For Opioid Use Disorders Saunders EC, Moore SK, Walsh O, Metcalf SA, Budney AJ, Scherer E, Marsch LA. *J Subst Abuse Treat.* 2020; 111: 54-66.

Treatment for opioid use disorders has recently evolved to include long-acting injectable and implantable formulations of medications for opioid use disorder (MOUD). Incorporating patient preferences into treatment for substance use disorders is associated with increased motivation and treatment satisfaction. This study sought to assess treatment preferences for long-acting injectable and implantable MOUD as compared to short-acting formulations among individuals with OUD. We conducted qualitative, semi-structured telephone interviews with forty adults recruited from across the United States through Craigslist advertisements and flyers posted in treatment programs. Eligible participants scored a two or greater on the heroin or opioid pain reliever sections of the Tobacco, Alcohol, Prescription Medications, and Other Substances (TAPS) Tool, indicative of a past-year OUD. Interviews were transcribed, coded, and thematically analyzed. Twenty-four participants (60%) currently or previously had been prescribed MOUD. Sixteen participants (40%) expressed general opposition to MOUD, citing concerns that MOUD is purely financial gain for pharmaceutical companies and/or a "band aid" solution replacing one drug with another, rather than a path to abstinence. Some participants expressed personal preference for long-acting injectable (n = 16/40: 40%) and implantable formulations (n = 12/40: 30%) over short-acting formulations. About half of the participants were not willing to use injectables (n = 19/40: 48%) or implantables (n = 22/40: 55%), preferring short-acting formulations. Mixed evaluations of long- and short-acting MOUD focused on considerations of medication-related beliefs (privacy, concern over an embedded foreign body), the medication-related burden (convenience, provision of structure and support, medication administration, potential side effects), and medication-taking practices (potential for non-prescribed use, control over dosage, and duration of treatment). Though many participants personally prefer short-acting to long-acting MOUD, some were open to including long-acting formulations in the range of options for those with OUD. Participants felt long-acting formulations may reduce medication-related burden and the risk of diversion. Conversely, participants expressed concern about invasive administration and loss of control over their treatment. Results suggest support for expanded access to a variety of formulations of MOUD. The use of shared decision making may also help patients select the formulation best aligned with their experiences, values, and treatment goals.

Inhibition Of Fatty Acid Amide Hydrolase In The CNS Prevents And Reverses Morphine Tolerance In Male And Female Mice Fotio Y, Palese F, Guaman TP, Ahmed F, Piomelli D. *Br J Pharmacol.* 2020; 177(13): 3024-3035.

Fatty acid amide hydrolase (FAAH) is an intracellular serine amidase that terminates the signalling of various lipid messengers involved in pain regulation, including anandamide and palmitoylethanolamide. Here, we investigated the effects of pharmacological or genetic FAAH removal on tolerance to the anti-nociceptive effects of morphine. We induced tolerance in male and female mice by administering twice-daily morphine for 7 days while monitoring nociceptive thresholds by the tail immersion test. The globally active FAAH inhibitor URB597 (1 and 3 mg·kg⁻¹, i.p.) or the peripherally restricted FAAH inhibitor URB937 (3 mg·kg⁻¹, i.p.) were administered daily 30 min prior to morphine, alone or in combination with the cannabinoid CB1 receptor antagonist AM251 (3 mg·kg⁻¹, i.p.), the CB2 receptor antagonist AM630 (3 mg·kg⁻¹,

i.p.), or the PPAR- α antagonist GW6471 (4 mg·kg⁻¹, i.p.). Spinal levels of FAAH-regulated lipids were quantified by LC/MS-MS. Gene transcription was assessed by RT-qPCR. URB597 prevented and reversed morphine tolerance in both male and female mice. This effect was mimicked by genetic FAAH deletion, but not by URB937. Treatment with AM630 suppressed, whereas treatment with AM251 or GW6471, attenuated the effects of URB597. Anandamide mobilization was enhanced in the spinal cord of morphine-tolerant mice. mRNA levels of the anandamide-producing enzyme N-acyl-phosphatidylethanolamine PLD (NAPE-PLD) and the palmitoylethanolamide receptor PPAR- α , but not those for CB2, CB1 receptors or FAAH, were elevated in spinal cord. CONCLUSION AND IMPLICATIONS: FAAH-regulated lipid signalling in the CNS modulated opiate tolerance, suggesting FAAH as a potential target for opiate-sparing medications.

Kappa Opioid Agonists Reduce Oxycodone Self-Administration In Male Rhesus Monkeys

Zamarripa CA, Naylor JE, Huskinson SL, Townsend EA, Prisinzano TE, Freeman KB. Psychopharmacology (Berl). 2020; 237(5): 1471-1480.

Combinations of mu and kappa opioid receptor (KOR) agonists have been proposed as potential analgesic formulations with reduced abuse liability. The current studies extend previous work by investigating the typical KOR agonist, salvinorin A, and the atypical KOR agonist, nalfurafine, as deterrents of oxycodone self-administration using a progressive ratio (PR) schedule of reinforcement. In separate experiments, adult male rhesus monkeys (N = 4/experiment) were trained under a PR schedule of reinforcement to self-administer cocaine (0.1 mg/kg/injection) and saline on alternating days. Oxycodone (0.01-0.1 mg/kg/injection) alone and combined with salvinorin A (experiment 1; 0.006, 0.012 mg/kg/injection) or nalfurafine (experiment 2; 0.0001-0.00032 mg/kg/injection) were tested within the alternating cocaine and saline baseline. The mechanism of nalfurafine's effects on oxycodone self-administration was investigated via pretreatment with the KOR antagonist, nor-binaltorphimine (nor-BNI; 10 mg/kg; i.m.). All subjects self-administered oxycodone alone above saline levels at sufficiently large doses, and combining salvinorin A or nalfurafine with oxycodone reduced the mean number of injections per session to saline levels (experiment 1) or to levels that were significantly lower than oxycodone alone (experiment 2). The ability of nalfurafine to reduce oxycodone self-administration was reversed by pretreatment with nor-BNI. These results demonstrate that KOR agonists, including the clinically used KOR agonist, nalfurafine, can punish self-administration of a prescription opioid analgesic, oxycodone, in rhesus monkeys and that nalfurafine's punishing effect is KOR-dependent. Combinations of KOR agonists with prescription opioids may have reduced abuse liability.

A Randomized, Double-Blind, Placebo-Controlled Study Of The Kappa Opioid Receptor Antagonist, CERC-501, In A Human Laboratory Model Of Smoking Behavior

Jones JD, Babalonis S, Marcus R, Vince B, Kelsh D, Lofwall MR, Fraser H, Paterson B, Martinez S, Martinez DM, Nunes EV, Walsh SL, Comer SD. Addict Biol. 2020; 25(4): e12799.

Preclinical data indicate that selective kappa opioid receptor antagonists reduce nicotine self-administration and withdrawal symptoms. The aim of the current study was to determine whether treatment with CERC-501, an orally available, potent, and selective kappa opioid receptor antagonist, could alleviate nicotine withdrawal and craving and mitigate mood alterations associated with nicotine withdrawal in humans. Healthy, adult cigarette smokers were enrolled into this randomized, multisite, double-blind, placebo-controlled, crossover study. Participants

completed two 8-day treatment phases during which they received either CERC-501 (15 mg, p.o., once daily) or placebo. On the seventh day of each dosing phase, participants were admitted as inpatients for an 18-hour cigarette abstinence period followed by experimental testing. The primary outcome measures were (a) performance on the McKee Smoking Lapse test (i.e., latency to smoke in exchange for money) and (b) number of cigarettes self-administered during a 60-minute ad lib smoking period. Other outcomes included measures of craving, mood, anxiety, nicotine withdrawal, and subjective effects of cigarette smoking. A total of 71 participants who smoked an average of approximately 23 cigarettes per day were enrolled, and 56 subjects completed the study. CERC-501 was well tolerated, but it did not significantly alter the latency to start smoking (CERC-501: 16.5 min vs placebo: 17.7 min) or the number of cigarettes smoked (CERC-501: 3.3 cigarettes vs placebo: 3.1 cigarettes). Compared with placebo, CERC-501 also did not affect cigarette craving, mood, anxiety, nicotine withdrawal, or subjective effects of smoking. These findings do not support a role for CERC-501 in the treatment of nicotine use disorder.

[Low Hepatitis C Reinfection Following Direct-Acting Antiviral Therapy Among People Who Inject Drugs On Opioid Agonist Therapy](#) Akiyama MJ, Lipsey D, Heo M, Agyemang L, Norton BL, Hidalgo J, Lora K, Litwin AH. Clin Infect Dis. 2020; 70(12): 2695-2702.

