



# DIRECTOR'S REPORT

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## TABLE OF CONTENTS

<b>RESEARCH HIGHLIGHTS.....</b>	<b>2</b>
<b>GRANTEE HONORS AND AWARDS.....</b>	<b>25</b>
<b>STAFF HONORS AND AWARDS.....</b>	<b>27</b>
<b>STAFF CHANGES.....</b>	<b>28</b>

## **RESEARCH HIGHLIGHTS**

### **BASIC AND BEHAVIORAL RESEARCH**

**Multi-Omic And Multi-Species Meta-Analyses Of Nicotine Consumption** Palmer RHC, Benca-Bachman CE, Huggett SB, Bubier JA, McGeary JE, Ramgiri N, Srijevantham J, Yang J, Visscher PM, Yang J, Knopik VS and Chesler EJ. *Translational Psychiatry*. 2021; 11(1): 98.

Cross-species translational approaches to human genomic analyses are lacking. The present study uses an integrative framework to investigate how genes associated with nicotine use in model organisms contribute to the genetic architecture of human tobacco consumption. First, we created a model organism geneset by collecting results from five animal models of nicotine exposure (RNA expression changes in brain) and then tested the relevance of these genes and flanking genetic variation using genetic data from human cigarettes per day (UK BioBank N 123,844; all European Ancestry). We tested three hypotheses: (1) DNA variation in, or around, the ‘model organism geneset’ will contribute to the heritability to human tobacco consumption, (2) that the model organism genes will be enriched for genes associated with human tobacco consumption, and (3) that a polygenic score based off our model organism geneset will predict tobacco consumption in the AddHealth sample (N = 1667; all European Ancestry). Our results suggested that: (1) model organism genes accounted for ~5–36% of the observed SNP heritability in human tobacco consumption (enrichment: 1.60–31.45), (2) model organism genes, but not negative control genes, were enriched for the gene-based associations (MAGMA, H-MAGMA, SMultiXcan) for human cigarettes per day, and (3) polygenic scores based on our model organism geneset predicted cigarettes per day in an independent sample. Altogether, these findings highlight the advantages of using multiple species evidence to isolate genetic factors to better understand the etiological complexity of tobacco and other nicotine consumption.

**Noninvasive Brain Stimulation Rescues Cocaine-Induced Prefrontal Hypoactivity And Restores Flexible Behavior** West EA, Niedringhaus M, Ortega HK, Frohlich F and Carelli RM. *Biological Psychiatry*. 2021; 89(10): 1001-1011.

To obtain desirable goals, individuals must predict the outcome of specific choices, use that information to direct appropriate actions, and adjust behavior accordingly in changing environments (behavioral flexibility). Substance use disorders are marked by impairments in behavioral flexibility along with decreased prefrontal cortical function that limits the efficacy of treatment strategies. Restoring prefrontal hypoactivity, ideally in a noninvasive manner, is an intriguing target for improving flexible behavior and treatment outcomes. A behavioral flexibility task was used in Long-Evans male rats (n = 97) in conjunction with electrophysiology, optogenetics, and a novel rat model of transcranial alternating current stimulation (tACS) to examine the prelimbic cortex (PrL) to nucleus accumbens (NAc) core circuit in behavioral flexibility and determine whether tACS can restore cocaine-induced neural and cognitive dysfunction. Optogenetic inactivation revealed that the PrL-NAc core circuit is necessary for the ability to learn strategies to flexibly shift behavior. Cocaine self-administration history caused aberrant PrL-NAc core neural encoding and deficits in flexibility. Optogenetics that selectively activated the PrL-NAc core pathway prior to learning rescued cocaine-induced cognitive flexibility deficits. Remarkably, tACS prior to learning the task reestablished adaptive signaling in the PrL-NAc circuit and restored flexible behavior in a relatively noninvasive and frequency-specific manner. We establish a role of NAc core-projecting PrL neurons in behavioral flexibility and provide a novel noninvasive brain stimulation method in rats to

rescue cocaine-induced frontal hypofunction and restore flexible behavior, supporting a role of tACS as a therapeutic to treat cognitive deficits in substance use disorders.

### **Ventral Pallidum DRD3 Potentiates A Pallido-Habenular Circuit Driving Accumbal Dopamine Release And Cocaine Seeking**

Pribiag H, Shin S, Wang EH-J, Sun G, Datta P, Okamoto A, Guss H, Jain A, Wang X-Y, De Freitas B, Honma P, Pate S, Lilascharoen V, Li Y and Lim BK. *Neuron*. 2021; 109(13): 2165-2182.

Drugs of abuse induce persistent remodeling of reward circuit function, a process thought to underlie the emergence of drug craving and relapse to drug use. However, how circuit-specific, drug-induced molecular and cellular plasticity can have distributed effects on the mesolimbic dopamine reward system to facilitate relapse to drug use is not fully elucidated. Here, we demonstrate that dopamine receptor D3 (DRD3)-dependent plasticity in the ventral pallidum (VP) drives potentiation of dopamine release in the nucleus accumbens during relapse to cocaine seeking after abstinence. We show that two distinct VP DRD3<sup>+</sup> neuronal populations projecting to either the lateral habenula (LHb) or the ventral tegmental area (VTA) display different patterns of activity during drug seeking following abstinence from cocaine self-administration and that selective suppression of elevated activity or DRD3 signaling in the LHb-projecting population reduces drug seeking. Together, our results uncover how circuit-specific DRD3-mediated plasticity contributes to the process of drug relapse.

### **Site Selective C-H Functionalization Of Mitragyna Alkaloids Reveals A Molecular Switch For Tuning Opioid Receptor Signaling Efficacy**

Bhowmik S, Galeta J, Havel V, Nelson M, Faouzi A, Bechand B, Ansonoff M, Fiala T, Hunkele A, Kruegel AC, Pintar JE, Majumdar S, Javitch JA, Sames D. *Nat Commun*. 2021; 12(1): 3858.

Mitragynine (MG) is the most abundant alkaloid component of the psychoactive plant material "kratom", which according to numerous anecdotal reports shows efficacy in self-medication for pain syndromes, depression, anxiety, and substance use disorders. We have developed a synthetic method for selective functionalization of the unexplored C11 position of the MG scaffold (C6 position in indole numbering) via the use of an indole-ethylene glycol adduct and subsequent iridium-catalyzed borylation. Through this work we discover that C11 represents a key locant for fine-tuning opioid receptor signaling efficacy. 7-Hydroxymitragynine (7OH), the parent compound with low efficacy on par with buprenorphine, is transformed to an even lower efficacy agonist by introducing a fluorine substituent in this position (11-F-7OH), as demonstrated in vitro at both mouse and human mu opioid receptors (mMOR/hMOR) and in vivo in mouse analgesia tests. Low efficacy opioid agonists are of high interest as candidates for generating safer opioid medications with mitigated adverse effects.

### **Reinforcement Learning Links Spontaneous Cortical Dopamine Impulses To Reward**

Foo C, Lozada A, Aljadef J, Li Y, Wang JW, Slesinger PA, Kleinfeld D. *Current Biology*. 2021; 31: 1-9.

In their pioneering study on dopamine release, Romo and Schultz speculated "...that the amount of dopamine released by unmodulated spontaneous impulse activity exerts a tonic, permissive influence on neuronal processes more actively engaged in preparation of self-initiated movements...." Motivated by the suggestion of "spontaneous impulses," as well as by the "ramp up" of dopaminergic neuronal activity that occurs when rodents navigate to a reward, we asked two questions. First, are there spontaneous impulses of dopamine that are released in cortex? Using cell-based optical sensors of extrasynaptic dopamine, [DA]<sub>ex</sub>, we found that spontaneous dopamine impulses in cortex of naive mice occur at a rate of  $\sim 0.01$  per second. Next, can mice be trained to

change the amplitude and/or timing of dopamine events triggered by internal brain dynamics, much as they can change the amplitude and timing of dopamine impulses based on an external cue? Using a reinforcement learning paradigm based solely on rewards that were gated by feedback from real-time measurements of [DA]ex, we found that mice can volitionally modulate their spontaneous [DA]ex. In particular, by only the second session of daily, hour-long training, mice increased the rate of impulses of [DA]ex, increased the amplitude of the impulses, and increased their tonic level of [DA]ex for a reward. Critically, mice learned to reliably elicit [DA]ex impulses prior to receiving a reward. These effects reversed when the reward was removed. We posit that spontaneous dopamine impulses may serve as a salient cognitive event in behavioral planning.

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

**Substance Use Among Men Who Have Sex With Men** Compton WM, Jones CM. N Engl J Med. 2021; 385(4): 352-356.

In this review, the authors highlight that high rates of substance use among MSM must be viewed in the context of differences in demographic characteristics, types of substances used, and patterns of use. Bisexual MSM have been found to have higher rates of substance use and substance use disorders than other subgroups of MSM and higher rates than heterosexual men. Use of methamphetamine, nitrite inhalants, and other drugs as part of sexual encounters is associated with high-risk sexual behaviors, such as unprotected anal intercourse, and contributes to the transmission of HIV infection and other STIs.

**Use of Medications For Alcohol Use Disorder In The US: Results From The 2019 National Survey on Drug Use and Health** Han B, Jones CM, Einstein EB, Powell PA, Compton WM. JAMA Psychiatry. 2021; 78(8): 922-924.

This article from NIDA and NIAAA scientists documents that just 1.6 percent of the millions of adults in the U.S. with alcohol use disorders had been prescribed medications for their drinking, building on a literature showing overall very low rates of any type of treatment for alcohol use disorder (e.g., 7.6% rate of any treatment among those with alcohol use disorders in 2019). While those with psychiatric cooccurring conditions and those with more severe alcohol use disorder were more likely to receive medications for alcohol use disorder, even in these high-risk groups, only a small percentage received such care. Enhancing use of medications and all proven approaches is essential for improving the treatment of all substance use disorders.

**E-Cigarette Use Is Associated With Subsequent Cigarette Use Among Young Adult Non-Smokers, Over And Above A Range Of Antecedent Risk Factors: A Propensity Score Analysis** Epstein M, Bailey JA, Kosterman R, Rhew IC, Furlong M, Oesterle S. Addiction. 2021; 116(5): 1224-1232.

There is a public health concern that the use of e-cigarettes among non-smoking young adults could be associated with transition to combustible cigarette use. The current study is a quasi-experimental test of the relationship between e-cigarette use and subsequent combustible cigarette use among young adult non-smokers, accounting for a wide range of common risk factors. Logistic regression was used to predict combustible cigarette use on three or more occasions at age 23 years based on age 21 e-cigarette use. Inverse probability weighting (IPW) was used to account for confounding variables. Data were drawn from the Community Youth Development Study (CYDS), a cohort study of youth recruited in 2003 in 24 rural communities in seven US states PARTICIPANTS: Youth in the CYDS study (n = 4407) were surveyed annually from ages 11 to 16, and at ages 18,

19, 21 and 23 years (in 2016). The sample was gender balanced (50% female) and ethnically diverse (20% Hispanic, 64% white, 3% black and 12% other race or ethnicity). The current study was limited to participants who had never used combustible cigarettes by age 21 (n = 1825). After applying IPW, e-cigarette use at age 21 was associated with a twofold increase in odds of combustible cigarette use on three or more occasions 2 years later (odds ratio = 2.16, confidence interval 1.23, 3.79). Among previously never-smoking US young adults, e-cigarette use appears to be strongly associated with subsequent combustible cigarette smoking, over and above measured preexisting risk factors.

**Concentration of Patient Care Among Buprenorphine-Prescribing Clinicians in the US** Stein BD, Saloner B, Schuler MS, Gurvey J, Sorbero M, Gordon AJ. JAMA. 2021; 325(21): 2206-2208. In the US, buprenorphine to treat OUD can be prescribed only by qualified clinicians. Policy initiatives have focused on enlarging the pool of available prescribers to increase buprenorphine treatment availability, but the concentration of patient care among current active prescribers is not well-characterized. Using IQVIA data which captures approximately 90% of prescriptions filled at retail pharmacies, this study examined active buprenorphine patients per month by provider type over a two-year period (Jan 2017 – Dec 2018). Half of all patient-months of buprenorphine treatment was prescribed by 4.9% of all providers; these high-volume providers treated a mean of 124.2 patients per month. High volume providers occurred in all provider types, with a majority being primary care providers. Most clinicians prescribed buprenorphine infrequently and had low patient caseloads. Supporting prescribing clinicians to increase patient caseload could increase treatment availability.

**Opioid Use Disorder And Health Service Utilization Among COVID-19 Patients In The US: A Nationwide Cohort From The Cerner Real-World Data** Qeadan F, Tingey B, Bern R, Porucznik CA, English K, Saeed AI, Madden EF. EClinicalMedicine. 2021; 37: 100938.

Background: Both opioid use and COVID-19 affect respiratory and pulmonary health, potentially putting individuals with opioid use disorders (OUD) at risk for complications from COVID-19. We examine the relationship between OUD and subsequent hospitalization, length of stay, risk for invasive ventilator dependence (IVD), and COVID-19 mortality. Methods: Multivariable logistic and exponential regression models using electronic health records data from the Cerner COVID-19 De-Identified Data Cohort from January through June 2020. Findings: Out of 52,312 patients with COVID-19, 1.9% (n=1,013) had an OUD. COVID-19 patients with an OUD had higher odds of hospitalization (aOR=3.44, 95% CI=2.81–4.21), maximum length of stay (=1.16, 95% CI=1.09–1.22), and odds of IVD (aOR=1.26, 95% CI=1.06–1.49) than patients without an OUD, but did not differ with respect to COVID-19 mortality. However, OUD patients under age 45 exhibited greater COVID-19 mortality (aOR=3.23, 95% CI=1.59–6.56) compared to patients under age 45 without an OUD. OUD patients using opioid agonist treatment (OAT) exhibited higher odds of hospitalization (aOR=5.14, 95% CI=2.75–10.60) and higher maximum length of stay (=1.22, 95% CI=1.01–1.48) than patients without OUDs; however, risk for IVD and COVID-19 mortality did not differ. OUD patients using naltrexone had higher odds of hospitalization (aOR=32.19, 95% CI=4.29–4,119.83), higher maximum length of stay (=1.59, 95% CI=1.06–2.38), and higher odds of IVD (aOR=3.15, 95% CI=1.04–9.51) than patients without OUDs, but mortality did not differ. OUD patients who did not use treatment medication had higher odds of hospitalization (aOR=4.05, 95% CI=3.32–4.98), higher maximum length of stay (=1.14, 95% CI=1.08–1.21), and higher odds of IVD (aOR=1.25, 95% CI=1.04–1.50) and COVID-19 mortality (aOR=1.31, 95% CI=1.07–1.61) than patients without OUDs. Interpretation: This study suggests people with OUD and COVID-19 often require higher

levels of care, and OUD patients who are younger or not using medication treatment for OUDs are particularly vulnerable to death due to COVID-19.

**Examining Proximity Exposure In A Social Network As A Mechanism Driving Peer Influence Of Adolescent Smoking** Khalil GE, Jones EC, Fujimoto K. *Addict Behav.* 2021; 117: 106853.

Adolescent peers' influence on tobacco smoking is a dynamic process affected by close friends and other network peers. Although research has examined the influence of immediate friends on smoking behavior (i.e., by cohesion exposure), the influence of all peers according to closeness (i.e., proximity exposure) remains unknown. This study introduces proximity exposure as a potential driver of peer influence. Using the Teenage Friends and Lifestyle Study dataset, the investigators examined 160 adolescents followed for 3 years and assessed their friendship ties and health behavior. Proximity exposure was calculated as the proportion of an individual's network peers who smoked, considering their distance from the individual. Path analysis was conducted with cross-lagged models testing the effect of proximity exposure on smoking frequency over time. Among nonsmokers without cohesion exposure (n = 80), proximity exposure at year 1 was significantly associated with smoking initiation by year 3. Path analysis (n = 160) indicated that smoking at year 1 predicted cohesion exposure by year 3. When proximity exposure was included, the effect of smoking on cohesion exposure was lost. Early smoking predicted future proximity exposure. However, the predictive value of early proximity toward future smoking was stronger. These results suggest that proximity exposure can predict smoking even among nonsmokers without direct ties to friends who smoke. In support of a peer selection hypothesis, early smoking predicted friendship formation with smokers through cohesion. Conversely, in support of a peer influence hypothesis, proximity exposure predicted smoking. Researchers may consider developing interventions that decrease proximity exposure among adolescents.

**Stimulant Use For Self-Management Of Pain Among Safety-Net Patients With Chronic Non-Cancer Pain** Beliveau CM, McMahan VM, Arenander J, Angst MS, Kushel M, Torres A, Santos GM, Coffin PO. *Subst Abus.* 2021 April 2: 1-8

Chronic pain affects one-fifth of US adults. Reductions in opioid prescribing have been associated with increased non-prescription opioid use and, chronologically, increased stimulant (methamphetamine and cocaine) use. While non-prescription opioid use is commonly attributed to pain self-management, the role of stimulants in managing pain is unclear. Baseline data comes from a longitudinal study of patients with chronic non-cancer pain in an urban safety-net healthcare system who had been prescribed an opioid for  $\geq 3$  of the last 12 months, and had a history of non-prescription opioid, cocaine, or amphetamine use (N = 300). Investigators estimated the prevalence and identified correlates of stimulant use to treat pain among a subgroup of patients who reported past-year stimulant use (N = 105). Fifty-two percent of participants with past-year stimulant use reported using stimulants in the past year to treat pain. Participants who used stimulants for pain reported slightly higher average pain in the past 3 months. Study findings suggest an underexplored motivation for stimulant use in an era of reduced access to prescribed opioids.

## **TREATMENT RESEARCH**

### **Methocinnamox Reverses And Prevents Fentanyl-Induced Ventilatory Depression In Rats**

Jimenez Jr, Victor M, Castaneda G, France CP. *J Pharmacol Exp Ther.* 2021; 377(1): 29-38.

Opioid use disorder affects over 2 million Americans with an increasing number of deaths due to overdose from the synthetic opioid fentanyl and its analogs. The Food and Drug Administration-approved opioid receptor antagonist naloxone (e.g., Narcan) is used currently to treat overdose; however, a short duration of action limits its clinical utility. Methocinnamox (MCAM) is a long-lasting opioid receptor antagonist that may reverse and prevent the ventilatory-depressant effects of fentanyl. This study compared the ability of naloxone (0.0001-10 mg/kg) and MCAM (0.0001-10 mg/kg) to reverse and prevent ventilatory depression by fentanyl and compared the duration of action of MCAM intravenously and subcutaneously in two procedures: ventilation and warm-water tail withdrawal. In male Sprague-Dawley rats (N = 8), fentanyl (0.0032-0.178 mg/kg, i.v.) decreased minute volume in a dose- and time-dependent manner with a dose of 0.178 mg/kg decreasing VE to less than 40% of control. MCAM and naloxone reversed the ventilatory-depressant effects of 0.178 mg/kg fentanyl in a dose-related manner. The day after antagonist administration, MCAM but not naloxone attenuated the ventilatory-depressant effects of fentanyl. The duration of action of MCAM lasted up to 3 days and at least 2 weeks after intravenous and subcutaneous administration, respectively. MCAM attenuated the antinociceptive effects of fentanyl, with antagonism lasting up to 5 days and more than 2 weeks after intravenous and subcutaneous administration, respectively. Reversal and prolonged antagonism by MCAM might provide an effective treatment option for the opioid crisis, particularly toxicity from fentanyl and related highly potent analogs. SIGNIFICANCE STATEMENT: This study demonstrates that like naloxone, methocinnamox (MCAM) reverses the ventilatory-depressant effects of fentanyl in a time- and dose-related manner. However, unlike naloxone, the duration of action of MCAM was greater than 2 weeks when administered subcutaneously and up to 5 days when administered intravenously. These data suggest that MCAM might be particularly useful for rescuing individuals from opioid overdose, including fentanyl overdose, as well as protecting against the reemergence of ventilatory depression (renarconization).

### **Effect Of Preexisting Immunity To Tetanus Toxoid On The Efficacy Of Tetanus Toxoid-Conjugated Heroin Vaccine In Mice**

Komla E, Torres OB, Jalah R, Sulima A, Beck Z, Alving CR, Jacobson AE, Rice KC, Matyas GR. *Vaccines (Basel).* 2021; 9(6): 573.

Opioid use disorder (OUD) is a serious health problem that has dramatically increased over the last decade. Although current therapies for the management of OUD can be effective, they have limitations. The complementary strategy to combat the opioid crisis is the development of a conjugate vaccine to generate high affinity antibodies in order to neutralize opioids in circulation before reaching the brain. The components of an opioid vaccine include an opioid hapten (6-AmHap) that is conjugated to a carrier protein (tetanus toxoid) with the addition of adjuvants (Army Liposome Formulation adsorbed to aluminum hydroxide-ALFA). There is no consensus in the literature as to whether preexisting immunity to the carrier protein may impact the immunogenicity of the conjugate vaccine by inducing an enhanced or suppressed immune response to the hapten. Here, we investigated whether pre-exposure to tetanus toxoid would affect the immunogenicity and efficacy of the heroin vaccine, TT-6-AmHap. Mice were primed with diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at weeks -4 and -2, then immunized with TT-6-AmHap vaccine



at weeks 0, 3, and 6. Using ELISA and behavioral assays, we found that preexisting immunity to tetanus toxoid had no influence on the immunogenicity and efficacy of the TT-6-AmHap vaccine.

### **Engineering Quick- And Long-Acting Naloxone Delivery Systems For Treating Opioid**

**Overdose** Sharifi F, Meqbil YJ, Otte A, Guttridge AM, Blaine AT, van Rijn RM, Park K. Pharm Res. 2021; 38(7): 1221-1234.

**PURPOSE:** Opioids have been the main factor for drug overdose deaths in the United States. Current naloxone delivery systems are effective in mitigating the opioid effects only for hours. Naloxone-loaded poly(lactide-co-glycolide) (PLGA) microparticles were prepared as quick- and long-acting naloxone delivery systems to extend the naloxone effect as an opioid antidote. **METHODS:** The naloxone-PLGA microparticles were made using an emulsification solvent extraction approach with different formulation and processing parameters. Two PLGA polymers with the lactide:glycolide (L:G) ratios of 50:50 and 75:25 were used, and the drug loading was varied from 21% to 51%. Two different microparticles of different sizes with the average diameters of 23  $\mu\text{m}$  and 50  $\mu\text{m}$  were produced using two homogenization-sieving conditions. All the microparticles were critically characterized, and three of them were evaluated with  $\beta$ -arrestin recruitment assays. **RESULTS:** The naloxone encapsulation efficiency (EE) was in the range of 70-85%. The EE was enhanced when the theoretical naloxone loading was increased from 30% to 60%, the L:G ratio was changed from 50:50 to 75:25, and the average size of the particles was reduced from 50  $\mu\text{m}$  to 23  $\mu\text{m}$ . The in vitro naloxone release duration ranged from 4 to 35 days. Reducing the average size of the microparticles from 50  $\mu\text{m}$  to 23  $\mu\text{m}$  helped eliminate the lag phase and obtain the steady-state drug release profile. The cellular pharmacodynamics of three selected formulations were evaluated by applying DAMGO, a synthetic opioid peptide agonist to a  $\mu$ -opioid receptor, to recruit  $\beta$ -arrestin 2. **CONCLUSIONS:** Naloxone released from the three selected formulations could inhibit DAMGO-induced  $\beta$ -arrestin 2 recruitment. This indicates that the proposed naloxone delivery system is adequate for opioid reversal during the naloxone release duration.

### **Effect Of Varenicline Directly Observed Therapy Versus Varenicline Self-Administered Therapy On Varenicline Adherence And Smoking Cessation In Methadone-Maintained Smokers: A Randomized Controlled Trial**

Nahvi S, Adams TR, Ning Y, Zhang C, Arnsten JH. Addiction. 2021; 116(4): 902-913.