Direct-acting antiviral (DAA) therapy is highly effective in people who inject drugs (PWID); however, rates, specific injection behaviors, and social determinants associated with hepatitis C virus (HCV) reinfection following DAA therapy among PWID on opioid agonist therapy (OAT) are poorly understood. PREVAIL was a randomized controlled trial that assessed models of HCV care for 150 PWID on OAT. Those who achieved sustained virologic response (SVR) (n = 141; 94%) were eligible for this extension study. Interviews and assessments of recurrent HCV viremia occurred at 6-month intervals for up to 24 months following PREVAIL. We used survival analysis to analyze variables associated with time to reinfection. Of 141 who achieved SVR, 114 had a least 1 visit in the extension study (62% male; mean age, 52 years). Injection drug use (IDU) was reported by 19% (n = 22) in the extension study. HCV reinfection was observed in 3 participants. Over 246 person-years of follow-up, the incidence of reinfection was 1.22/100 person-years (95% CI, 0.25-3.57). All reinfections occurred among participants reporting ongoing IDU. The incidence of reinfection in participants reporting ongoing IDU (41 person-years of follow-up) was 7.4/100 person-years (95% CI, 1.5-21.6). Reinfection was associated with reporting ongoing IDU in the follow-up period (P < .001), a lack confidence in the ability to avoid contracting HCV (P < .001), homelessness (P = .002), and living with a PWID (P = .007). HCV reinfection was low overall, but more common among people with ongoing IDU following DAA therapy on OAT, as well as those who were not confident in the ability to avoid contracting HCV, homeless, or living with a PWID. Interventions to mediate these risk factors following HCV therapy are warranted.

[The Contribution Of Syndemic Conditions To Cardiovascular Disease Risk](#) Rodriguez VJ, Chahine A, Parrish MS, Alcaide ML, Lee TK, Hurwitz B, Sawhney M, Weiss SM, Jones DL, Kumar M. AIDS Care. 2020; 1-9.

The syndemic conditions of low education, childhood maltreatment, depression, HIV, alcohol and cocaine use, and obesity have been established as independent risk factors for cardiovascular risk, but research examining the association between syndemic conditions and cardiovascular risk in high-risk populations is lacking. A total of N = 503 participants underwent an ultrasound

of the carotid artery to assess for atherosclerotic plaque. Participants, HIV-infected (n = 202) and HIV-uninfected (n = 301) with and without a history of cocaine use, were a mean age of 36.13 years (SD = 9.51); 50% were male, and 62% were African-American. Each syndemic condition was associated with 8% greater odds of atherosclerotic plaque (OR = 1.08), 9% greater odds of systolic blood pressure (OR = 1.09), and 10% greater odds of diastolic blood pressure (OR = 1.10). Multilevel research, interventions, and public policy initiatives are needed to activate stakeholders at each level to maximize their impact at a community level among populations with high rates of syndemic conditions.

HIV/AIDS RELATED RESEARCH

[HIV and Opiates Dysregulate K⁺-Cl⁻ Cotransporter 2 \(KCC2\) To Cause GABAergic Dysfunction In Primary Human Neurons And Tat-Transgenic Mice](#)

Barboura AJ, Hauser KF, McQuistona AR, Knappa PN. *Neurobiol Dis.* 2020; 141: 104878. Approximately half of people infected with HIV (PWH) exhibit HIV-associated neuropathology (neuroHIV), even when receiving combined antiretroviral therapy. Opiate use is widespread in PWH and exacerbates neuroHIV. While neurons themselves are not infected, they incur sublethal damage and GABAergic disruption is selectively vulnerable to viral and inflammatory factors released by infected/affected glia. Here, we demonstrate diminished K⁺-Cl⁻ cotransporter 2 (KCC2) levels in primary human neurons after exposure to HIV-1 or HIV-1 proteins Å morphine. Resulting disruption of GABAAR-mediated hyperpolarization/inhibition was shown using genetically- encoded voltage (Archon1) and calcium (GCaMP6f) indicators. The HIV proteins Tat (acting through NMDA receptors) and R5-gp120 (acting via CCR5) but not X4-tropic gp120 (acting via CXCR4), and morphine (acting through μ-opioid receptors) all induced KCC2 loss. We demonstrate that modifying KCC2 levels or function, or antagonizing NMDAR, CCR5 or MOR rescues KCC2 and GABAAR-mediated hyperpolarization/inhibition in HIV, Tat, or gp120 Å morphine-exposed neurons. Using an inducible, Tat-transgenic mouse neuroHIV model, we found that chronic exposure to Tat also reduces KCC2. Our results identify KCC2 as a novel therapeutic target for ameliorating the pathobiology of neuroHIV, including PWH exposed to opiates.

[Single Cell Transcriptomics Reveals Opioid Usage Evokes Widespread Suppression Of Antiviral Gene Program](#)

Karagiannis TT, Cleary Jr JP, Gok B, Henderson AJ, Martin NG, Yajima M, Nelson EC, Cheng CS. *Nature Communications.* 11: 2611-2621, May 26, 2020. Chronic opioid usage not only causes addiction behavior through the central nervous system, but also modulates the peripheral immune system. However, how opioid impacts the immune system is still barely characterized systematically. In order to understand the immune modulatory effect of opioids in an unbiased way, here we perform single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells from opioid-dependent individuals and controls to show that chronic opioid usage evokes widespread suppression of antiviral gene program in naive monocytes, as well as in multiple immune cell types upon stimulation with the pathogen component lipopolysaccharide. Furthermore, scRNA-seq reveals the same phenomenon after a short in vitro morphine treatment. These findings indicate that both acute and chronic opioid exposure may be harmful to our immune system by suppressing the antiviral gene program. Our

results suggest that further characterization of the immune modulatory effects of opioid is critical to ensure the safety of clinical opioids.

Modelling Integrated Antiretroviral Treatment And Harm Reduction Services On HIV And Overdose Among People Who Inject Drugs In Tijuana, Mexico

Cepeda JA, Bórquez A, Magana C, Vo A, Rafful C, Rangel G, Medina-Mora ME, Strathdee S, Martin NK. J Int AIDS Soc. 2020 June; 23(Suppl 1): e25493.

Introduction: The HIV epidemic in Tijuana, Mexico is concentrated in key populations, including people who inject drugs (PWID). However, HIV interventions among PWID are minimal, and federal funding was provided for compulsory abstinence programmes associated with HIV and overdose. Alternatively, opioid agonist therapy reduces overdose, reincarceration, HIV, while improving antiretroviral therapy (ART) outcomes. We assessed potential impact and synergies of scaled-up integrated ART and opioid agonist therapy, compared to scale-up of each separately, and potential harms of compulsory abstinence programmes on HIV and fatal overdose among PWID in Tijuana. Methods: We developed a dynamic model of HIV transmission and overdose among PWID in Tijuana. We simulated scale-up of opioid agonist therapy from zero to 40% coverage among PWID. We evaluated synergistic benefits of an integrated harm reduction and ART scale-up strategy (40% opioid agonist therapy coverage and 10-fold ART recruitment), compared to scale-up of each intervention alone or no scale-up of low coverage ART and no harm reduction). We additionally simulated compulsory abstinence programmes (associated with 14% higher risk of receptive syringe sharing and 76% higher odds of overdose) among PWID. Results: Without intervention, HIV incidence among PWID could increase from 0.72 per 100 person-years (PY) in 2020 to 0.92 per 100 PY in 2030. Over ten years, opioid agonist therapy scale-up could avert 31% (95% uncertainty interval (UI): 18%, 46%) and 22% (95% UI: 10%, 28%) new HIV infections and fatal overdoses, respectively, with the majority of HIV impact from the direct effect on HIV transmission due to low ART coverage. Integrating opioid agonist therapy and ART scale-up provided synergistic benefits, with opioid agonist therapy effects on ART recruitment/retention averting 9% more new infections compared to ART scale-up alone. The intervention strategy could avert 48% (95% UI: 26%, 68%) of new HIV infections and one-fifth of fatal overdoses over ten years. Conversely, compulsory abstinence programmes could increase HIV and overdoses. Conclusions: Integrating ART with opioid agonist therapy could provide synergistic benefits and prevent HIV and overdoses among PWID in Tijuana, whereas compulsory abstinence programmes could cause harm. Policymakers should consider the benefits of integrating harm reduction and HIV services for PWID.

Barriers and Facilitators to PrEP Use Among People Who Inject Drugs In Rural

Appalachia: A Qualitative Study Allen ST, O'Rourke A, White, Hamilton R, Smith KC, Weir B, Lucas GM, Sherman SG, Grieb SM. AIDS Behav. 2020 June; 24(6): 1942-1950.

The opioid crisis has increased risks for injection drug use-associated HIV outbreaks in rural communities throughout the United States. Existing research has examined pre-exposure prophylaxis (PrEP) utilization among people who inject drugs (PWID); however, no studies have been conducted to explore barriers and facilitators of PrEP use among rural PWID in Appalachia. We conducted qualitative interviews with PWID (n = 48) in two rural counties in West Virginia to explore barriers and facilitators of PrEP use. Among our participants, the majority (68.8%) had never heard of PrEP. Upon learning about PrEP, most participants

expressed willingness to use it. Rural PWID described several factors that may impede PrEP utilization (e.g., housing instability, forgetting to take PrEP). Participants also identified practical strategies to support sustained PrEP utilization, such as integrating PrEP services into venues PWID access. This research provides important insights into the barriers and facilitators of PrEP utilization among rural PWID.