**BACKGROUND AND AIMS:** Level of adherence to tobacco cessation medication regimens is believed to be causally related to medication effectiveness. This study aimed to evaluate the efficacy of varenicline directly observed therapy (DOT) on varenicline adherence and smoking cessation rates among smokers with opioid use disorder (OUD) receiving methadone treatment. **DESIGN:** Multicenter, parallel-group two-arm randomized controlled trial. **SETTING:** Urban opioid treatment program (OTP) in the Bronx, New York, USA. **PARTICIPANTS:** Daily smokers of  $\geq 5$  cigarettes/day, interested in quitting (ladder of change score 6-8), in methadone treatment for  $\geq 3$  months, attending OTP  $\geq 3$  days/week. Participants' mean age was 49 years, 56% were male, 44% Latino, 30% Black, and they smoked a median of 10 cigarettes/day. **INTERVENTIONS:** Individual, block, random assignment to 12 weeks of varenicline, either directly observed with methadone (DOT, n = 50) or via unsupervised self-administered treatment (SAT, n = 50). **MEASUREMENTS:** The primary outcome was adherence measured by pill count. The secondary outcome was 7-day point prevalence tobacco abstinence verified by expired carbon monoxide (CO)  $< 8$  parts per million. **FINDINGS:** Retention at 24 weeks was 92%. Mean adherence was 78.5% [95% confidence interval (CI) = 71.8-85.2%] in the DOT group versus 61.8% in the SAT group

(95% CI = 55.0-68.6%); differences were driven by DOT effects in the first 6 weeks. CO-verified abstinence did not differ between groups during the intervention (P = 0.26), but was higher in the DOT than the SAT group at intervention end (DOT = 18% versus SAT = 10%, difference = 8%, 95% CI = -13, 28); this difference was not significant (P = 0.39) and was not sustained at 24-week follow-up. CONCLUSIONS: Among daily smokers attending opioid treatment programs, opioid treatment program-based varenicline directly observed therapy was associated with early increases in varenicline adherence compared with self-administered treatment, but findings were inconclusive as to whether directly observed therapy was associated with a difference in tobacco abstinence.

### **Development And Feasibility Study Of An Addiction-Focused Phenotyping Assessment**

**Battery** Keyser-Marcus LA, Ramey T, Bjork J, Adams A, Moeller FG. Am J Addict. 2021; 30(4): 398-405.

**BACKGROUND AND OBJECTIVES:** Current methods of classifying individuals with substance use disorder (SUD) result in vast heterogeneity among persons within a given diagnosis. These approaches, while clinically allowing for distinctions between patient groups, are less than ideal when attempting to recruit a neurobehaviorally defined subset of subjects into clinical trials. To address this gap, alternative strategies have been proposed, including behavioral phenotyping. The NIDA Phenotyping Assessment Battery (PhAB) is a modular package of assessments and neurocognitive tasks that was developed for use in clinical trials. The goal of the present study is to assess the feasibility of the NIDA PhAB with regard to ease of administration and time burden. **METHODS:** Healthy controls, persons with cocaine use disorder (CocUD), opioid use disorder (OUD), cannabis use disorder (CanUD), and combined opioid and cocaine use disorder (OCUD) were recruited from various sources (N = 595). Participants completed screening and one to three assessment visits. Time to complete the measures was recorded and a satisfaction interview was administered. **RESULTS:** Of the participants enrolled, 381 were deemed eligible. The majority of eligible participants (83%) completed all assessments. The average completion time was 3 hours. High participant satisfaction ratings were noted, with over 90% of participants endorsing a willingness to participate in a similar study and recommend the study to others. **CONCLUSION AND SCIENTIFIC SIGNIFICANCE:** These findings corroborate the ease with which the PhAB may be easily incorporated into a study assessment visit without undue participant burden. The PhAB is an efficient method for behavioral phenotyping in addiction clinical trials.

### **Racial Disparities In Intensity Of Smoke Exposure And Nicotine Intake Among Low-Dependence Smokers**

Ho JTK, Tyndale RF, Baker TB, Amos CI, Chiu A, Smock N, Chen J, Bierut LJ, Chen L-S. Drug Alcohol Depend. 2021; 221: 108641.

**BACKGROUND:** Compared to white smokers, Black smokers are at disproportionately higher risk for smoking-related disease, despite consuming fewer cigarettes per day (CPD). To examine racial disparities in biobehavioral influences on smoking and disease risk, we analyzed the relationship between self-reported tobacco dependence and intensity of tobacco smoke exposure per cigarette, on the one hand, and intensity of nicotine intake per cigarette, on the other. **METHODS:** In 270 Black and 516 white smokers, smoke exposure was measured by expired carbon monoxide (CO), and nicotine intake was measured by plasma cotinine (COT) and cotinine+3'-hydroxycotinine ([COT + 3HC]). Using linear regression analyses, we analyzed how the Fagerström Test for Cigarette Dependence (FTCD) predicted intensity of smoke exposure per cigarette (CO/CPD) and intensity of nicotine intake per cigarette (COT/CPD; [COT + 3HC]/CPD), and how race moderated these relations. **RESULTS:** Overall, Black smokers consumed fewer CPD than white smokers and had higher levels of CO/CPD, COT/CPD, and [COT + 3HC]/CPD. These elevations were most

pronounced at lower levels of dependence: amongst Black smokers, FTCD negatively predicted intensity of smoke exposure as measured by CO/CPD ( $B = -0.12$ , 95% CI =  $-0.18, -0.05$ ,  $p = 0.0003$ ) and intensity of nicotine intake as measured by  $[COT + 3HC]/CPD$  ( $B = -1.31$ , 95% CI =  $-2.15, -0.46$ ,  $p = 0.002$ ). CONCLUSIONS: Low-dependence Black smokers had higher intensities of both smoke exposure and nicotine intake per cigarette compared to similarly dependent white smokers, suggesting that measures of dependence, exposure, and intake underestimate incremental risk of each cigarette to Black smokers.

**[Sleep And Substance Use Disorder Treatment: A Preliminary Study Of Subjective And Objective Assessment Of Sleep During An Intensive Outpatient Program](#)** Wilkerson AK,

Simmons RO, Sahlem GL, Taylor DJ, Smith JP, Book S, McRae-Clark AL. Am J Addict. Online ahead of print. 2021 June 23.

BACKGROUND AND OBJECTIVES: Characteristics of sleep concerns and their relationship to mental health in heterogeneous substance use disorder (SUD) treatment settings are not well understood. The purpose of this preliminary study was to assess sleep using subjective and objective measures at two time points during SUD treatment and compare sleep changes to changes in mental health measures. METHODS: Treatment-seeking participants completed an assessment battery at the beginning of treatment (Time 1,  $N = 30$ ) and again upon treatment completion (Time 2, approximately 4 weeks later,  $N = 22$ ). The majority of participants were White (80%), male (63%), and presenting for alcohol use disorder (60.0%), though almost half reported polysubstance abuse (43%). Comorbidity was common (53%). Sleep and mental health questionnaires with 1 week of actigraphy and sleep diaries were completed at both time points. RESULTS: Most participants met the criteria for a sleep disorder and mean scores on questionnaires showed poor sleep quality, insomnia symptoms, and frequent nightmares, with sleep quality and insomnia improving over time but remaining clinically significant. Nightmares did not improve. Actigraphy indicated poor sleep at both time points. Improvement in insomnia was related to improvement in measures of mental health while changes in actigraphy variables were not related to these measures. DISCUSSION AND CONCLUSIONS: Multiple types of sleep disturbance are prevalent in this population, with nightmares persisting throughout treatment and insomnia symptoms showing a relationship with mental health symptoms. SCIENTIFIC SIGNIFICANCE: This was the first study to longitudinally assess mental health with subjective and objective measures of sleep across multiple types of SUDs in a community SUD treatment setting.

## **HIV/AIDS RELATED RESEARCH**

**[Improving Health Equity And Ending The HIV Epidemic In The USA: A Distributional Cost-Effectiveness Analysis In Six Cities](#)** Quan AML, Mah C, Krebs E, Zang X, Chen S...Nosyk B, on

behalf of the Localized HIV Economic Modeling Study Group\* Lancet HIV. 2021; S2352-3018(21)00147-8.

Background: In the USA, Black and Hispanic or Latinx individuals continue to be disproportionately affected by HIV. Applying a distributional cost-effectiveness framework, we estimated the cost-effectiveness and epidemiological impact of two combination implementation approaches to identify the approach that best meets the dual objectives of improving population health and reducing racial or ethnic health disparities. Methods: We adapted a dynamic, compartmental HIV transmission model to characterize HIV micro-epidemics in six US cities: Atlanta, Baltimore, Los Angeles, Miami, New York, and Seattle. We considered combinations of 16

evidence-based interventions to diagnose, treat, and prevent HIV transmission according to previously documented levels of scale-up. We then identified optimal combination strategies for each city, with the distribution of each intervention implemented according to existing service levels (proportional services approach) and the racial or ethnic distribution of new diagnoses (between Black, Hispanic or Latinx, and White or other ethnicity individuals; equity approach). We estimated total costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios of strategies implemented from 2020 to 2030 (health-care perspective; 20-year time horizon; 3% annual discount rate). We estimated three measures of health inequality (between-group variance, index of disparity, Theil index), incidence rate ratios, and rate differences for the selected strategies under each approach. Findings: In all cities, optimal combination strategies under the equity approach generated more QALYs than those with proportional services, ranging from a 3.1% increase (95% credible interval [CrI] 1.4–5.3) in New York to more than double (101.9% [75.4–134.6]) in Atlanta. Compared with proportional services, the equity approach delivered lower costs over 20 years in all cities except Los Angeles; cost reductions ranged from \$22.9 million (95% CrI 5.3–55.7 million) in Seattle to \$579.8 million (255.4–940.5 million) in Atlanta. The equity approach also reduced incidence disparities and health inequality measures in all cities except Los Angeles. Interpretation: Equity-focused HIV combination implementation strategies that reduce disparities for Black and Hispanic or Latinx individuals can significantly improve population health, reduce costs, and drive progress towards Ending the HIV Epidemic goals in the USA.

**Care Facilitation Advances Movement Along The Hepatitis C Care Continuum For Persons With Human Immunodeficiency Virus, Hepatitis C, and Substance Use: A Randomized Clinical Trial (CTN-0064)** Metsch LR, Feaster DJ, Gooden LK, Masson C, Perlman DC, Jain MK, Matheson T, Nelson CM, Jacobs P, Tross S, Haynes L, Lucas GM, Colasanti JA, Rodriguez A, Drainoni ML, Osorio G, Nijhawan AE, Jacobson JM, Sullivan M, Metzger D, Vergara-Rodriguez P, Lubelchek R, Duan R, Batycki JN, Matthews AG, Munoz F, Jelstrom E, Mandler R, del Rio C. *Open Forum Infectious Diseases*. 2021; 8(8): ofab334.

**Background:** Direct-acting antivirals can cure HCV. Persons with HCV/HIV and living with substance use are disadvantaged in benefitting from advances in HCV treatment. **Methods:** In this randomized controlled trial, participants with HCV/HIV were randomized between February 2016 and January 2017 to either care facilitation or control. Twelve-month follow-up assessments completed in January 2018. Care facilitation group participants received motivation and strengths-based case-management addressing retrieval of HCV load results, engagement in HCV/HIV care and medication adherence. Control group participants received referral to HCV evaluation and an offer of assistance in making care appointments. Primary outcome was number of steps achieved along a series of 8 clinical steps (e.g., receiving HCV results, initiating treatment, sustained viral response) of the HCV/HIV care continuum over 12 months post-randomization. **Results:** Three hundred and eighty-one individuals were screened and 113 randomized. Median age was 51 years; 58.4% male and 72.6% Black/African American. Median HIV-1 viral load was 27,209 copies/ml with 69% having a detectable viral load. Mean number of steps completed was statistically significantly higher in the intervention (2.44 steps) vs. control group (1.68 steps) [ $\chi^2(1)=7.36$ ,  $p=0.0067$ ]. Men in the intervention (vs. control) group completed a statistically significantly higher number of steps. Eleven participants achieved sustained viral response with no difference by treatment group. **Conclusions:** The care facilitation intervention increased progress along the HCV/HIV care continuum, as observed for men and not women. Study findings also highlight the continued challenges to achieve individual patient sustained viral responses and population level HCV elimination.

### **HIV-1 Tat And Morphine Differentially Disrupt Pyramidal Cell Structure And Function And Spatial Learning In Hippocampal Area CA1: Continuous Versus Interrupted Morphine**

**Exposure** Marks WD, Paris JJ, Barbou AJ, Moon J, Carpenter VJ, McLane VD, Lark ARS, Nass SR, Zhang J, Yarotsky V, McQuiston AR, Knapp PE and Hauser KF. *eNeuro*. 2021; 8(3): ENEURO.0547-20.2021.