Initiation Of Antiretroviral Therapy In The Hospital Is Associated With Linkage To HIV Care For Persons Living With HIV And Substance Use Jacobs P, Feaster DJ, Pan Y, Gooden L, Daar ES, Lucas G, Jain MK, Marsh E, Armstrong WS, Rodriguez A, Del Rio C, Metsch LR. Clin Infect Dis. 2020 Jun 22: ciaa838. Online ahead of print.

Background: Studies have demonstrated benefits of ART initiation on the day of HIV testing or at first clinical visit, regardless of CD4 count. The hospital setting is under-studied for immediate ART initiation. Methods: CTN0049, a linkage to care randomized clinical trial, enrolled 801 persons living with HIV (PLWH) and substance use disorder (SUD) from 11 hospitals across the U.S. This secondary analysis examined factors related to initiating (including re-initiating) ART in the hospital and its association with linkage to HIV care, frequency of outpatient care visits, retention in care and viral suppression. Results: Of 801 participants, 15% (124/801) initiated ART in the hospital, with more than two-thirds of these participants (65%;80/124) initiating ART for the first time. Time to first HIV care visit among those who initiated ART in the hospital and those who did not was 29 and 54 days, respectively, ($p=0.0145$). Hospital initiation of ART was associated with increased frequency of HIV outpatient care visits at 6-month (aOR=1.39, 95% CI [1.02, 1.88]) and 12-month follow-up assessments (aOR=1.53, 95% CI [1.15, 2.04]). There was no association with ART initiation in the hospital and retention in HIV care and viral suppression over a 12-month period. Participants recruited in Southern hospitals (compared to non-Southern hospitals) were less likely to initiate ART in the hospital ($p<0.001$). History of participation in substance use treatment was associated with greater likelihood of hospital ART initiation ($p=0.008$). Conclusions: Previous research demonstrated benefits of immediate ART initiation, yet this approach is not widely implemented, particularly in the hospital setting with PLWH and SUD. Findings suggest starting ART in the hospital is beneficial for increasing linkage to HIV care and frequency of visits for PLWH and SUD. Implementation research should address patient and provider barriers to early ART initiation in the hospital.

Perceived Risks And Amelioration Of Harm In Research Using Mobile Technology To Support Antiretroviral Therapy Adherence In The Context Of Methamphetamine Use: A Focus Group Study Among Minorities Living With HIV Pasipanodya EC, Kohli M, Fisher CB, Moore DJ, Curtis B. Harm Reduct J. 17(1): 1-11, 2020.

Methamphetamine use poses a barrier to antiretroviral therapy (ART) adherence. Black and Hispanic men who have sex with men living with HIV (PLWH) shoulder much of the health burden resulting from the methamphetamine and HIV syndemic. Smartphones are nearly ubiquitous in the USA and may be promising vehicles for delivering interventions for ART adherence and drug use cessation. However, the acceptability of using applications to collect sensitive information and deliver feedback in this population has not been adequately explored. This study examined minority PLWH's appraisals of the risks of participating in smartphone-based research to promote ART adherence in the context of methamphetamine use and explored their views on appropriate steps to mitigate perceived risks of participation. Three focus groups were conducted among Black and Hispanic PLWH who use methamphetamine. Of the 13

participants, 5 had previously participated in a smartphone-based observational study of ART adherence and substance use. Discussants provided feedback on smartphone-based research, including receiving probes for HIV medication adherence, mood, and substance use as well as feedback on passive location-tracking for personalized messages. Transcribed audio-recordings were thematically coded and analyzed using the qualitative software MAXQDA. Participants expressed confidentiality concerns related to potential unintentional disclosure of their HIV status and methamphetamine use and to possible legal consequences. They additionally expressed concerns around the invasiveness of daily assessments and the potential of methamphetamine use questions to trigger cravings. To mitigate these concerns, they suggested maintaining participant privacy by indirectly asking sensitive questions, focusing on positive behaviors (e.g., number of days sober), allowing user-initiated reporting of location to tailor messages, and ensuring adequate data protections. In addition to financial compensation, participants cited altruism (specifically, continuing a tradition of volunteerism in HIV research) as a motivator for potentially engaging in such research. Minority PLWH have concerns regarding the use of smartphones for ART adherence and methamphetamine sobriety intervention research. However, minority PLWH are likely to participate if studies include appropriate protections against risks to confidentiality and experimental harm and are designed to offer future benefit to themselves and other PLWH.

[Perceived Confidentiality Risks Of Mobile Technology-Based Ecologic Momentary Assessment To Assess High-Risk Behaviors Among Rural Men Who Have Sex With Men](#)

Hubach RD, O’Neil A, Stowe M, Giano Z, Curtis B, Fisher CB. Arch Sex Behav. 1-10 2020.

Although men who have sex with men (MSM) within rural communities are disproportionately impacted by HIV, limited HIV research and programmatic resources are directed to these communities within the U.S. There is a need for improved behavioral data collection methods to obtain more detailed information on the relationship between rural environments, sexual behavior, and substance use. Utilization of mobile health (mHealth) technologies, such as ecologic momentary assessment (EMA), has been advocated for; however, limited research has evaluated its utility among rural MSM. Forty MSM residing in rural Oklahoma were recruited to complete in-depth interviews related to participating online/mobile-based HIV prevention research. Men described a willingness to participate in HIV and substance use studies that use EMA methodologies for data collection; however, they raised various research-related concerns. In particular, participants indicated potential privacy and confidentiality concerns related to the use of the mobile technology-based EMA in public and the storage of data by researchers. Given the varying degree of sexual orientation and substance use disclosure by participants, rural MSM were largely concerned with being inadvertently “outed” within their communities. Men described the various strategies they could employ to protect private information and methods to minimize research risk. Study findings suggest that EMA is an acceptable research methodology for use among rural MSM in the context of HIV and sexual health information, when privacy and confidentiality concerns are adequately addressed. Input from community members and stakeholders is necessary to identify potential areas of concerns for participants prior to data collection.

CLINICAL TRIALS NETWORK RESEARCH

Barriers and Facilitators To Clinician Readiness To Provide Emergency Department-Initiated Buprenorphine

Hawk KF, D'Onofrio G, Chawarski MC, O'Connor PG, Cowan E, Lyons MS, Richardson L, Rothman RE, Whiteside LK, Owens PH, Martel SH, Coupet E Jr, Pantaloni M, Curry L, Fiellin DA, Edelman EJ. *JAMA Netw Open*. 2020 May 1; 3(5): e204561. Importance: Treatment of opioid use disorder (OUD) with buprenorphine decreases opioid use and prevents morbidity and mortality. Emergency departments (EDs) are an important setting for buprenorphine initiation for patients with untreated OUD; however, readiness varies among ED clinicians. Objective: To characterize barriers and facilitators of readiness to initiate buprenorphine for the treatment of OUD in the ED and identify opportunities to promote readiness across multiple clinician types. Design, setting, and participants: Using data collected from April 1, 2018, to January 11, 2019, this mixed-methods formative evaluation grounded in the Promoting Action on Research Implementation in Health Services framework included 4 geographically diverse academic EDs. Attending physicians (n = 113), residents (n = 107), and advanced practice clinicians (APCs) (n = 48) completed surveys electronically distributed to all ED clinicians (n = 396). A subset of participants (n = 74) also participated in 1 of 11 focus group discussions. Data were analyzed from June 1, 2018, to February 22, 2020. Main outcomes and measures: Clinician readiness to initiate buprenorphine and provide referral for ongoing treatment for patients with OUD treated in the ED was assessed using a visual analog scale. Responders (268 of 396 [67.7%]) were dichotomized as less ready (scores 0-6) or most ready (scores 7-10). An ED-adapted Organizational Readiness to Change Assessment (ORCA) and 11 focus groups were used to assess ratings and perspectives on evidence and context-related factors to promote ED-initiated buprenorphine with referral for ongoing treatment, respectively. Results: Among the 268 survey respondents (153 of 260 were men [58.8%], with a mean [SD] of 7.1 [9.8] years since completing formal training), 56 (20.9%) indicated readiness to initiate buprenorphine for ED patients with OUD. Nine of 258 (3.5%) reported Drug Addiction Treatment Act of 2000 training completion. Compared with those who were less ready, clinicians who were most ready to initiate buprenorphine had higher mean scores across all ORCA Evidence subscales (3.50 [95% CI, 3.35-3.65] to 4.33 [95% CI, 4.13-4.53] vs 3.11 [95% CI, 3.03-3.20] to 3.60 [95% CI, 3.49-3.70]; $P < .001$) and on the Slack Resources of the ORCA Context subscales (3.32 [95% CI, 3.08-3.55] vs 3.0 [95% CI, 2.87-3.12]; $P = .02$). Barriers to ED-initiated buprenorphine included lack of training and experience in treating OUD with buprenorphine, concerns about ability to link to ongoing care, and competing needs and priorities for ED time and resources. Facilitators to ED-initiated buprenorphine included receiving education and training, development of local departmental protocols, and receiving feedback on patient experiences and gaps in quality of care. Conclusions and relevance: Only a few ED clinicians had a high level of readiness to initiate buprenorphine; however, many expressed a willingness to learn with sufficient supports. Efforts to promote adoption of ED-initiated buprenorphine will require clinician and system-level changes.