About half the people infected with human immunodeficiency virus (HIV) have neurocognitive deficits that often include memory impairment and hippocampal deficits, which can be exacerbated by opioid abuse. To explore the effects of opioids and HIV on hippocampal CA1 pyramidal neuron structure and function, we induced HIV-1 transactivator of transcription (Tat) expression in transgenic mice for 14 d and co-administered time-release morphine or vehicle subcutaneous implants during the final 5 d (days 9–14) to establish steady-state morphine levels. Morphine was withheld from some *ex vivo* slices during recordings to begin to assess the initial pharmacokinetic consequences of opioid withdrawal. Tat expression reduced hippocampal CA1 pyramidal neuronal excitability at lower stimulating currents. Pyramidal cell firing rates were unaffected by continuous morphine exposure. Behaviorally, exposure to Tat or high dosages of morphine impaired spatial memory. Exposure to Tat and steady-state levels of morphine appeared to have largely independent effects on pyramidal neuron structure and function, a response that is distinct from other vulnerable brain regions such as the striatum. By contrast, acutely withholding morphine (from morphine-tolerant *ex vivo* slices) revealed unique and selective neuroadaptive shifts in CA1 pyramidal neuronal excitability and dendritic plasticity, including some interactions with Tat. Collectively, the results show that opioid-HIV interactions in hippocampal area CA1 are more nuanced than previously assumed, and appear to vary depending on the outcome assessed and on the pharmacokinetics of morphine exposure.

**Binding Mode Of Human Norepinephrine Transporter Interacting With HIV-1 Tat** Adeniran C, Yuan Y, Davis SE, Lin C, Xu J, Zhu J, and Zhan C-G. *ACS Chem. Neurosci*. 2021; 12(9): 1519-1527.

The increase of HIV infection in macrophages results in HIV proteins being released, like HIV Tat which impairs the function of monoamine transporters. HIV-infected patients have displayed increased synaptic levels of dopamine (DA) due to reduced binding and function of monoamine transporters such as the norepinephrine transporter (NET) and the dopamine transporter (DAT). Development of a three-dimensional model of the HIV-1 Tat-human NET (hNET) binding complex would help reveal how HIV-1 Tat causes toxicity in the neuron by affecting DA uptake. Here we use computational techniques such as molecular modeling to study microscopic properties and molecular dynamics of the HIV-1 Tat-hNET binding. These modeling techniques allow us to analyze noncovalent interactions and observe residue–residue contacts to verify a model structure. The modeling results studied here show that HIV-1 Tat-hNET binding is highly dynamic and that HIV-1 Tat preferentially binds to hNET in its outward-open state. In particular, HIV-1 Tat forms hydrogen bond interactions with side chains of hNET residues Y84, K88, and T544. The favorable hydrogen bonding interactions of HIV-1 Tat with the hNET side chain residues Y84 and T544 have been validated by our subsequently performed DA uptake activity assays and site-directed mutagenesis, suggesting that the modeled HIV-1 Tat-hNET binding mode is reasonable. These mechanistic and structural insights gained through homology models discussed in this study are expected to encourage the pursuit of pharmacological and biochemical studies on HIV-1 Tat interacting with hNET mechanisms and detailed structures.

**Substance Use Stigma, Avoidance Coping, And Missed HIV Appointments Among MSM Who Use Substances** Batchelder AW, Foley JD, Wirtz MR, Mayer K, O'Cleirigh C. AIDS Behav. 2021; 25(5): 1454-1463.

Men who have sex with men (MSM) living with HIV who use substances have multiple stigmatized identities. Theory suggests that internalization of stigma may elicit avoidance behaviors associated with these stigmas, potentially resulting in suboptimal engagement in HIV care. Interrelationships between internalized stigmas related to HIV, sexual orientation, and substance use; avoidance coping; and missed HIV appointments were assessed among 202 MSM living with HIV who use substances. Neither HIV nor sexual orientation-related internalized stigmas were associated with missed appointments, however, internalized substance use stigma was associated. Avoidance coping fully accounted for the relationship between anticipated substance use stigma and missed appointments. Results suggest that avoidance strategies to manage anticipated substance use stigma may result in substance using MSM forgoing HIV care appointments.

**Awareness Of And Interest In Oral Pre-Exposure Prophylaxis (Prep) For HIV Prevention And Interest In Hypothetical Forms Of Prep Among People Who Inject Drugs In Rural West Virginia** Schneider KE, White RH, O'Rourke A, Kilkenny ME, Perdue M, Sherman SG, Grieb SM, Allen ST. 2021; 33(6): 721-728.

Injection drug use-associated HIV outbreaks have occurred in rural communities throughout the United States, which often have limited HIV prevention services for people who inject drugs (PWID). Pre-exposure prophylaxis (PrEP) is one tool that may help fill gaps in HIV prevention programming in rural settings. Oral PrEP has been approved for use, and new PrEP formulations are under development. Research is needed to better understand interest in oral and possible forthcoming PrEP formulations among PWID. We used survey data from 407 PWID in rural West Virginia. We asked if participants had heard of, taken, and were interested in taking PrEP, and about interest in several hypothetical forms of PrEP (arm injections, abdomen injections, implants, intravenous infusions). We estimated the prevalence of interest in each formulation and assessed correlates using Chi-squared tests. A minority had heard of oral PrEP (32.6%), and few had used it (3.7%). Many were interested in using oral PrEP (58.3%). Half were interested in arm injections (55.7%). Common correlates of interest across PrEP formulations were sexual minority status, comfort talking to a doctor about sex, sex work, and sharing injection equipment. Oral and injectable PrEP have the potential to fill HIV prevention gaps for rural PWID.

**Comparative Impact Of Methamphetamine And Other Drug Use On Viral Suppression Among Sexual Minority Men On Antiretroviral Therapy** Fulcher JA, Javanbakht M, Shover CL, Ragsdale A, Brookmeyer R, Shoptaw S, Gorbach PM. Drug Alcohol Depend. 2021; 221: 108622. BACKGROUND: Substance use decreases the likelihood of achieving undetectable HIV viremia; however, the comparative effects by drug have not been fully described. In this study, we compare the effects of methamphetamine use versus other drugs on viremia in sexual minority men on antiretroviral therapy (ART). METHODS: HIV-positive participants currently on ART (N = 230) were selected from an ongoing cohort of diverse young sexual minority men (mSTUDY) enrolled from August 2014 to May 2018. Substance use and sociodemographic factors associated with viremia outcomes were assessed using ordinal regression analysis with generalized estimating equations. Viremia outcomes were grouped as undetectable (200 copies/mL). RESULTS: The prevalence of drug use across 825 study visits was 73 %, with methamphetamine use most prevalent (50 %). After adjusting for unstable housing and ART adherence, methamphetamine use, either alone (adjusted OR = 1.87; 95 % CI 1.03-3.40) or with other drugs (adjusted OR = 1.82; 95 % CI

1.12-2.95), was associated with higher odds of increasing viremia compared to no drug use. Other drug use excluding methamphetamine did not show a similar association (adjusted OR = 1.29; 95 % CI 0.80-2.09). Among our study population, nearly half the instances of viremia could be reduced if methamphetamine was discontinued (attributable fraction = 46 %; 95 % CI 3-71 %).

CONCLUSIONS: Methamphetamine use, either alone or in combination with other drugs, is associated with failure of viral suppression among sexual minority men on ART independent of adherence and sociodemographic factors. This accounts for nearly half of the observed instances of unsuppressed viremia in this study.

### **Evidence For The Model Of Gender Affirmation: The Role Of Gender Affirmation And Healthcare Empowerment In Viral Suppression Among Transgender Women Of Color Living With HIV**

Sevelius J, Chakravarty D, Neilands TB, Keatley JA, Shade SB, Johnson MO, Rebchook G, HRSA SPNS Transgender Women of Color Study Group. *AIDS Behav.* 2021; 25(Suppl 1): 64-71.

Transgender women of color are disproportionately impacted by HIV, poor health outcomes, and transgender-related discrimination (TD). We tested the Model of Gender Affirmation (GA) to identify intervention-amenable targets to enhance viral suppression (VS) using data from 858 transgender women of color living with HIV (49% Latina, 42% Black; 36% virally suppressed) in a serial mediation model. Global fit statistics demonstrated good model fit; statistically significant ( $p \leq 0.05$ ) direct pathways were between TD and GA, GA and healthcare empowerment (HCE), and HCE and VS. Significant indirect pathways were from TD to VS via GA and HCE ( $p = 0.036$ ) and GA to VS via HCE ( $p = 0.028$ ). Gender affirmation and healthcare empowerment significantly and fully mediated the total effect of transgender-related discrimination on viral suppression. These data provide empirical evidence for the Model of Gender Affirmation. Interventions that boost gender affirmation and healthcare empowerment may improve viral suppression among transgender women of color living with HIV.

### **Web-Based Cognitive Training To Improve Working Memory In Persons With Co-Occurring HIV Infection And Cocaine Use Disorder: Outcomes From A Randomized Controlled Trial**

Towe SL, Hartsock JT, Xu Y, Meade CS. *AIDS Behav.* 2021; 25(5): 1542-1551.

Neurocognitive impairment (NCI) remains a persistent complication of HIV disease that nearly half of persons with HIV experience, and rates are even higher in persons who use substances such as cocaine. Cognitive training is a promising intervention for HIV-associated NCI. In this randomized controlled trial, we examined the feasibility and effectiveness of a web-based cognitive training program to improve working memory in a sample of 58 persons with HIV and cocaine use disorder. Participants were randomly assigned to either the experimental working memory training arm or the attention control training arm and completed up to 48 daily sessions over 10 weeks. Overall, treatment completion (74%) and retention rates (97%) were high, and participant feedback indicated the intervention was acceptable. Our results show that the intervention successfully reduced working memory deficits in the experimental arm relative to the control arm. Our findings support both the feasibility and effectiveness of cognitive training in this population.

## **CLINICAL TRIALS NETWORK RESEARCH**

**Comparison Of Methods For Alcohol And Drug Screening In Primary Care Clinics** McNeely J, Adam A, Rotrosen J, Wakeman SE, Wilens TE, Kannry J, Rosenthal RN, Wahle A, Pitts S,

Farkas S, Rosa C, Peccoralo L, Waite E, Vega A, Kent J, Craven CK, Kaminski TA, Firmin E, Isenberg B, Harris M, Kushniruk A, Hamilton L. *JAMA Netw Open*. 2021; 4(5): e2110721.

**Importance:** Guidelines recommend that adult patients receive screening for alcohol and drug use during primary care visits, but the adoption of screening in routine practice remains low. Clinics frequently struggle to choose a screening approach that is best suited to their resources, workflows, and patient populations. **Objective:** To evaluate how to best implement electronic health record (EHR)-integrated screening for substance use by comparing commonly used screening methods and examining their association with implementation outcomes. **Design, setting, and participants:** This article presents the outcomes of phases 3 and 4 of a 4-phase quality improvement, implementation feasibility study in which researchers worked with stakeholders at 6 primary care clinics in 2 large urban academic health care systems to define and implement their optimal screening approach. Site A was located in New York City and comprised 2 clinics, and site B was located in Boston, Massachusetts, and comprised 4 clinics. Clinics initiated screening between January 2017 and October 2018, and 93,114 patients were eligible for screening for alcohol and drug use. Data used in the analysis were collected between January 2017 and October 2019, and analysis was performed from July 13, 2018, to March 23, 2021. **Interventions:** Clinics integrated validated screening questions and a brief counseling script into the EHR, with implementation supported by the use of clinical champions (i.e., clinicians who advocate for change, motivate others, and use their expertise to facilitate the adoption of an intervention) and the training of clinic staff. Clinics varied in their screening approaches, including the type of visit targeted for screening (any visit vs annual examinations only), the mode of administration (staff-administered vs self-administered by the patient), and the extent to which they used practice facilitation and EHR usability testing. **Main outcomes and measures:** Data from the EHRs were extracted quarterly for 12 months to measure implementation outcomes. The primary outcome was screening rate for alcohol and drug use. Secondary outcomes were the prevalence of unhealthy alcohol and drug use detected via screening, and clinician adoption of a brief counseling script. **Results:** Patients of the 6 clinics had a mean (SD) age ranging from 48.9 (17.3) years at clinic B2 to 59.1 (16.7) years at clinic B3, were predominantly female (52.4% at clinic A1 to 64.6% at clinic A2), and were English speaking. Racial diversity varied by location. Of the 93,114 patients with primary care visits, 71.8% received screening for alcohol use, and 70.5% received screening for drug use. Screening at any visit (implemented at site A) in comparison with screening at annual examinations only (implemented at site B) was associated with higher screening rates for alcohol use (90.3%-94.7% vs 24.2%-72.0%, respectively) and drug use (89.6%-93.9% vs 24.6%-69.8%). The 5 clinics that used a self-administered screening approach had a higher detection rate for moderate- to high-risk alcohol use (14.7%-36.6%) compared with the 1 clinic that used a staff-administered screening approach (1.6%). The detection of moderate- to high-risk drug use was low across all clinics (0.5%-1.0%). Clinics with more robust practice facilitation and EHR usability testing had somewhat greater adoption of the counseling script for patients with moderate-high risk alcohol or drug use (1.4%-12.5% vs 0.1%-1.1%). **Conclusions and relevance:** In this quality improvement study, EHR-integrated screening was feasible to implement in all clinics and unhealthy alcohol use was detected more frequently when self-administered screening was used at any primary care visit. The detection of drug use was low at all clinics, as was clinician adoption of counseling. These findings can be used to inform the decision-making of health care systems that are seeking to implement screening for substance use.