Substance Use And Mental Health In Emerging Adult vs Older Adult Men And Women With Opioid Use Disorder

Barbosa-Leiker C, Campbell ANC, Pavlicova M, Scodes J, Burlew AK, Hatch-Maillette MA, Mennenga SE, Mitchell SG, Novo P, Nunes EV, Rotrosen J, Greenfield SF. *Am J Addict*. 2020;10.1111/ajad.13059. [published online ahead of print, 2020 May 21].

Background and objectives: We examined age differences across genders in clinical characteristics in emerging adult (≤ 25 years) vs older adult patients (26+ years) with opioid use disorder (OUD). Methods: Participants (N = 570; 30% female) entering a comparative effectiveness medication trial of buprenorphine vs extended-release naltrexone. Results: Differences in clinical characteristics in emerging adult vs older participants were similar across genders. However, women 26+ years reported more mental health problems compared with women ≤ 25 , while men ≤ 25 years reported more mental health problems compared with men 26+ years. Discussion and conclusion: Different strategies for emerging adult and older patients seeking OUD treatment may be necessary to address psychiatric comorbidities that differ across genders in this population. Scientific significance: Comprehensive psychiatric assessment should be systematically included in OUD treatment for all genders. Treatment should focus on the emerging adult developmental phase when appropriate, with psychiatric treatment tailored for women and men, separately, across the lifespan.

Extended-Release Naltrexone Versus Buprenorphine-Naloxone To Treat Opioid Use

Disorder Among Black Adults Haeny AM, Montgomery L, Burlew AK, Campbell ANC, Scodes J, Pavlicova M, Rotrosen J, Nunes EV. *Addict Behav.* 2020 Nov; 110: 106514. Epub 2020 Jun 18.

Few studies examine the effectiveness of treatments for opioid use disorder (OUD) among Black individuals despite recent evidence suggesting opioid overdose death rates are, in some cases, highest and increasing at a faster rate among Black people compared to other racial/ethnic groups. This secondary analysis study investigated treatment preference, retention, and relapse rates amongst a subgroup of 73 Black participants with OUD (81% male, mean age 39.05, SD = 11.80) participating in a 24-week multisite randomized clinical trial ("X:BOT") comparing the effectiveness of extended-release naltrexone (XR-NTX) and sublingual buprenorphine-naloxone (BUP-NX) between 2014 and 2017. Chi-square analyses were used to investigate treatment preference assessed at baseline, and logistic regression analyses were used to investigate differences in the odds of retention and relapse assessed over the 24-week course of treatment between treatment groups. Our findings suggest no differences in preference for XR-NTX versus BUP-NX. However, similar to the parent trial, there was an induction hurdle such that only 59.5% of those randomized to XR-NTX successfully initiated medication compared to 91.6% of those randomized to BUP-NX (OR = 0.13, 95% CI = 0.04, 0.52). No significant differences were found in treatment retention (intention-to-treat: OR = 1.19, 95% CI = 0.43, 3.28; per-protocol [i.e., those who initiated medication]: OR = 0.60, 95% CI = 0.20, 1.82) or relapse rates between treatment groups (intention-to-treat: OR = 1.53, 95% CI = 0.57, 4.13; per-protocol: OR = 0.69, 95% CI = 0.23, 2.06). Although there is a significant initiation hurdle with XR-NTX, once inducted, both medications appear similar in effectiveness, but as in the main study, dropout rates were high. Future research is needed on how to improve adherence.

Problem Opioid Use And HIV Primary Care Engagement Among Hospitalized People

Who Use Drugs And/Or Alcohol Critchley L, Carrico A, Gukasyan N, Jacobs P, Mandler RN, Rodriguez AE, Del Rio C, Metsch LR, Feaster DJ. *Addict Sci Clin Pract.* 2020 Jun 19;15(1): 19. Background: There is growing public health concern around the potential impact of the opioid crisis on efforts to eradicate HIV. This secondary analysis seeks to determine if those who report opioids as their primary problem drug compared to those who report other drugs and/or alcohol differ in engagement in HIV primary care among a sample of hospitalized people with HIV

(PWH) who use drugs and/or alcohol, a traditionally marginalized and difficult to engage population key to ending the HIV epidemic. Setting and participants: A total of 801 participants (67% male; 75% Black, non-Hispanic; mean age 44.2) with uncontrolled HIV and reported drug and/or alcohol use were recruited from 11 hospitals around the U.S. in cities with high HIV prevalence from 2012 to 2014 for a multisite clinical trial to improve HIV viral suppression. Methods: A generalized linear model compared those who reported opioids as their primary problem drug to those who reported other problem drugs and/or alcohol on their previous engagement in HIV primary care, controlling for age, sex, race, education, income, any previous drug and/or alcohol treatment, length of time since diagnosis, and study site. Results: A total of 95 (11.9%) participants reported opioids as their primary problem drug. In adjusted models, those who reported opioids were significantly less likely to have ever engaged in HIV primary care than those who reported no problem drug use (adjusted risk ratio, ARR = 0.84, 95% Confidence Interval, CI 0.73, 0.98), stimulants (ARR = 0.84, 95% CI 0.74, 0.95), and polydrug use but no alcohol (ARR = 0.79, 95% CI 0.68, 0.93). While not statistically significant, the trend in the estimates of the remaining drug and/or alcohol categories (alcohol, cannabis, polydrug use with alcohol, and [but excluding the estimate for] other), point to a similar phenomena—those who identify opioids as their primary problem drug are engaging in HIV primary care less. Conclusions: These findings suggest that for hospitalized PWH who use drugs and/or alcohol, tailored and expanded efforts are especially needed to link those who report problem opioid use to HIV primary care.

[The Association Between Regular Cocaine Use, With And Without Tobacco Co-Use, And Adverse Cardiovascular And Respiratory Outcomes](#)

Winhusen T, Theobald J, Kaelber DC, Lewis D. Drug Alcohol Depend. 2020 Jun 27; 214: 108136. Online ahead of print.

Background: Understanding the potential impact of cocaine use on health is increasingly important as cocaine use rises in the U.S. Objectives: This study evaluated the associations of regular cocaine use, with and without tobacco co-use, with cardiovascular and respiratory outcomes. Methods: Analysis of a limited dataset obtained through IBM Watson Health Explorys, a platform integrating electronic health record data. Matched controls were defined for: 1) cocaine-using patients (n = 8244; 44 % female); and subgroups of cocaine-using patients: 2) with an encounter diagnosis for tobacco use disorder (TUD; n = 4706); and 3) without a TUD diagnosis (non-TUD; n = 3538). Patients had at least one documented medical evaluation in the MetroHealth System (Cleveland, Ohio). Cocaine-using patients had an encounter diagnosis of cocaine abuse/dependence and/or ≥ 2 cocaine-positive drug screens. Control patients, with no documented cocaine-use, were matched to the cocaine-using patients on demographics, residential zip code median income, body mass index, and, for the total sample, TUD-status. Outcomes were encounter diagnosis (yes/no) of cerebrovascular accident, heart arrhythmia, myocardial infarction, subarachnoid hemorrhage, asthma, chronic obstructive pulmonary disease (COPD), pneumonia, and all-cause mortality. Results: TUD-patients had the greatest prevalence of cardiovascular and respiratory disease, regardless of cocaine-use indication. In the total sample, TUD, and non-TUD subgroups, regular cocaine use was significantly associated with greater risk for cerebrovascular accident, arrhythmia, myocardial infarction, asthma, COPD, pneumonia and mortality. Conclusions: Cocaine use is associated with significantly greater risk of adverse cardiovascular and respiratory diagnoses and all-cause mortality.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

Neighborhood Deprivation Shapes Motivational-Neurocircuit Recruitment In Children

Mullins TS, Campbell EM, Hogeveen J. Psychol Sci 2020 July; 31(7): 881-889.

Implementing motivated behaviors on the basis of prior reward is central to adaptive human functioning, but aberrant reward-motivated behavior is a core feature of neuropsychiatric illness. Children from disadvantaged neighborhoods have decreased access to rewards, which may shape motivational neurocircuits and risk for psychopathology. Here, we leveraged the unprecedented neuroimaging data from the Adolescent Brain Cognitive Development (ABCD) study to test the hypothesis that neighborhood socioeconomic disadvantage shapes the functional recruitment of motivational neurocircuits in children. Specifically, via the ABCD study's monetary-incentive-delay task (N = 6,396 children; age: 9-10 years), we found that children from zip codes with a high Area Deprivation Index demonstrate blunted recruitment of striatum (dorsal and ventral nuclei) and pallidum during reward anticipation. In fact, blunted dorsal striatal recruitment during reward anticipation mediated the association between Area Deprivation Index and increased attention problems. These data reveal a candidate mechanism driving elevated risk for psychopathology in children from socioeconomically disadvantaged neighborhoods.