**High-Dose Buprenorphine Induction In The Emergency Department For Treatment of Opioid Use Disorder**

Herring AA, Vosooghi AA, Luftig J, Anderson ES, Zhao X, Dziura J, Hawk KF, McCormack RP, Saxon A, D'Onofrio G. JAMA Netw Open. 2021; 4(7): e2117128.

Importance: Emergency departments (EDs) sporadically use a high-dose buprenorphine induction strategy for the treatment of opioid use disorder (OUD) in response to the increasing potency of the illicit opioid drug supply and commonly encountered delays in access to follow-up care. Objective: To examine the safety and tolerability of high-dose (>12 mg) buprenorphine induction for patients with OUD presenting to an ED. Design, setting, and participants: In this case series of ED encounters, data were manually abstracted from electronic health records for all ED patients with OUD treated with buprenorphine at a single, urban, safety-net hospital in Oakland, California, for the calendar year 2018. Data analysis was performed from April 2020 to March 2021.

Interventions: ED physicians and advanced practice practitioners were trained on a high-dose sublingual buprenorphine induction protocol, which was then clinically implemented. Main outcomes and measures: Vital signs; use of supplemental oxygen; the presence of precipitated withdrawal, sedation, and respiratory depression; adverse events; length of stay; and hospitalization during and 24 hours after the ED visit were reported according to total sublingual buprenorphine dose (range, 2 to >28 mg). Results: Among a total of 391 unique patients (median [interquartile range] age, 36 [29-48] years), representing 579 encounters, 267 (68.3%) were male and 170 were (43.5%) Black. Homelessness (88 patients [22.5%]) and psychiatric disorders (161 patients [41.2%]) were common. A high dose of sublingual buprenorphine (>12 mg) was administered by 54 unique clinicians during 366 (63.2%) encounters, including 138 doses (23.8%) greater than or equal to 28 mg. No cases of respiratory depression or sedation were reported. All 5 (0.8%) cases of precipitated withdrawal had no association with dose; 4 cases occurred after doses of 8 mg of buprenorphine. Three serious adverse events unrelated to buprenorphine were identified. Nausea or vomiting was rare (2%-6% of cases). The median (interquartile range) length of stay was 2.4 (1.6-3.75) hours. Conclusions and relevance: These findings suggest that high-dose buprenorphine induction, adopted by multiple clinicians in a single-site urban ED, was safe and well tolerated in patients with untreated OUD. Further prospective investigations conducted in multiple sites would enhance these findings.

**Prevalence Of Medical Cannabis Use And Associated Health Conditions Documented In Electronic Health Records Among Primary Care Patients In Washington State**

Matson TE, Carrell DS, Bobb JF, Cronkite DJ, Oliver MM, Luce C, Ghitza UE, Hsu CW, Campbell CI, Browne KC, Binswanger IA, Saxon AJ, Bradley KA, Lapham GT. JAMA Netw Open. 2021; 4(5): e219375.

Importance: Many people use cannabis for medical reasons despite limited evidence of therapeutic benefit and potential risks. Little is known about medical practitioners' documentation of medical cannabis use or clinical characteristics of patients with documented medical cannabis use.

Objectives: To estimate the prevalence of past-year medical cannabis use documented in electronic health records (EHRs) and to describe patients with EHR-documented medical cannabis use, EHR-documented cannabis use without evidence of medical use (other cannabis use), and no EHR-documented cannabis use. Design, setting, and participants: This cross-sectional study assessed adult primary care patients who completed a cannabis screen during a visit between November 1, 2017, and October 31, 2018, at a large health system that conducts routine cannabis screening in a US state with legal medical and recreational cannabis use. Exposures: Three mutually exclusive categories of EHR-documented cannabis use (medical, other, and no use) based on practitioner documentation of medical cannabis use in the EHR and patient report of past-year cannabis use at screening. Main outcomes and measures: Health conditions for which cannabis use has potential

benefits or risks were defined based on National Academies of Sciences, Engineering, and Medicine's review. The adjusted prevalence of conditions diagnosed in the prior year were estimated across 3 categories of EHR-documented cannabis use with logistic regression. Results: A total of 185,565 patients (mean [SD] age, 52.0 [18.1] years; 59% female, 73% White, 94% non-Hispanic, and 61% commercially insured) were screened for cannabis use in a primary care visit during the study period. Among these patients, 3,551 (2%) had EHR-documented medical cannabis use, 36,599 (20%) had EHR-documented other cannabis use, and 145,415 (78%) had no documented cannabis use. Patients with medical cannabis use had a higher prevalence of health conditions for which cannabis has potential benefits (49.8%; 95% CI, 48.3%-51.3%) compared with patients with other cannabis use (39.9%; 95% CI, 39.4%-40.3%) or no cannabis use (40.0%; 95% CI, 39.8%-40.2%). In addition, patients with medical cannabis use had a higher prevalence of health conditions for which cannabis has potential risks (60.7%; 95% CI, 59.0%-62.3%) compared with patients with other cannabis use (50.5%; 95% CI, 50.0%-51.0%) or no cannabis use (42.7%; 95% CI, 42.4%-42.9%). Conclusions and relevance: In this cross-sectional study, primary care patients with documented medical cannabis use had a high prevalence of health conditions for which cannabis use has potential benefits, yet a higher prevalence of conditions with potential risks from cannabis use. These findings suggest that practitioners should be prepared to discuss potential risks and benefits of cannabis use with patients.

**Sublingual Buprenorphine-Naloxone Compared With Injection Naltrexone For Opioid Use Disorder: Potential Utility of Patient Characteristics in Guiding Choice Of Treatment** Nunes

EV Jr, Scodes JM, Pavlicova M, Lee JD, Novo P, Campbell ANC, Rotrosen J. Am J Psychiatry. 2021; 178(7): 660-671.

Objective: Sublingual buprenorphine-naloxone and extended-release injection naltrexone are effective treatments, with distinct mechanisms, for opioid use disorder. The authors examined whether patients' demographic and clinical characteristics were associated with better response to one medication or the other. Methods: In a multisite 24-week randomized comparative-effectiveness trial of assignment to buprenorphine-naloxone (N=287) compared with extended-release naltrexone (N=283) comprising inpatients planning to initiate medication treatment for opioid use disorder, 50 demographic and clinical characteristics were examined as moderators of the effect of medication assignment on relapse to regular opioid use and failure to initiate medication. Moderator-by-medication interactions were estimated using logistic regression with correction for multiple testing. Results: In the intent-to-treat sample, patients who reported being homeless had a lower relapse rate if they were assigned to receive extended-release naltrexone (51.6%) compared with buprenorphine-naloxone (70.4%) (odds ratio=0.45, 95% CI=0.22, 0.90); patients who were not homeless had a higher relapse rate if they were assigned to extended-release naltrexone (70.9%) compared with buprenorphine-naloxone (53.1%) (odds ratio=2.15, 95% CI=1.44, 3.21). In the subsample of patients who initiated medication, the interaction was not significant, with a similar pattern of lower relapse with extended-release naltrexone (41.4%) compared with buprenorphine (68.6%) among homeless patients (odds ratio=0.32, 95% CI=0.15, 0.68) but less difference among those not homeless (extended-release naltrexone, 57.2%; buprenorphine, 52.0%; odds ratio=1.24, 95% CI=0.80, 1.90). For failure to initiate medication, moderators were stated preference for medication (failure was less likely if the patient was assigned to the medication preferred), parole and probation status (fewer failures with extended-release naltrexone for those on parole or probation), and presence of pain and timing of randomization (more failure with extended-release naltrexone for patients endorsing moderate to severe pain and randomized early while still undergoing medically managed withdrawal). Conclusions: Among

patients with opioid use disorder admitted to inpatient treatment, homelessness, parole and probation status, medication preference, and factors likely to influence tolerability of medication initiation may be important in matching patients to buprenorphine or extended-release naltrexone.

**[A Pilot Study Of The Functionality And Clinician Acceptance Of A Clinical Decision Support Tool To Improve Primary Care Of Opioid Use Disorder](#)**

Rossom RC, Sperl-Hillen JM, O'Connor PJ, Crain AL, Nightingale L, Pylkas A, Huntley KV, Bart G. *Addict Sci Clin Pract.* 2021; 16(1): 37.

**Objective:** Most Americans with opioid use disorder (OUD) do not receive indicated medical care. A clinical decision support (CDS) tool for primary care providers (PCPs) could address this treatment gap. Our primary objective was to build OUD-CDS tool and demonstrate its functionality and accuracy. Secondary objectives were to achieve high use and approval rates and improve PCP confidence in diagnosing and treating OUD. **Methods:** A convenience sample of 55 PCPs participated. Buprenorphine-waivered PCPs (n = 8) were assigned to the intervention. Non-waivered PCPs (n = 47) were randomized to intervention (n = 24) or control (n = 23). Intervention PCPs received access to the OUD-CDS, which alerted them to patients at potentially increased risk for OUD or overdose and guided diagnosis and treatment. Control PCPs provided care as usual. **Results:** The OUD-CDS was functional and accurate following extensive multi-phased testing. PCPs used the OUD-CDS in 5% of encounters with at-risk patients, far less than the goal of 60%. OUD screening confidence increased for all intervention PCPs and OUD diagnosis increased for non-waivered intervention PCPs. Most PCPs (65%) would recommend the OUD-CDS and found it helpful with screening for OUD and discussing and prescribing OUD medications. **Discussion:** PCPs generally liked the OUD-CDS, but use rates were low, suggesting the need to modify CDS design, implementation strategies and integration with existing primary care workflows. **Conclusion:** The OUD-CDS tool was functional and accurate, but PCP use rates were low. Despite low use, the OUD-CDS improved confidence in OUD screening, diagnosis and use of buprenorphine.

**ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH**

**[Child Reward Neurocircuitry And Parental Substance Use History: Findings From The Adolescent Brain Cognitive Development Study](#)**

Kwarteng AE, Rahman MM, Gee DG, Infante MA, Tapert SF, Curtis BL *Addictive Behaviors.* 2021; 122: 107034.

**Background:** Substance use research has focused on family history of alcohol use disorders but less on other addictions in biological family members. We examined how parental substance use history relates to reward system functioning, specifically nucleus accumbens (NAcc) and putamen activation at age 9-10 in the Adolescent Brain Cognitive Development (ABCD) Study. This research hopes to address limitations in prior literature by focusing analyses on a large, substance-naïve sample. **Method:** We included ABCD participants with valid Monetary Incentive Delay task fMRI Baseline data and parent substance use history at project baseline from Data Release 2.0 (N =10,622). Parent-history-positive (PH+) participants had one or both biological parents with a history of two+ problems with alcohol (n = 741; PH+A) and/or other drugs (n =638; Ph+D). Of participants who were parent-history-negative (PH-) for alcohol and/or drugs, a stratified random sample based on six sociodemographic variables was created and matched to the PH+ group (PH-A n = 699; PH-D n = 615). The contrast of interest was anticipation of a large reward vs. neutral response. **Results:** PH+A youth had more activation in the right NAcc during large reward

anticipation than PH-A. PH+D youth showed enhanced left putamen activation during large reward anticipation than PH-D youth. Bayesian hypothesis testing showed moderate evidence ( $BF > 3$ ) in favor of the null hypothesis. Conclusion: These findings suggest that pre-adolescents whose biological parents had a history of substance-related problems show small differences in reward processing compared to their PH- peers.