Adverse Childhood Experiences And Psychotic-Like Experiences Are Associated Above And Beyond Shared Correlates: Findings From The Adolescent Brain Cognitive Development Study Karcher NR, Niendam TA, Barch DM. Schizophrenia Res. 2020 Jun 8; S0920-9964(20): 30299-1.

Adverse childhood experiences (ACEs) are associated with increased risk for psychotic-like experiences (PLEs). However, ACEs and PLEs are also both associated with several shared factors (e.g., internalizing symptoms, suicidality). Few studies have explicitly examined whether the association between ACEs and PLEs remains over and above shared correlates. To address this question, using 10,800 9-11-year-olds, we examined whether ACEs and school-aged PLEs were associated when accounting for shared correlates, and whether there was evidence of mediation in associations between PLEs, ACEs, and these shared factors. Greater number of ACEs were associated with greater PLEs, including several specific ACEs (e.g., bullying). Importantly, ACEs and PLEs were related even when accounting for shared correlates. Further, PLEs partially mediated the relationships between ACEs and both internalizing symptoms and suicidality, including suicidal behavior. The current study helps clarify the nature of the associations between PLEs and ACE and has important clinical implications for addressing PLEs.

Parental And Social Factors In Relation To Child Psychopathology, Behavior, And Cognitive Function Zhang H, Lee ZX, White T, Qiu A. Transl Psych. 2020 Feb 26; 10(1): 80.

Parental and social factors have long-term impact on the neurodevelopment of offspring, but tend to highly covary with each other. Thus, it is difficult to parse out which parental and social factor contributes most to neurodevelopmental outcomes. This study aimed to assess clusters of parental and social factors associated with child psychopathology, behavioral problems, and cognition. This study employed the data of 11,875 children (9 to 11 years) from the Adolescent Brain Cognitive Development (ABCD) study. Principal component analysis (PCA) was performed on 39 environmental measures and 30 child behavior and cognitive measures separately to identify clusters of parental and social factors and clusters of child

psychopathology, behaviour, and cognition. Regression analysis was used to examine independent effects of each cluster of parental and social factors on child psychopathology, behavioral problems, and cognition. Greater Parent Psychopathology cluster was associated with greater Child Psychopathology cluster. Moreover, greater Socioeconomic Status cluster was associated with greater child General Cognition and Executive Function but less Behavioral Inhibition clusters. Greater Proximal Social Environment and Interaction cluster were associated with less child Impulsive Behavior and Behavioral Inhibition, but greater Behavioral Activation cluster. The environmental clusters related to birth outcomes, maternal tobacco, and drug use were not significantly related to child psychopathology, behavior, and cognition. Our findings suggest that socioeconomic status, parental psychopathology, and social environment and interactions are the strongest risks for behavioral problems and cognitive performance in a general child population. Intervention programs should target modifiable factors within these domains.

INTRAMURAL RESEARCH

[Converging Structural And Functional Evidence For A Rat Salience Network](#) Tsai P-J, Keeley RJ, Carmack SA, Vendruscolo JCM, Lu H, Gu H, Vendruscolo LF, Koob GF, Lin C-P, Stein EA, Yang Y. *Biological Psychiatry*. July 2, 2020. (In press).

We used modularity analysis on resting-state functional MRI data of rats (n=32) to parcellate rat insula into functional subdivisions and to identify a potential rat SN based on functional connectivity patterns from the insular subdivisions. We then used mouse tract tracing data from the Allen brain atlas to confirm the network's underlying structural connectivity. We next compared functional connectivity profiles of the SN across rat, marmoset (n=10) and humans (n=30). Finally, we assessed rat SN's response to conditioned cues in rats (n=21) with a history of heroin self-administration. We identified a putative rat SN, which consists of primarily the ventral anterior insula and anterior cingulate cortex, based on functional connectivity patterns from the ventral anterior insular division. Functional connectivity architecture of the rat SN is supported by the mouse neuronal tracer data. Moreover, the anatomical profile of the identified rat SN is similar to that of non-human primates and humans. Finally, we demonstrate that the rat SN responds to conditioned cues and increases functional connectivity to the Default Mode Network during conditioned heroin withdrawal. The neurobiological identification of a rat SN together with a demonstration of its functional relevance provides a novel platform with which to interrogate its functional significance in normative and neuropsychiatric disease models.

[VTA Glutamatergic Neurons Mediate Innate Defensive Behaviors](#) Barbano MF, Wang H-L, Zhang S, Miranda-Barrientos J, Estrin DJ, Figueroa-González A, Liu B, Barker DJ, Morales M. *Neuron*. 2020 Jul 22;107(2):368-382.e8.

The ventral tegmental area (VTA) has dopamine, GABA, and glutamate neurons, which have been implicated in reward and aversion. Here, we determined whether VTA-glutamate or -GABA neurons play a role in innate defensive behavior. By VTA cell-type-specific genetic ablation, we found that ablation of glutamate, but not GABA, neurons abolishes escape behavior in response to threatening stimuli. We found that escape behavior is also decreased by chemogenetic inhibition of VTA-glutamate neurons and detected increases in activity in VTA-glutamate neurons in response to the threatening stimuli. By ultrastructural and electrophysiological analysis, we established that VTA-glutamate neurons receive a major

monosynaptic glutamatergic input from the lateral hypothalamic area (LHA) and found that photoinhibition of this input decreases escape responses to threatening stimuli. These findings indicate that VTA-glutamate neurons are activated by and required for innate defensive responses and that information on threatening stimuli to VTA-glutamate neurons is relayed by LHA-glutamate neurons.

Labeled Oxytocin Administered Via The Intranasal Route Reaches The Brain In Rhesus

Macaques Lee MR, Shnitko TA, Blue SW, Kaucher AV, Winchell AJ, Erikson DW, Grant KA, Leggio L. Nat Commun. 11: 2783. 2020.

Oxytocin may have promise as a treatment for neuropsychiatric disorders. Its therapeutic effect may depend on its ability to enter the brain and bind to the oxytocin receptor. To date, the brain tissue penetrance of intranasal oxytocin has not been demonstrated. In this nonhuman primate study, we administer deuterated oxytocin intranasally and intravenously to rhesus macaques and measure, with mass spectrometry, concentrations of labeled (exogenously administered) and endogenous oxytocin in 12 brain regions two hours after oxytocin administration. Labeled oxytocin is quantified after intranasal (not intravenous) administration in brain regions (orbitofrontal cortex, striatum, brainstem, and thalamus) that lie in the trajectories of the olfactory and trigeminal nerves. These results suggest that intranasal administration bypasses the blood–brain barrier, delivering oxytocin to specific brain regions, such as the striatum, where oxytocin acts to impact motivated behaviors. Further, high concentrations of endogenous oxytocin are in regions that overlap with projection fields of oxytocinergic neurons.

Fentanyl Vapor Self-Administration Model In Mice To Study Opioid Addiction

Moussawi K, Ortiz MM, Gantz SC, Tunstall BJ, Marchette RCN, Bonci A, Koob GF, Vendruscolo LF. Sci Adv. 2020.

Intravenous drug self-administration is considered the “gold standard” model to investigate the neurobiology of drug addiction in rodents. However, its use in mice is limited by frequent complications of intravenous catheterization. Given the many advantages of using mice in biomedical research, we developed a noninvasive mouse model of opioid self-administration using vaporized fentanyl. Mice readily self-administered fentanyl vapor, titrated their drug intake, and exhibited addiction-like behaviors, including escalation of drug intake, somatic signs of withdrawal, drug intake despite punishment, and reinstatement of drug seeking.

Electrophysiological recordings from ventral tegmental area dopamine neurons showed a lower amplitude of GABAB receptor–dependent currents during protracted abstinence from fentanyl vapor self-administration. This mouse model of fentanyl self-administration recapitulates key features of opioid addiction, overcomes limitations of the intravenous model, and allows the investigation of the neurobiology of opioid addiction in unprecedented ways.

Modafinil Potentiates Cocaine Self-Administration By A Dopamine-Independent

Mechanism: Possible Involvement Of Gap Junctions Mereu M, Hiranita T, Jordan CJ, Chun LE, Lopez JP, Coggiano MA, Quarterman JC, Bi G-H, Keighron JD, Xi Z-X, Newman AH, Katz JL, Tanda G. Neuropsychopharmacology. 45: 1518-1526 2020.

Modafinil and methylphenidate are medications that inhibit the neuronal reuptake of dopamine, a mechanism shared with cocaine. Their use as “smart drugs” by healthy subjects poses health concerns and requires investigation. We show that methylphenidate, but not modafinil, maintained intravenous self-administration in Sprague-Dawley rats similar to cocaine. Both

modafinil and methylphenidate pretreatments potentiated cocaine self-administration. Cocaine, at self-administered doses, stimulated mesolimbic dopamine levels. This effect was potentiated by methylphenidate, but not by modafinil pretreatments, indicating dopamine-dependent actions for methylphenidate, but not modafinil. Modafinil is known to facilitate electrotonic neuronal coupling by actions on gap junctions. Carbenoxolone, a gap junction inhibitor, antagonized modafinil, but not methylphenidate potentiation of cocaine self-administration. Our results indicate that modafinil shares mechanisms with cocaine and methylphenidate but has a unique pharmacological profile that includes facilitation of electrotonic coupling and lower abuse liability, which may be exploited in future therapeutic drug design for cocaine use disorder.

[The Mechanism Of A High-Affinity Allosteric Inhibitor Of The Serotonin Transporter](#)

Plenge P, Abramyan AM, Sørensen G, Mørk A, Weikop P, Gether U, Bang-Andersen B, Shi L, Loland CJ. Nat Commun. 11, 2020.

The serotonin transporter (SERT) terminates serotonin signaling by rapid presynaptic reuptake. SERT activity is modulated by antidepressants, e.g., S-citalopram and imipramine, to alleviate symptoms of depression and anxiety. SERT crystal structures reveal two S-citalopram binding pockets in the central binding (S1) site and the extracellular vestibule (S2 site). In this study, our combined in vitro and in silico analysis indicates that the bound S-citalopram or imipramine in S1 is allosterically coupled to the ligand binding to S2 through altering protein conformations. Remarkably, SERT inhibitor Lu AF60097, the first high-affinity S2-ligand reported and characterized here, allosterically couples the ligand binding to S1 through a similar mechanism. The SERT inhibition by Lu AF60097 is demonstrated by the potentiated imipramine binding and increased hippocampal serotonin level in rats. Together, we reveal a S1-S2 coupling mechanism that will facilitate rational design of high-affinity SERT allosteric inhibitors.

GRANTEE HONORS AND AWARDS

Kevin Beier, Ph.D., Assistant Professor, University of California Irvine, was an honorable mention for the 2020 Freedman prize.

Matthew Gurka, Ph.D., University of Florida, was elected fellow of the American Statistical Association (ASA) in April 2020.

Allyson Mackey, Ph.D., University of Pennsylvania, has been selected as a CIFAR Azrieli Global Scholar in Child and Brain Development.

Charles Nelson, Ph.D., Harvard Medical School, was elected to The British Academy in July 2020.

Marina Picciotto, Ph.D., Professor, Yale University, was awarded the 2021 Langley Award that honors scientists who have made groundbreaking advances in nicotine research in the areas of pharmacology, neuroscience, and/or genetics.

Daniel Shaw, Ph.D., University of Pittsburgh, was accepted into the 2020 cohort of Society for Prevention Research Fellows. The SPR Fellowship is awarded to a small and select group of members who have a particularly distinguished record of contributions in the field of prevention research that has had a broad and significant impact on prevention science.

Cody Siciliano, Ph.D., Assistant Professor, Vanderbilt University, was awarded the 2020 Freedman Prize for exceptional basic science studies.

Elizabeth Stormshak, Ph.D., University of Oregon, received the 2020 Society for Prevention Research Translational Science Award in recognition of her contributions to the field of prevention science in the area of Type 2 translational research.

Gustavo Turecki, M.D., Ph.D., McGill University, was a co-awardee of the Colvin Prize for Outstanding Achievement in Mood Disorders Research, given by the Brain & Behavior Research Foundation.

Clinical Trials Network (CTN) Pacific Northwest Node

Evergreen Treatment Services (ETS) in Seattle is one of the Pacific Northwest Node's longest and staunchest community-based treatment program partners. Given that Seattle experienced the first COVID-19 outbreak in the nation, ETS drafted, sought, and implemented exceptions to opioid use disorder treatment regulations that ultimately led to SAMHSA's current guidelines. An interdisciplinary team of researchers and clinicians at ETS published a brief paper on this topic in *AIDS and Behavior* ([available here](#)). The lead author, Michelle Peavy, got her start as a Clinical Trials Network (CTN) Research Coordinator at ETS in the early years of the Pacific Northwest Node. She went on to earn her Ph.D. in Clinical Psychology, did her postdoctoral training at Veterans Affairs Puget Sound Health Care System, returned to the Node as a CTN Research Fellow, and then went back to ETS as their Research and Training Manager.

Clinical Trials Network (CTN) Western States Node

Western States Node investigators received three Health Resources and Services Administration ([HRSA](#)) [Addiction Medicine Fellowship Awards](#) to expand training of physicians from diverse medical specialties in addiction medicine. Newly-funded fellowships at [University of California, San Francisco](#) (Program Director Paula Lum), [Stanford University](#) (Program Director Anna Lembke), and [Oregon Health & Science University](#) (Program Director Todd Korthis) offer a one-year comprehensive curriculum in clinical addiction medicine. Graduates integrate addiction medicine skills throughout the health care system, and some pursue additional research training following their clinical fellowship. This is the first federal funding for addiction medicine physician workforce expansion.

STAFF HONORS AND AWARDS

Will Aklin, Ph.D., Division of Therapeutics and Medical Consequences, is the recipient of the prestigious 2020 College on Problems of Drug Dependence J. Michael Morrison Award for leading advancements in behavioral therapies for the treatment of substance use disorders.

Cole Calva, Ph.D., of the Neurocircuitry of Motivation Section of the New Drug Application's Intramural Research Program, received a fellowship from the Center on Compulsive Behaviors.

Ron Dobbins, M.B.A., P.M.P., Center for the Clinical Trials Network, has been selected to receive the 2020 NIH Director's Award for "exceptional leadership and management in facilitating the NIDA Clinical Trials Network's participation in the NIH Helping to End Addiction Long-term (HEAL) Initiative."

Ewa Galaj, Ph.D., a postdoc Intramural Research Training Award recipient in the Xi/Newman Lab of NIDA's Intramural Research Program, received the NIH Center on Compulsive Behaviors Fellowship and a travel fellowship to the 2020 and 2021 American College of Neuropsychopharmacology meetings.

Brenton Laing, Ph.D., a postdoc Intramural Research Training Award recipient in the Aponte Lab of NIDA's Intramural Research Program, received several awards, including the East Carolina University Mathematics, Physical Sciences, and Engineering Doctoral Dissertation Award; the NIH Center on Compulsive Behaviors Fellowship; and the NIH Fellows Award for Research Excellence.

Ivan Montoya, M.D., M.P.H., Division of Therapeutics and Medical Consequences, was invited to give the 11th Annual Johns Hopkins Bayview Summer Scholars Levi Watkins Jr., M.D., Lectureship. Ivan was the first Black chief resident and full professor at Johns Hopkins. He worked tirelessly to advocate for fairness and diversity.

Sarah Sarsfield, M.S., of the Aponte Lab of NIDA's Intramural Research Program, received the Kelly Government Distinguished Achievement Award.

Justin Siemian, Ph.D., a postdoctoral Intramural Research Training Award recipient in the Aponte Lab of NIDA's Intramural Research Program, received the NIH Center on Compulsive Behaviors Fellowship.

Jack Stein, M.S.W, Ph.D., NIDA Chief of Staff and Office of Science Policy and Communications Director received the National Association of State Alcohol and Drug Abuse Directors Harwood/Anderson Service Award in recognition of distinguished service in the field of addiction research, training, and evaluation.

STAFF CHANGES

New Appointments

In May 2020, **Liza Zeinert, M.A.**, joined the Center for the Clinical Trials Network (CCTN) at NIDA as a Clinical Trials Program Specialist. In this role, Liza will serve as a scientific resource to the study investigators and Center staff and will assist in the administration and coordination of the Clinical Trial Network research portfolio. Prior to joining CCTN, Liza was with NIDA's Division of Therapeutics and Medical Consequences, supporting the clinical trials program, managing Interagency Agreements and contracts, and managing the Clinical Trials Portfolio System.

New Staff

Kevin Alvarez joined NIDA's Office of Management, Office of Acquisitions as a Contract Specialist on May 24, 2020. Kevin comes to NIDA from the National Heart, Lung, and Blood Institute.

Subramaniam (Sam) Ananthan, Ph.D., has joined the Division of Neuroscience and Behavior as the new Chief of the Chemistry, Pharmacology, Physiology Branch. Sam is a medicinal chemist with more than 30 years of experience in the discovery and development of new therapeutics for the treatment of pain, addiction, and other central nervous system disorders. Following his postdoctoral research with Professor Donald T. Witiak at The Ohio State University, he joined Southern Research Institute in 1987 and held various positions from a research chemist to a Fellow. He also served as an Adjunct Professor of chemistry at the University of Alabama at Birmingham. He has been a Principal Investigator on multiple grants and contracts and a recipient of continuous funding from NIDA for more than 25 years. His NIDA-funded research has focused on the development of opioids possessing mixed functional activity, D3 receptor antagonists for treatment of substance use disorders, and allosteric regulators of the dopamine transporter for treatment of substance use disorders. He has published over 85 peer-reviewed papers in the areas of medicinal chemistry and structure-based drug design. He is an inventor on 21 U.S. patents and has been inducted as a Fellow of National Academy of Inventors. He has been an active member of the American Chemical Society and has served as a Long-Range Planning Committee member in the Division of Medicinal Chemistry.

Miguel Arenivar, who holds a postbaccalaureate Intramural Research Training Award in the Aponte Lab's Intramural Research Program, began a Ph.D. program in the NIH-Brown Graduate Partnership Program.