### **Polygenic Risk Scores For Alcohol Involvement Relate To Brain Structure In Substance-Naïve Children: Results From The ABCD Study**

Hatoum AS, Johnson EC, Baranger DAA, Paul SE, Agrawal A, Bogdan R Genes Brain Behav. 2021; e12756.

Background and aims: Brain imaging-derived structural correlates of alcohol involvement have largely been speculated to arise as a consequence of alcohol exposure. However, they may also reflect predispositional risk. Methods: In substance naïve children of European ancestry who completed the baseline session of the Adolescent Brain Cognitive Development (ABCD) Study ( $n=3,013$ ), mixed-effects models estimated whether polygenic risk scores (PRS) for Problematic Alcohol Use (PAU-PRS) and Drinks Per Week (DPW-PRS) are associated with magnetic resonance imaging-derived brain structure phenotypes (i.e., total and regional: cortical thickness, surface area and volume; subcortical volume; white matter volume, fractional anisotropy, mean diffusivity). Follow-up analyses evaluated whether any identified regions were also associated with polygenic risk among substance naïve children of African ancestry ( $n=898$ ). Results: After adjustment for multiple testing correction, polygenic risk for problematic alcohol use was associated with lower volume of the left frontal pole and greater cortical thickness of the right supramarginal gyrus ( $|\beta_s| > 0.009$ ;  $p_s < 0.001$ ;  $psfdr < 0.046$ ;  $r^2_s < 0.004$ ). PAU PRS and DPW PRS showed nominally significant associations with a host of other regional brain structure phenotypes (e.g., insula surface area and volume). None of these regions showed any, even nominal association among children of African ancestry. Conclusions: Genomic liability to alcohol involvement may manifest as variability in brain structure during middle childhood prior to alcohol use initiation. Broadly, alcohol-related variability in brain morphometry may partially reflect predisposing genomic influence. Larger discovery GWASs and target samples of diverse ancestries are needed to determine whether observed associations may generalize across ancestral origins.

### **Prediction Of Suicidal Ideation And Attempt In 9- And 10-Year-Old Children Using Transdiagnostic Risk Features**

Harman G, Kliamovich D, Morales AM, Gilbert S, Barch DM, Mooney MA, Feldstein Ewing SW, Fair DA, Nagel BJ. PLoS One. 2021; 16(5): e0252114.

The objective of the current study was to build predictive models for suicidal ideation in a sample of children aged 9-10 using features previously implicated in risk among older adolescent and adult populations. This case-control analysis utilized baseline data from the Adolescent Brain and Cognitive Development (ABCD) Study, collected from 21 research sites across the United States ( $N = 11,369$ ). Several regression and ensemble learning models were compared on their ability to classify individuals with suicidal ideation and/or attempt from healthy controls, as assessed by the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. When comparing control participants (mean age:  $9.92 \pm 0.62$  years; 4944 girls [49%]) to participants with suicidal ideation (mean age:  $9.89 \pm 0.63$  years; 451 girls [40%]), both logistic regression with feature selection and elastic net without feature selection predicted suicidal ideation with an AUC of 0.70 (CI 95%: 0.70-0.71). The random forest with feature selection trained to predict suicidal ideation predicted a holdout set of children with a history of suicidal ideation and attempt (mean age:  $9.96 \pm 0.62$  years; 79 girls [41%]) from controls with an AUC of 0.77 (CI 95%: 0.76-0.77). Important features from these models included feelings of loneliness and worthlessness, impulsivity,

prodromal psychosis symptoms, and behavioral problems. This investigation provided an unprecedented opportunity to identify suicide risk in youth. The use of machine learning to examine a large number of predictors spanning a variety of domains provides novel insight into transdiagnostic factors important for risk classification.

**Concurrent And Prospective Associations Between Fitbit Wearable-Derived RDoC Arousal And Regulatory Constructs And Adolescent Internalizing Symptoms**

Nelson BW, Flannery JE, Flournoy J, Duell N, Prinstein MJ, Telzer E. J Child Psychol Psychiatry. 2021 Jun 29. Online ahead of print.

Background: Adolescence is characterized by alterations in biobehavioral functioning, during which individuals are at heightened risk for onset of psychopathology, particularly internalizing disorders. Researchers have proposed using digital technologies to index daily biobehavioral functioning, yet there is a dearth of research examining how wearable metrics are associated with mental health. Methods: We preregistered analyses using the Adolescent Brain Cognitive Development Study dataset using wearable data collection in 5,686 adolescents (123,862 person-days or 2,972,688 person-hours) to determine whether wearable indices of resting heart rate (RHR), step count, and sleep duration and variability in these measures were cross-sectionally associated with internalizing symptomatology. All models were also run controlling for age, sex, body mass index, socioeconomic status, and race. We then performed prospective analyses on a subset of this sample ( $n = 143$ ) across 25 months that had Fitbit data available at baseline and follow-up in order to explore directionality of effects. Results: Cross-sectional analyses revealed a small, yet significant, effect size ( $R^2 = .053$ ) that higher RHR, lower step count and step count variability, and greater variability in sleep duration were associated with greater internalizing symptoms. Cross-lagged panel model analysis revealed that there were no prospective associations between wearable variables and internalizing symptoms (partial  $R^2 = .026$ ), but greater internalizing symptoms and higher RHR predicted lower step count 25 months later (partial  $R^2 = .010$ ), while higher RHR also predicted lower step count variability 25 months later (partial  $R^2 = .008$ ). Conclusions: Findings indicate that wearable indices concurrently associate with internalizing symptoms during early adolescence, while a larger sample size is likely required to accurately assess prospective or directional effects between wearable indices and mental health. Future research should capitalize on the temporal resolution provided by wearable devices to determine the intensive longitudinal relations between biobehavioral risk factors and acute changes in mental health.

### **Evaluation Of Attention-Deficit/Hyperactivity Disorder Medications, Externalizing Symptoms, And Suicidality In Children**

Shoval G, Visoki E, Moore TM, DiDomenico GE, Argabright ST, Huffnagle NJ, Alexander-Bloch AF, Waller R, Keele L, Benton TD, Gur RE, Barzilay R. JAMA Netw Open. 2021; 4(6): e2111342.

Importance: Childhood suicidality (i.e., suicidal ideation or attempts) rates are increasing, and attention-deficit/hyperactivity disorder (ADHD) and externalizing symptoms are common risk factors associated with suicidality. More data are needed to describe associations of ADHD

pharmacotherapy with childhood suicidality. Objective: To investigate the associations of ADHD

pharmacotherapy with externalizing symptoms and childhood suicidality. Design, setting, and

participants: In this cohort study, cross-sectional and 1-year-longitudinal associations were

examined using data (collected during 2016-2019) from the Adolescent Brain Cognitive

Development (ABCD) Study, a large, diverse US sample of children aged 9 to 11 years. Data

analysis was performed from November to December 2020. Exposures: Main and interaction

associations of externalizing symptoms (hyperactivity ADHD symptoms, oppositional defiant, and

conduct disorder symptoms) and ADHD medication treatment (methylphenidate and amphetamine

derivatives,  $\alpha$ -2-agonists, and atomoxetine) at baseline assessment. Main outcomes and measures:

Child-reported suicidality (past and present at baseline; current at longitudinal assessment).

Covariates were age, sex, race/ethnicity, parents' education, marital status, and concomitant child

psychiatric pharmacotherapy (antidepressants and antipsychotics). Results: Among 11,878 children

at baseline assessment (mean [SD] age, 9.9 [0.6] years; 6196 boys [52.2%]; 8805 White [74.1%]),

1006 (8.5%) were treated with ADHD medication and 1040 (8.8%) reported past or current

suicidality. Externalizing symptoms (median [range], 1 [0-29] symptom count) were associated with

suicidality (for a change of 1 SD in symptoms, odds ratio [OR], 1.34; 95% CI, 1.26-1.42;  $P < .001$ ),

as was ADHD medication treatment (OR, 1.32; 95% CI, 1.06-1.64;  $P = .01$ ). ADHD medication use

was associated with less suicidality in children with more externalizing symptoms (significant

symptom-by-medication interaction,  $B = -0.250$ ;  $SE = 0.086$ ;  $P = .004$ ), such that for children who

were not receiving ADHD medications, there was an association between more externalizing

symptoms and suicidality (for a change of 1 SD in symptoms, OR, 1.42; 95% CI, 1.33-1.52;  $P <$

$.001$ ); however, for children who were receiving ADHD medication, there was no such association

(OR, 1.15; 95% CI, 0.97-1.35;  $P = .10$ ). The association with medication remained even when

covarying for multiple confounders, including risk and protective factors for suicidality in ABCD,

and was replicated in 1-year longitudinal follow-up. Sensitivity analyses matching participants with

high numbers of externalizing symptoms taking and not taking ADHD medication treatment

confirmed its association with less suicidality. Conclusions and relevance: These findings suggest

that ADHD medication treatment is associated with less suicidality in children with substantial

externalizing symptoms and may be used to inform childhood suicide prevention strategies.

## **INTRAMURAL RESEARCH**

**Hypothalamic Control Of Interoceptive Hunger** Siemian JN, Arenivar MA, Sarsfield S, Aponte Y. *Curr Biol.* 2021; S0960-9822(21)00877-0.

While energy balance is critical to survival, many factors influence food intake beyond caloric need or "hunger." Despite this, some neurons that drive feeding in mice are routinely referred to as "hunger neurons," whereas others are not. To understand how specific hypothalamic circuits control interoceptive hunger, we trained mice to discriminate fasted from sated periods. We then manipulated three hypothalamic neuronal populations with well-known effects on feeding while mice performed this task. While activation of ARC<sup>AGRP</sup> neurons in sated mice caused mice to report being food-restricted, LH<sup>VGAT</sup> neuron activation or LH<sup>VGLUT2</sup> neuron inhibition did not. In contrast, LH<sup>VGAT</sup> neuron inhibition or LH<sup>VGLUT2</sup> neuron activation in fasted mice attenuated natural hunger, whereas ARC<sup>AGRP</sup> neuron inhibition did not. Each neuronal population evoked distinct effects on food consumption and reward. After satiety- or sickness-induced devaluation, ARC<sup>AGRP</sup> neurons drove calorie-specific feeding, while LH<sup>VGAT</sup> neurons drove calorie-indiscriminate food intake. Our data support a role for ARC<sup>AGRP</sup> neurons in homeostatic feeding and implicate them in driving a hunger-like internal state that directs behavior toward caloric food sources. Moreover, manipulations of LH circuits did not evoke hunger-like effects in sated mice, suggesting that they may govern feeding more related to reward, compulsion, or generalized consumption than to energy balance, but also that these LH circuits can be powerful negative appetite modulators in fasted mice. This study highlights the complexity of hypothalamic feeding regulation and can be used as a framework to characterize how other neuronal circuits affect hunger and identify potential therapeutic targets for eating disorders.

**An Excitatory Lateral Hypothalamic Circuit Orchestrating Pain Behaviors In Mice** Siemian JN, Arenivar MA, Sarsfield S, Borja CB, Erbaugh LJ, Eagle AL, Robison AJ, Leininger G, Aponte Y. *Elife.* 2021; 10:e66446.

Understanding how neuronal circuits control nociceptive processing will advance the search for novel analgesics. We use functional imaging to demonstrate that lateral hypothalamic parvalbumin-positive (LH<sup>PV</sup>) glutamatergic neurons respond to acute thermal stimuli and a persistent inflammatory irritant. Moreover, their chemogenetic modulation alters both pain-related behavioral adaptations and the unpleasantness of a noxious stimulus. In two models of persistent pain, optogenetic activation of LH<sup>PV</sup> neurons or their ventrolateral periaqueductal gray area (vlPAG) axonal projections attenuates nociception, and neuroanatomical tracing reveals that LH<sup>PV</sup> neurons preferentially target glutamatergic over GABAergic neurons in the vlPAG. By contrast, LH<sup>PV</sup> projections to the lateral habenula regulate aversion but not nociception. Finally, we find that LH<sup>PV</sup> activation evokes additive to synergistic antinociceptive interactions with morphine and restores morphine antinociception following the development of morphine tolerance. Our findings identify LH<sup>PV</sup> neurons as a lateral hypothalamic cell type involved in nociception and demonstrate their potential as a target for analgesia.