Tamika Cloyd joined NIDA's Office of Management's Office of the Director on August 2, 2020, as a Program Specialist. Tamika comes to NIDA from a position with the National Institute of Allergy and Infectious Diseases.

Christopher Conrad, Ph.D., joined NIDA's Office of Translational Initiatives & Program Innovations on June 21, 2020, as a Health Scientist Administrator. Christopher's areas of responsibility include Translational Initiatives in Drug Discovery; Small Business Innovation Research/Small Business Technology Transfer Programs; and New Drugs and Biologics. Christopher comes to NIDA from a position in the private sector.

Llakim Dubroff joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on August 16, 2020. Llakim comes to NIDA from a position with the U.S. Consumer Protection Agency.

Lydia Erbaugh began a postbaccalaureate Intramural Research Training Award position with the Aponte Lab of NIDA's Intramural Research Program in June 2020.

John Fedota, Ph.D., joined the Division of Neuroscience and Behavior as a Program Officer in the Behavioral Cognitive Neuroscience Branch. John holds a B.A. in Biology from Oberlin College; he earned an M.A. in Human Factors and Applied Cognition and a Ph.D. in Psychology from George Mason University. John completed postdocs at the Center for Excellence in Neuroergonomics and Technology at George Mason University with Raja Parasuraman and James Thompson, followed by an Intramural Research Training Award fellowship at the National Institute of Drug Abuse with Elliot Stein. John then served as a Staff Scientist in the Neuroimaging Research Branch at NIDA, where his work focused on the development of neuroimaging biomarkers for smoking cessation treatment. In each position, his research focused on the intersection of attention, cognitive control, and substance use disorders and employed a variety of methodologies including fMRI, EEG, and TMS. At DNB, John will oversee a portfolio on neuroimaging and neurostimulation of circuitry relevant to substance use disorders.

Lindsey Friend, Ph.D., joined NIDA as a Health Science Administrator in the Office of Research Training, Diversity, and Health Disparities in July 2020. Her priority is to assist NIDA's extramural research training and career development programs. Lindsey received her doctorate in neuroscience from Brigham Young University, where she studied cocaine and cannabinoid effects on reward circuitry. She did a postdoctoral fellowship at the National Institute of Child Health and Human Development studying glutamate receptor physiology before joining NIDA.

Beth Han, M.D., Ph.D., M.P.H., joined the Office of Science Policy and Communications (OSPC) as an Epidemiologist in the Science Policy Branch. Prior to coming to NIDA, Beth worked at the Substance Abuse and Mental Health Services Administration, where she conducted research on addiction, substance use treatments, suicide prevention, mental illnesses, mental health care, and co-occurring disorders and related treatments. She is the recipient of the American Public Health Association's 2003 James G. Zimmer New Investigator Research Award. Beth has been elected a Fellow of the Gerontological Society of America and served as an editorial board member of *The Gerontologist*. She has authored or co-authored over 80 peer-reviewed journal articles and about 50 government reports and book chapters. Her articles have been published in journals including the *Journal of the American Medical Association (JAMA)*; *the Annals of Internal Medicine*; *Lancet Psychiatry*; *the American Journal of Psychiatry*; and many other journals, books, and government reports. Beth's research findings have been reported

by numerous Media outlets including NBC Nightly News, ABC, CBS, CNN, *The Washington Post*, and *The New York Times*, informing clinicians, policy makers, and the public about behavioral health issues, treatment gaps, and related clinical and policy implications.

Evan Herrmann, Ph.D., joined the Division of Therapeutics and Medical Consequences as a Health Scientist Administrator. Evan is a behavioral pharmacologist with advanced training in experimental therapeutics research on substance use disorders, including laboratory human drug administration and clinical outpatient studies testing pharmacological and behavioral treatments. At NIDA, Evan will serve as a Program Officer for nicotine and tobacco-related clinical research studies. He completed his Ph.D. at the University of Vermont and postdoctoral training at Johns Hopkins and Columbia Universities.

Angela Holmes, Ph.D., joined the NIDA Office of Diversity and Health Disparities in July 2020 as a Health Scientist Administrator (Program Officer). She currently manages and oversees the NIDA Diversity Supplement Program. Before joining extramural research, Angela did her postdoctoral fellowship in Movement Disorders with a focus on cervical dystonia in the National Institute of Neurological Disorders and Stroke (NINDS), completed a detail as a Health Program Specialist in the NINDS Division of Translational Research, and had government contract positions at the Walter Reed National Military Medical Center and the Defense Centers for Psychological Health and Traumatic Brain Injury. She also had the opportunity to do an internship in the American Psychological Association's Office of Ethnic Minority Affairs, where the goals were focused on increasing the recruitment, retention, and training of underrepresented groups in psychology. She earned her Ph.D. in Neuroscience from Georgetown University with support from a diversity National Research Service Award predoctoral fellowship and received postdoctoral training at NIH in the NINDS Human Motor Control Section with diversity supplement support. She earned a B.S. in Psychology and an M.S. in Clinical Psychology from the University of the District of Columbia.

Jagdeep Kathuria joined NIDA's Office of Management's Information & Resource Management Branch as an IT Specialist on July 19, 2020. Jagdeep comes to NIDA from a position with the Defense Logistics Agency.

S. Janet Kuramoto-Crawford, Ph.D., M.H.S., joined the Division of Epidemiology, Services, and Prevention Research as a Social Behavioral Scientist Administrator in the Epidemiology Research Branch on June 7, 2020. Janet will primarily support the Population Assessment of Tobacco and Health Study and will oversee a research portfolio on topics relating to epidemiology of substance use. Prior to joining NIDA, Janet served as a health statistician within the Division of Transplantation at the Health Resources and Services Administration. From 2015 to 2017, she served as an Epidemic Intelligence Service Officer with the Centers for Disease Control assigned to the District of Columbia Department of Health and was involved in opioid overdose response. Janet also worked at the Center for Behavioral Health Statistics and Quality within the Substance Abuse and Mental Health Services Administration, and at the American Psychiatric Association as part of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 multisite field trials team. Her Ph.D. training was funded by an individual National Research Service Award from NIDA to examine social network and suicide risk among individuals who use heroin or cocaine. Janet received her B.A. in Public Health Studies from the

Johns Hopkins University, and her Ph.D. in Public Health from the Department of Mental Health and concurrently her M.H.S. in Biostatistics from the Johns Hopkins Bloomberg School of Public Health.

Judy Lavelle, M.S., joined the Communications Branch of the Office of Science Policy and Communications as a Technical Writer/Editor in the in June of 2020. Judy oversees the NIDA content management team—responsible for many of NIDA’s publications and webpages—and is a member of the NIDA press team. She is passionate about providing science-driven, non-stigmatizing information on substance use disorders and substance use research to those who need it most. Prior to coming to NIDA, Judy served as a science writer for the National Institute of Allergy and Infectious Diseases, where she created content on COVID-19, HIV, allergy, immunology, and transplantation research and supported media relations. Judy received a Master of Science degree in Science Journalism from Boston University. Her science writing and multimedia work have appeared in the *Boston Globe*, *Chemical & Engineering News*, *Scientific American Online*, National Public Radio, and on the walls of Philadelphia's Mütter Museum.

Sara Lioi, Ph.D., joined the NIDA Office of the Director’s Office of Translational Initiatives & Program Innovations as a Health Specialist on August 16, 2020. Sara’s areas of responsibility include Translational Initiatives in Drug Discovery, and Challenges and Prize Competitions. Sara comes to NIDA from a position with Leidos.

Mary MacDonald, Ph.D., recently joined the Division of Therapeutics and Medical Consequences as a Medicinal Chemist in the Chemistry and Pharmaceutics Branch (CPB). Mary holds a B.S. in Chemistry from Ursinus College and a Ph.D. in Medicinal Chemistry from the University of Kansas School of Pharmacy, where she was mentored by Jeffrey Aubè. Her postdoctoral appointment was with Kim Janda at The Scripps Research Institute in La Jolla, CA. Mary remained in San Diego and worked in the biotechnology and pharmaceutical industries focusing on metabolic disease, inflammation, and pain. In 2016 she returned to the East Coast and worked as a government contractor supporting the Defense Threat Reduction Agency, then the Walter Reed Army Institute of Research. Mary’s expertise lies in drug design and synthesis, hit-to-lead, structure-activity relationship studies, and lead optimization of both small molecule and peptide therapeutics.

Hugo Matamoros joined the NIDA Office of Management’s Financial Management Branch as a Budget Analyst on July 5, 2020. Hugo was a budget analyst in multiple Department of Defense organizations since 2014, where he managed various appropriated funds, administrated the travel system, provided training for subordinate organization travel system accountable officials and administrators, and prepared reports and briefings for senior staff members. Most recently, he worked in the U.S. Army Reserve Legal Command in Gaithersburg, MD, where he coordinated program budget advisory committees and command and staff briefs, and provided guidance and advice to command and program managers on all aspects of financial management, budget execution and other financial issues. Among other duties, Hugo will be the lead analyst for the Helping to End Addiction Long-term Research Management and Support budget, Food and Drug Administration-funded programs (including the Population Assessment of Tobacco and Health), and the Commercial Operations Advisory Committee budget. He will also assist in managing the funding meetings process.