**Inactivation Of The Infralimbic Cortex Decreases Discriminative Stimulus-Controlled Relapse To Cocaine Seeking In Rats** Madangopal R, Ramsey LA, Weber SJ, Brenner MB, Lennon VA, Drake OR, Komer LE, Tunstall BJ, Bossert JM, Shaham Y, Hope BT.

*Neuropsychopharmacology.* 2021 Jun 23. Online ahead of print.

Persistent susceptibility to cue-induced relapse is a cardinal feature of addiction. Discriminative stimuli (DSs) are one type of drug-associated cue that signal drug availability (DS+) or

unavailability (DS-) and control drug seeking prior to relapse. We previously established a trial-based procedure in rats to isolate DSs from context, conditioned stimuli, and other drug-associated cues during cocaine self-administration and demonstrated DS-controlled cocaine seeking up to 300 abstinence days. The behavioral and neural mechanisms underlying trial-based DS-control of drug seeking have rarely been investigated. Here we show that following discrimination training in our trial-based procedure, the DS+ and DS- independently control the expression and suppression of cocaine seeking during abstinence. Using microinjections of GABA<sub>A</sub> + GABA<sub>B</sub> receptor agonists (muscimol + baclofen) in medial prefrontal cortex, we report that infralimbic, but not prelimbic, subregion of medial prefrontal cortex is critical to persistent DS-controlled relapse to cocaine seeking after prolonged abstinence, but not DS-guided discriminated cocaine seeking or DS-controlled cocaine self-administration. Finally, using ex vivo whole-cell recordings from pyramidal neurons in the medial prefrontal cortex, we demonstrate that the disruption of DS-controlled cocaine seeking following infralimbic cortex microinjections of muscimol+baclofen is likely a result of suppression of synaptic transmission in the region via a presynaptic mechanism of action.

**[Supramammillary Neurons Projecting To The Septum Regulate Dopamine And Motivation For Environmental Interaction In Mice](#)** Kesner AJ, Shin R, Calva CB, Don RF, Junn S, Potter CT, Ramsey LA, Abou-Elnaga AF, Cover CG, Wang DV, Lu H, Yang Y, Ikemoto S. *Nat Commun.* 2021; 12(1): 2811.

The supramammillary region (SuM) is a posterior hypothalamic structure, known to regulate hippocampal theta oscillations and arousal. However, recent studies reported that the stimulation of SuM neurons with neuroactive chemicals, including substances of abuse, is reinforcing. We conducted experiments to elucidate how SuM neurons mediate such effects. Using optogenetics, we found that the excitation of SuM glutamatergic (GLU) neurons was reinforcing in mice; this effect was relayed by their projections to septal GLU neurons. SuM neurons were active during exploration and approach behavior and diminished activity during sucrose consumption. Consistently, inhibition of SuM neurons disrupted approach responses, but not sucrose consumption. Such functions are similar to those of mesolimbic dopamine neurons. Indeed, the stimulation of SuM-to-septum GLU neurons and septum-to-ventral tegmental area (VTA) GLU neurons activated mesolimbic dopamine neurons. We propose that the supramammillo-septo-VTA pathway regulates arousal that reinforces and energizes behavioral interaction with the environment.

**[A Closer Look At Alcohol-Induced Changes In The Ghrelin System: Novel Insights From Preclinical And Clinical Data](#)** Deschaine SL, Farokhnia M, Gregory-Flores A, Zallar LJ, You ZB, Sun H, Harvey DM, Marchette RCN, Tunstall BJ, Mani BK, Moose JE, Lee MR, Gardner E, Akhlaghi F, Roberto M, Hougland JL, Zigman JM, Koob GF, Vendruscolo LF, Leggio L. *Addict Biol.* 2021: e13033.

Ghrelin is a gastric-derived peptide hormone with demonstrated impact on alcohol intake and craving, but the reverse side of this bidirectional link, that is, the effects of alcohol on the ghrelin system, remains to be fully established. To further characterize this relationship, we examined (1) ghrelin levels via secondary analysis of human laboratory alcohol administration experiments with heavy-drinking participants; (2) expression of ghrelin, ghrelin receptor, and ghrelin-O-acyltransferase (GOAT) genes (GHRL, GHSR, and MBOAT4, respectively) in post-mortem brain tissue from individuals with alcohol use disorder (AUD) versus controls; (3) ghrelin levels in Ghnr knockout and wild-type rats following intraperitoneal (i.p.) alcohol administration; (4) effect of alcohol on ghrelin secretion from gastric mucosa cells ex vivo and GOAT enzymatic activity in vitro; and (5) ghrelin levels in rats following i.p. alcohol administration versus a calorically



equivalent non-alcoholic sucrose solution. Acyl- and total-ghrelin levels decreased following acute alcohol administration in humans, but AUD was not associated with changes in central expression of ghrelin system genes in post-mortem tissue. In rats, alcohol decreased acyl-ghrelin, but not des-acyl-ghrelin, in both Ghrelin knockout and wild-type rats. No dose-dependent effects of alcohol were observed on acyl-ghrelin secretion from gastric mucosa cells or on GOAT acylation activity. Lastly, alcohol and sucrose produced distinct effects on ghrelin in rats despite equivalent caloric value. Our findings suggest that alcohol acutely decreases peripheral ghrelin concentrations in vivo, but not in proportion to alcohol's caloric value or through direct interaction with ghrelin-secreting gastric mucosal cells, the ghrelin receptor, or the GOAT enzyme.

### **Functional Connectivity Of Dorsolateral Prefrontal Cortex Predicts Cocaine Relapse: Implications For Neuromodulation Treatment**

Zhai T, Salmeron BJ, Gu H, Adinoff B, Stein EA, Yang Y. *Brain Commun.* 2021; 3(2): fcab120.

Relapse is one of the most perplexing problems of addiction. The dorsolateral prefrontal cortex is crucially involved in numerous cognitive and affective processes that are implicated in the phenotypes of both substance use disorders and other neuropsychiatric diseases and has become the principal site to deliver transcranial magnetic stimulation for their treatment. However, the dorsolateral prefrontal cortex is an anatomically large and functionally heterogeneous region, and the specific dorsolateral prefrontal cortex locus and dorsolateral prefrontal cortex-based functional circuits that contribute to drug relapse and/or treatment outcome remain unknown. We systematically investigated the relationship of cocaine relapse with functional circuits from 98 dorsolateral prefrontal cortex regions-of-interest defined by evenly sampling the entire surface of bilateral dorsolateral prefrontal cortex in a cohort of cocaine dependent patients ( $n = 43$ , 5 Fr) following a psychosocial treatment intervention. Cox regression models were utilized to predict relapse likelihood based on dorsolateral prefrontal cortex functional connectivity strength. Functional connectivity from only 3 of the 98 dorsolateral prefrontal cortex loci, one in the left and two in the right hemisphere, significantly predicted cocaine relapse with an accuracy of 83.9%, 84.6% and 85.4%, respectively. Combining all three loci significantly improved prediction validity to 87.5%. Protective and risk circuits related to these dorsolateral prefrontal cortex loci were identified that have previously been implicated to support 'bottom up' drive to use drug and 'top down' control over behaviour together with social emotional, learning and memory processing. Three dorsolateral prefrontal cortex-centric circuits were identified that predict relapse to cocaine use with high accuracy. These functionally distinct dorsolateral prefrontal cortex-based circuits provide insights into the multiple roles played by the dorsolateral prefrontal cortex in cognitive and affective functioning that affects treatment outcome. The identified dorsolateral prefrontal cortex loci may serve as potential neuromodulation targets to be tested in subsequent clinical studies for addiction treatment and as clinically relevant biomarkers of its efficacy. Zhai et al. identify three dorsolateral prefrontal cortex (dlPFC)-centric circuits that predict cocaine relapse with high accuracy, providing insights into the multiple roles of the dlPFC in brain functioning that affects treatment outcome and suggesting the dlPFC loci as potential neuromodulation targets for addiction treatment.

## **GRANTEE HONORS AND AWARDS**

### **Grantee Awards**

**Kathleen Brady, M.D., Ph.D.**, Medical University of South Carolina and a Principal Investigator (PI) of the NIDA Clinical Trials Network (CTN) Southern Consortium Node, was selected to receive the 2020 Julius Axelrod Award for Excellence in mentorship from the American College of Neuropsychopharmacology.

**Vince Calhoun, Ph.D.**, Professor, Georgia State University and **Russ Poldrack, Ph.D.**, Professor, Stanford University were named Fellows of the Organization of Human Brain Mapping (OHBM). The Fellow of OHBM distinction honors outstanding active members who have demonstrated academic and intellectual leadership in the disciplines represented by the Society over an extended period.

**Sarah Clingan, Ph.D.**, and **Zhe Fei, Ph.D.**, both of the NIDA CTN Greater Southern California Node, received the 2021 CPDD Early Career Investigator Award. **Sarah** is a postdoctoral research fellow at UCLA Integrated Substance Abuse Programs working with Yih-Ing Hser, Ph.D. and Larissa Mooney, M.D. **Zhe** is an Assistant Professor In-Residence in the Biostatistics Department at UCLA.

**Meaghan Creed, Ph.D.**, Assistant Professor, Washington University, St. Louis, was awarded the Freeman Prize for exceptional basic research from the Brain Behavior Research Foundation. She was recognized for her studies on optimizing neuromodulation therapies for disorders of reward processing, specifically for affective symptoms of chronic pain and substance use disorders.

**Gail D’Onofrio, M.D., M.S.**, Yale School of Medicine and one of the CTN New England Consortium Node PIs, received the [R. Brinkley Smithers Distinguished Scientist Award](#). The Award recognizes and honors an individual who has made highly meritorious contributions in advancing the scientific understanding of addiction, its prevention and treatment.

**Cassandra (Cassie) Gipson-Reichardt, Ph.D.**, Associate Professor, University of Kentucky College of Medicine, was awarded the 2021 Joseph Cochin Young Investigator Award for her contribution in preclinical addiction neuroscience focused on glutamatergic, cholinergic, ovarian hormone and neuroimmune mechanisms involved in nicotine use and opioid/stimulant polysubstance use in rodent models.

**Adam Gordon, M.D., M.P.H.**, University of Utah Health and a PI of the NIDA CTN Greater Intermountain Node, received the 2020 HSR&D Health System Impact Award. This award honors HSR&D- and QUERI-funded research that has had a direct and important impact on clinical practice or clinical policy within the Veterans Affairs (VA) health care system—and that has been successfully translated into VA’s policy or operations.

**Tom Gould, Ph.D.**, Professor, Penn State University, was elected President-Elect, Division on Psychopharmacology and Substance Use (Division 28) of the American Psychological Association 2022-2023.

**Yasmin Hurd, Ph.D.**, Professor, Icahn School of Medicine Mount Sinai, was invited to give the Presidential Plenary Lecture at the 2021 Annual Meeting of the International Cannabinoid Research Society.

**Larry Leeman, M.D., M.P.H.**, NIDA CTN investigator in the Southwest Node and professor in The University of New Mexico Department of Family and Community Medicine, received the 2021 Family Medicine Excellence in Education Award from the Society of Teachers of Family Medicine. The annual award recognizes a family physician educator who has demonstrated excellence in teaching, curriculum development, mentoring, research, or leadership in education at regional or national levels.

**Trudy Mackay, Ph.D.**, Professor, Clemson University, was elected to the American Philosophical Society.

**Klaus Miczek, Ph.D.**, Professor, Tufts University, was awarded the MED Associates Brady-Schuster Award. The MED Associates Brady-Schuster Award honors a mid-career or senior scientist who conducts outstanding research that underscores the fundamental importance of behavioral science to psychopharmacology or substance abuse.

**Madhavan Nair, Ph.D.**, Chair and Professor of the Department of Immunology at Florida International University, was named a Fellow of the National Academy of Inventors for his work in nanotechnology and HIV research.