Ritvik Peesapati, a recent graduate of the University of Georgia, joined the Molecular Neuropsychiatry Research Branch of NIDA's Intramural Research Program in July 2020.

Vicky Perez joined the Office of Management's Financial Management Branch as a Budget Analyst on June 7, 2020. Vicky was a budget analyst at the National Cancer Institute from 2005 to 2015, where she managed non-appropriated funds and reimbursable agreements, prepared briefing materials for the NCI Director, and responded to financial data requests. For the past five years, she worked in scientific operations in an NCI intramural program, where she managed scientific review committees, worked on acquisitions planning, and developed responses for narrative reports. Among other duties, Vicky will be the lead analyst for the Research Management and Support budget, Interagency Agreements, and Gift Funds.

Manuel (Manny) Rodriguez joined NIDA's Management Analysis Branch on August 30, 2020. Manny served in the U.S. Army for 20 years and then transitioned to the private sector as a senior leader over business operations, shared services, and organizational effectiveness. In 2019, Manny joined the Department of Veterans Affairs as a Program Analyst. In this role, he spearheaded the creation and management of a Department-level working group on workforce management, change management processes, and standards. He also served as the Program Manager responsible for overseeing the implementation of the Office of Personnel Management Human Capital Framework across the Department. Manny holds a master's degree in management and is trained as a Six Sigma Green Belt. At NIDA his responsibilities will include senior Title 42 recruitment, Federal Employee Viewpoint Survey, Emergency Coordination, Onboarding, and MD-715 (reporting on diversity and inclusion initiatives).

Christina Rinaldi came to NIDA from the National Institute of General Medical Sciences grants management branch and previously served as both a Grants Management Specialist and Program Analyst at the National Heart, Lung, and Blood Institute (NHLBI). Prior to joining the NIH, Christina worked on the grantee side at the Henry M. Jackson Foundation.

Jeanette Russell joined the Office of Management's Office of Acquisitions as a Contract Specialist on August 30, 2020. Jeanette comes to NIDA from Jefferson Consulting.

Shayna Simpson joined the Office of Management's Office of Acquisitions as a Contract Specialist on August 16, 2020.

Kiran Vemuri, Ph.D., joined the Division of Neuroscience and Behavior as a Program Officer in the Chemistry, Pharmacology, Physiology Branch. Kiran's career spans over two decades across both industry and academia, during which he spent 15 years developing research tools and studying novel treatments for substance-use disorders. His research interests include chemical synthesis, route selection and optimization, in vitro and in vivo pharmacology, and the therapeutic assessment of biologically active compounds. After receiving his Ph.D. in chemistry from Osmania University in India, Kiran worked at Northeastern University as faculty, ultimately taking on the role of Deputy Director at the University's Center for Drug Discovery. Kiran is known for his research on the chemistry of cannabinoid receptors. Beyond addiction science research, he actively worked on the discovery and development of therapeutics for treating diabetic nephropathy, pulmonary inflammation and fibrosis, and liver disorders. He

holds 20 issued patents and has contributed to more than 65 peer-reviewed papers in areas encompassing chemical synthesis and molecular and cell biology.

Jorge Vizcaino-Riveros, M.P.H., joined the Division of Epidemiology, Services and Prevention Research (DESPR) as a Health Specialist on June 21, 2020. Jorge's prior work experiences in research have been at various Boston-area hospitals. Jorge also served as a Peace Corps Volunteer in Paraguay, which led him to Boston University School of Public Health, where he earned his master's degree with concentrations in epidemiology and monitoring and evaluation. Jorge received a B.S. in Dietetics from the University of Delaware.

Jennifer Wong, Ph.D., joined the Division of Therapeutics and Medical Consequences Regulatory Affairs Branch as Health Scientist Administrator on August 2, 2020. Jennifer completed her Ph.D. in physiology at the University of Tennessee Health Science Center. From 2003 to 2005, she worked for NIDA's DTMC, and subsequently for the National Cancer Institute Cancer Therapy Evaluation Program, generic pharma, and St. Luke's Hospital in Boise, ID, where she managed the Mountain States Tumor Medical Research Institute. Most recently, she served as an American Association for the Advancement of Science Science and Technology Fellow at NIH in the Office of the Director, Office of Science Policy, where she focused on technology transfer and innovation policy. Jennifer continues to serve on the Milken Institute's FasterCures Biomedical Ecosystem Metrics workgroup, focusing on equitable use and access.

Prerna Yadav started a postbaccalaureate Intramural Research Training Award position in the Aponte Lab of NIDA's Intramural Research Program in July 2020.

Staff Departures

Darius Bickham, an Administrative Officer from NIDA's Administrative Management and Analysis Branch, left the Institute on May 9, 2020, for a position with the Health Resources and Services Administration.

Marcus Brown, an Administrative Officer from NIDA's Administrative Management and Analysis Branch, left the Institute on July 4, 2020, for a position with the National Institute of Nursing Research.

Cynthia Fortis, a Budget Analyst from the Office of Management's Financial Management Branch, left NIDA on May 23, 2020, for a position in the NIH Office of the Director.

Juaneshia Hamiel-Schaub, an Administrative Officer from NIDA's Administrative Management and Analysis Branch, left the Institute on August 1, 2020, for a position with Naval Sea Systems Command.

Andrew Hotaling, a Supervisory Contract Specialist with the Office of Management's Office of Acquisitions, NIDA Research and Development, left on May 23, 2020, for a position with the General Services Administration.

Christina Mack, a Budget Analyst from the Office of Management's Financial Management Branch, left NIDA on June 20, 2020, for a position with the National Oceanic and Atmospheric Administration .

Hiromi Ono, Ph.D., left NIDA's Division of Extramural Research in June 2020 to join the NIH Office of Extramural Research in the Office of the Director. As a Scientific Review Officer , Hiromi managed the peer review of applications for several major HIV-related initiatives developed by NIDA. In her new position, she is supporting NIH's investigations in allegations of research misconduct in NIH-funded extramural activities.

Rajeev Subu has left the Molecular Neuropsychiatry Research Branch of NIDA's Intramural Research Program and will be an M.D. candidate at The Medical College of Georgia, Georgia Regents University.

Jennifer Wenzel, Ph.D., a program officer in the Behavioral Cognitive Neuroscience Branch, Division of Neuroscience and Behavior, left her position at NIDA in July 2020 and has taken a faculty position at the University of San Diego.

Retirements

Susan O. McGuire, Ph.D., will retire from NIDA on September 27, 2020. Susan has been a NIDA Scientific Review Officer since 2014. Before joining NIDA, she served as faculty at Rush University Medical School, Loyola University Medical School, and the University of Illinois at Chicago. Her research focused on neuroinflammation, brain injury and neurologic disease, and its modification by diet. She also served as Treasurer, Council member, and Chair of the Young Investigators Committee for the American Society for Neurochemistry and with the Advanced School training committee for the International Society for Neurochemistry.

IN MEMORIAM

The Western States Node and the Clinical Trials Network (CTN) lost one of the founding Principal Investigators with the death of **Dr. Merwyn (Mitch) Greenlick** on Friday May 15, 2020, from natural causes. He was 85 years of age and had dealt with multiple health problems in the past year. Dr. Greenlick, a member of the Oregon House of Representatives (2003-2020) served for many years as the Chair of the House Health Care Committee sponsoring and passing progressive legislation that enhanced access to health care for many Oregonians. The *Willamette Weekly* noted, “Greenlick was famed in the Legislature for his utter lack of bedside manner—he suffered fools tartly, if at all.” His traits and skills shaped health care and research in the Kaiser Permanente Health Care Systems and the CTN. He leaves a unique legacy and will be missed. Betty Tai, Director of the Center for the Clinical Trials Network, reflected, “Upon the CTN’s creation, Mitch’s big voice and warm heart were critical components of our steering committee....My fondest memories of Mitch are of his passion, his energy, and his tireless commitment to the well-being of the most underserved populations.”

We are saddened by the sudden loss of **Robert Malison, M.D.**, Professor of Psychiatry, Yale University, who passed away on July 25, 2020, at age 60, at his home in Guilford, CT. At the time of his death, Bob was director of the Clinical Neuroscience Research Unit of the Abraham Ribicoff Research Facilities of the Connecticut Mental Health Center. He was the leader of the Neuroscience Research Training Program, the neuroscience research track of the Yale Psychiatry Residency. He also led the Integrated Mentored Patient-Oriented Research Training program) in Psychiatry and an addiction training grant based in Thailand while concurrently being Principal Investigator on two independent project grants (R01s). Bob was a consummate clinician and scientist, with a three-decade career of groundbreaking research into the neurobiology, genetics, and treatment of substance abuse disorders. His body of work has helped countless patients, friends, family members, students, and colleagues, and his legacy will continue through all those who were touched by Bob and inspired by his work. Bob was a beloved mentor to a generation of research-oriented psychiatrists at Yale, with many of his mentees now leading prestigious programs across the world.



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