**Richard Saitz, M.D., M.P.H.**, Boston University Medicine and one of the NIDA CTN New England Consortium Node PIs, received the [ASAM Educator of the Year Award](#). The ASAM Educator of the Year Award recognizes and honors an educator who has made outstanding contributions to ASAM's addiction medicine education.

**Andrew Saxon, M.D.**, University of Washington and investigator in the NIDA CTN Pacific Northwest Node, is one of six recipients of the [2021 Nyswander/Dole "Marie" Award](#). Named after Vincent Dole, M.D., and Marie Nyswander, M.D., who founded methadone maintenance treatment in the 1960s, the award is the preeminent recognition in the field of opioid use disorder treatment.

**Talia Swartz, M.D., Ph.D.**, Assistant Professor, Icahn School of Medicine Mount Sinai, was awarded a Junior Faculty Research Award from the Infectious Diseases Society of New York.

**Jeanette M. Tetrault, M.D.**, Yale School of Medicine and one of the NIDA CTN New England Consortium Node PIs, received the [ASAM Training Directors Award](#). This award recognizes and honors an individual who has demonstrated outstanding training in the evaluation, treatment, research and teaching of substance use disorders.

## **STAFF HONORS AND AWARDS**

**Carlos Blanco, M.D., Ph. D., M.S.**, Director, DESPR, was the recipient of the 2021 Senior Health Services Award of the American Psychiatric Association.

**Tisha Wiley, Ph.D.**, Chief, Services Research Branch, was one of 12 U.S. Government employees selected for the 2021 Arthur S. Flemming Award. The Flemming award is a prestigious award established in 1948 to recognize outstanding public service. Tisha was recognized for her work leading the Justice Community Opioid Innovation Network (JCOIN).

## STAFF CHANGES

### New Appointments

**Iván Montoya, M.D., M.P.H.**, is serving as Acting Director for the DTMC. Iván is a psychiatrist and epidemiologist who specializes in the development of therapeutics for Substance Use Disorders (SUDs). He provides programmatic oversight for grants and contracts in DTMC and manages activities and resources of the Division involved in the research of new therapeutics and the medical consequences of SUDs. Iván also provides medical oversight to grants and contracts, as well as supports the development and implementation of policies and procedures for data and medical safety monitoring of clinical trials. He leads the NIH's Helping to End Addiction Long Term (HEAL) Initiative to develop new interventions to prevent and treat opioid use disorders and overdose. Previous experience includes seven years as a clinical investigator in the Intramural Research Program of NIDA, and four years in academia. Iván joined NIDA Extramural Research Program in December of 1999 and has served as the Deputy Director, DTMC.

**Jane B. Acri, Ph.D.**, is serving as Acting Deputy Director for DTMC. Jane was Chief of the Medication Discovery and Toxicology Branch from 2009 to 2021 and Director of the Addiction Treatment Discovery Program from 1998 to 2010. She received her doctoral degree from the Uniformed Services University of the Health Sciences where she conducted pre-clinical and clinical studies on the effects of nicotine. She joined the NIDA Intramural Research Program in 1992 and the Extramural Program in 1996.

**Nathan Appel, Ph.D.**, is serving as Acting Branch Chief for the Medications Discovery and Toxicology Branch, DTMC. He oversees the Addiction Treatment Discovery Program, directs the Division's Toxicology Program and serves as project officer/scientist on related contracts and grants. Nathan joined the NIDA Extramural Program in 1999 after eight years of previous experience at the U.S. Food and Drug Administration (FDA). His doctorate degree is from the University of Toronto and he holds B.A. and M.S. degrees from Rutgers University.

**Olivier Berton, Ph.D.**, has been appointed Acting Chief of the Integrative Neuroscience Branch (INB) as of August 1, 2021. He is a Program Officer in INB who oversees a grant portfolio that encompasses basic research on cells & circuits in models of addiction and reward, with an emphasis on projects employing genetics or neuro-engineering approaches to interrogate and modulate circuit function. Olivier also serves as a co-Lead of the BRAIN Initiative Team A Cells and Circuits, where he manages a portfolio of grants pertaining to the cell census network, integrated circuits analyses of and tool dissemination efforts.

### New Staff

**Jenny Browning, Ph.D.**, has joined DER's Scientific Review Branch. She is a neuroscientist with 15 years of research experience. Before joining NIDA, Jenny was serving as an SRO with CSR where she managed the Chronic Dysfunction and Integrative Neurodegeneration study section. She received her Ph.D. in neuroscience from Washington State University. Her doctoral research focused on investigating the role of paraventricular nucleus of the thalamus in drug addiction

circuitry. Subsequently, she conducted her postdoctoral studies in pharmacology at University of Maryland Cellular and Integrative Neuroscience Training Program where she investigated the use of hormones (estrogen and progesterone) against methamphetamine-induced drug withdrawal. Before joining NIH, Jenny was a scientist with the Department of Brain Trauma and Neuroprotection at Walter Reed Army Institute of Research where she developed animal models for severe brain injury.

**Hashim Dasti** joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on August 1, 2021.

**Rebekah Feng, Ph.D.**, has joined DER's Scientific Review Branch. Rebekah is a trained neuroscientist with over nine years of biomedical, biobehavioral, and clinical research experience. She obtained her Ph.D. in Neuroscience from Georgetown University in 2012. She subsequently worked as a postdoctoral fellow at the Max Planck Institute in Germany. Her postdoctoral work focused on mechanisms of protein misfolding mediated toxicity in neurons and embryonic stem cells in neurodegenerative diseases. Rebekah subsequently joined National Institute of Nursing Research (NINR) as a Clinical Research Specialist and within a year was promoted to a Research Fellow (Title 42 FTE) position. In this role she investigated cancer-related fatigue and cognitive impairment and served as an Associate Investigator for several clinical studies for NINR, NINDS, and the Clinical Center.

**Christopher Halstead** joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on July 4, 2021. Christopher comes to NIDA from a position with the Department of Energy.

**Leslie Hickman** joined NIDA's Grants Management Branch on May 10, 2021. Leslie is a Grants Management Officer with close to twenty years of NIH grants management experience. Leslie has worked at NICHD, NIDCD and most recently at NCI. Leslie has a Bachelor of Mathematics from Hood College.

**Nic Johnston** joined the office of the Director of NIDA's DNB as a Health Program Specialist on July 18, 2021. Nic comes to NIDA from a position in the private sector.

**Stacy Lu** joined NIDA in August 2021 and will serve as a health and science writer within the Content Management team in the Communications Branch. Stacy is a seasoned writer, and has written about psychology, neuroscience, medicine, and public health for numerous publications and organizations as staff or a steady freelancer, including the *New York Times*, NBC, ABC, Forbes, UNICEF, TEDMED, and the Robert Wood Johnson Foundation. She has a particular interest in neuropsychology, after getting to know this space as a writer for the American Psychological Association. She has an M.S. in journalism from Columbia University.

**Jeffrey Moore** joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on July 4, 2021. Jeffrey comes to NIDA from a position with the Private sector.

**Allison Moyal** joined NIDA's Grants Management Branch on May 10, 2021. Allison is a grants management specialist, and worked at NHLBI prior to joining NIDA. Prior to joining Grants

Management, Allison worked in NIH OD OMA for over ten years in the Division of Program Integrity. Allison has a bachelor's degree from Virginia Polytechnic Institute and State University.

**Janani Prabhakar, Ph.D.**, joined the Behavioral Cognitive Neuroscience Branch as a Program Officer for the HEALthy Brain and Child Development Study and to develop a developmentally focused portfolio within the Behavioral and Cognitive Neuroscience branch. Dr. Prabhakar received her Ph.D. from Rutgers University, New Brunswick, NJ, and completed a postdoctoral fellowship at the University of California, Davis. Her research career examined the neurocognitive mechanisms that underlie memory and future-oriented processes in early childhood. She is actively involved in multiple trans-NIH initiatives focused on child development, including the Environmental Influences on Child Health Outcomes (ECHO) program and NIDA's Adolescent Brain Cognitive Development (ABCD) study.

**Samson Shaifaraw** joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on July 4, 2021. Samson comes to NIDA from a position in the private sector.

**Morgen Slager** joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on August 29, 2021.

**Sarah Steverman, Ph.D.**, joined DESPR in August 2021.

**Tiffany Stone** joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on July 4, 2021. Tiffany comes to NIDA from a position with Re/Max Allegiance.

**Rachel Tillage, Ph.D.**, has joined NIDA in the Office of Science Policy and Communications as an American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow. Rachel completed her Ph.D. in Neuroscience at Emory University in 2020 where her dissertation work focused on the neural circuitry underlying stress-related disorders. During her graduate work, Rachel gained experience in science policy, advocacy, and communication through leading the Emory Science Advocacy Network and participating in science outreach events. Rachel obtained her B.S. in Biology from the University of Richmond.

**Jeremy Tran** joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on April 11, 2021. Jeremy comes to NIDA from a position with the Department of Defense.

**Nichole Wise** joined NIDA's Office of Management's Administrative Management Branch as an Administrative Officer on July 18, 2021.

**Kwesi Wright** joined DER's Grants Management Branch as a Grants Management Specialist on September 26, 2021. Kwesi comes to NIDA from NIBIB.

**Troy J. Zarcone, Ph.D.**, has joined the Division of Extramural Research as the Director of the Office of Extramural Policy and Review. Troy received his Ph.D. in Psychology from the University of Florida where he studied Behavioral Pharmacology. During his postdoctoral fellowship, Troy conducted basic research on addiction at the Division of Behavioral Biology, Department of Psychiatry and Behavioral Sciences at Johns Hopkins School of Medicine. He expanded his basic research into behavioral genetics at the University Kansas before branching into

behavioral toxicology at the University of Rochester School of Medicine and Dentistry. Troy joined NIH at NIAAA in the Office of Science Policy and Communication as a Health Science Administrator and was the Editor-in-Chief of the institute's journal "Alcohol Research: Current Reviews".

### **Staff Departures**

**Ram Arudchandran, Ph.D.**, Health Scientist Administrator in the Office of the Director's Translational Research Branch, left NIDA on May 22, 2021, for a position with NINDS.

**David Bochner, Ph.D.**, a Health Science Policy Analyst in OSPC's Science Policy Branch, left NIDA on July 3, 2021, for a position at NIGMS.

**Minki Chatterji, Ph.D.**, DESPR, moved to NIA in July 2021.

**Jennifer Cho**, a Grants Management Specialist in DER's Grants Management Branch, left NIDA on June 5, 2021, for a position with NCI.

**Erin Dwyer**, a Contract Specialist in the Office of Management's Blue Branch, left NIDA on June 19, 2021, for a position at NCI.

**Tara Garwood**, a Social Media Strategist in OSPC's Communications Branch, left NIDA in August 2021 for a position in video production outside the government.

**Ivan Navarro, Ph.D.**, a Health Scientist Administrator from DER's Scientific Review Branch, left NIDA on April 10, 2021, for a position at NIMHD.

**Kurt Rasmussen, Ph.D.**, DTMC, has accepted a position with Delix Therapeutics as their Chief Scientific Officer. Kurt was the Director of DTMC for 3 years.

**Tracey Waldeck, Ph.D.**, a Supervisory Health Scientist Administrator from DER's Office of Extramural Policy and Review, left NIDA on April 24, 2021 for a position at NIMH.

### **Retirements**

**Roger Sorensen, Ph.D.**, Chief of the Integrative Neuroscience Branch (INB) retired July 31, 2021. Roger joined NIDA in 2007. Under his leadership, INB developed a rich and diverse research portfolio focused on neuronal excitability, synaptic plasticity, homeostasis, neural network interactions and the role of non-neuronal cells in the processes underlying substance use disorders and addiction. He assured that INB supported a strong innovative research program focused on elucidating the intersection between HIV and addictive drugs. Roger was particularly passionate about training and career development of the upcoming generation of neuroscientists and he managed the Pathways to Independence Award [K99/R00] program in basic research. He also served as co-Chair of the NIDA-NIAAA Neuroscience Workgroup that is responsible for the annual NIDA-NIAAA Frontiers in Addiction Research Mini-convention. Roger will serve as a retired annuitant to assist in the transition to the next Branch Chief.





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