DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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Director
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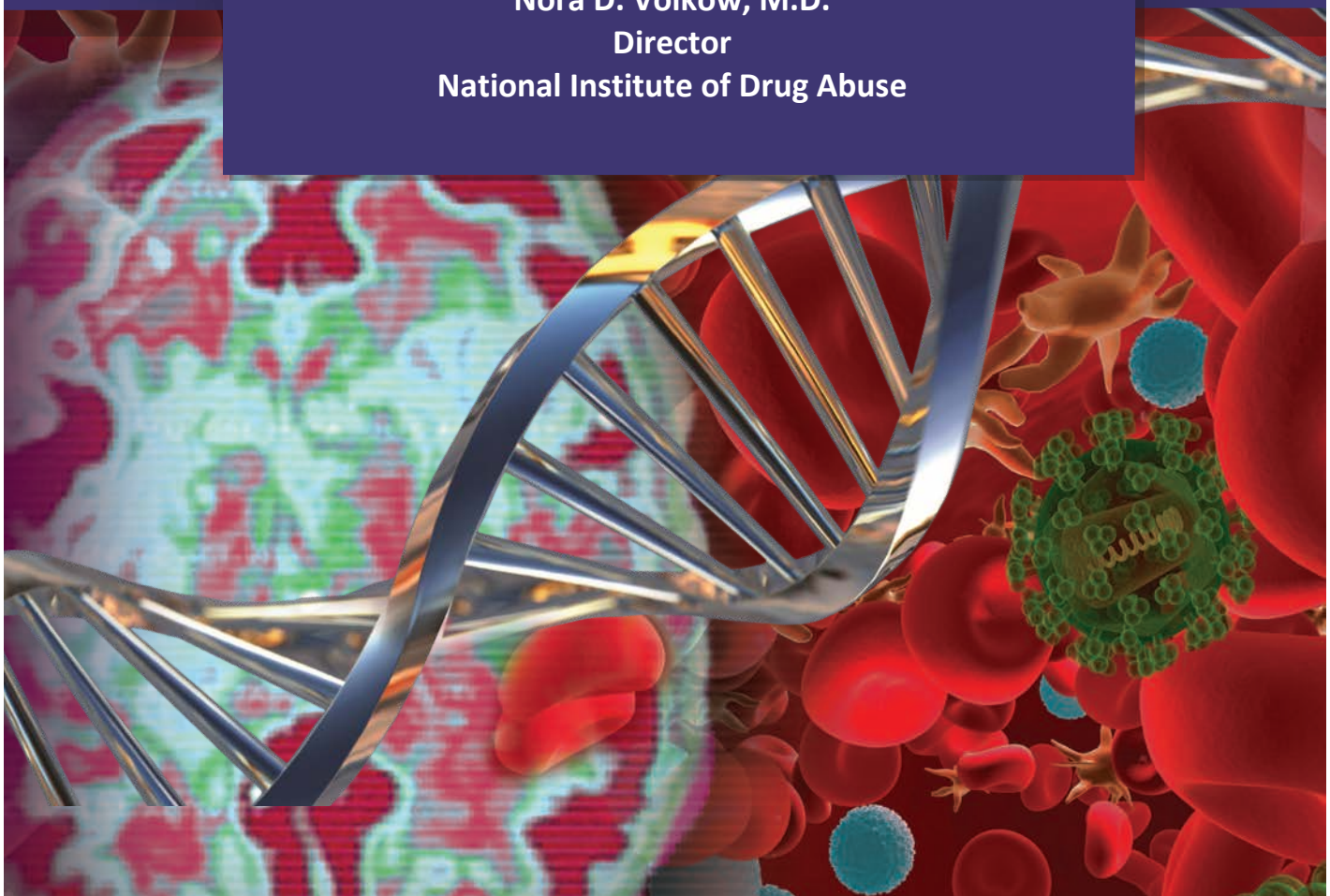

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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Structure Of A Hallucinogenic-Activated Gq-Coupled 5-HT_{2A} Serotonin Receptor Kim K, Che T, Panova O, DiBerto JF, Lyu J, Krumm BE, Wacker D, Robertson MJ, Seven AB, Nichols DE, Shoichet BK, Skiniotis G, Roth BL. Cell. 2020; 182: 1574-1588.
Hallucinogens like lysergic acid diethylamide (LSD), psilocybin, and substituted N-benzyl phenylalkylamines are widely used recreationally with psilocybin being considered as a therapeutic for many neuropsychiatric disorders including depression, anxiety, and substance abuse. How psychedelics mediate their actions— both therapeutic and hallucinogenic—are not understood, although activation of the 5-HT2A serotonin receptor (HTR2A) is key. To gain molecular insights into psychedelic actions, we determined the active-state structure of HTR2A bound to 25-CN-NBOH—a prototypical hallucinogen—in complex with an engineered Gaq heterotrimer by cryoelectron microscopy (cryo-EM). We also obtained the X-ray crystal structures of HTR2A complexed with the arrestin-biased ligand LSD or the inverse agonist methiothepin. Comparisons of these structures reveal determinants responsible for HTR2A-Gaq protein interactions as well as the conformational rearrangements involved in active-state transitions. Given the potential therapeutic actions of hallucinogens, these findings could accelerate the discovery of more selective drugs for the treatment of a variety of neuropsychiatric disorders.

Cocaine And Sucrose Rewards Recruit Different Seeking Ensembles In The Nucleus Accumbens Core Bobadilla AC, Dereschewitz E, Vaccaro L, Heinsbroek JA, Scofield MD, Kalivas PW. Mol Psychiatry. 2020; 25(12): 3150-3163.
Poorly regulated reward seeking is a central feature of substance use disorder. Recent research shows that rewarding drug-related experiences induce synchronous activation of a discrete number of neurons in the nucleus accumbens that are causally linked to reward-related contexts. Here we comprehensively characterize the specific ensemble of neurons built through experience that are linked to seeking behavior. We additionally address the question of whether or not addictive drugs usurp the neuronal networks recruited by natural rewards by evaluating cocaine- and sucrose-associated ensembles within the same mouse. We used $Fos^{CreERT2/+}$/Ai14 transgenic mice to tag cells activated by and potentially encoding cocaine and sucrose seeking. We tagged ~1% of neurons in the core subregion of the accumbens (NAcore) activated during cue-induced seeking for cocaine or sucrose. The majority of tagged cells in the seeking ensembles were D1-MSNs, and specifically activated during seeking, not during extinction or when mice remained in the home cage. To compare different reward-specific ensembles within the same mouse, we used a dual cocaine and sucrose self-administration protocol allowing reward-specific seeking. Using this model, we found ~70% distinction between the cells constituting the cocaine- compared to the sucrose-seeking ensemble. Establishing that cocaine recruits an ensemble of NAcore neurons largely distinct from neurons recruited into an ensemble coding for sucrose seeking suggest a finely tuned specificity of ensembles. The findings allow further exploration of the mechanisms that transform reward-based positive reinforcement into maladaptive drug seeking.

Neuroadaptations In The Dorsal Hippocampus Underlie Cocaine Seeking During Prolonged Abstinence Werner CT, Mitra S, Auerbach BD, Wang Z-J, Martin JA, Stewart AF, Gobira PH, Iida

M, An C, Cobb MM, Caccamise A, Salvi RJ, Neve RL, Gancarz AM, Dietz DM. Proc. Natl. Acad. Sci. U.S.A. 2020; 117(42): 26460-26469.
Relapse vulnerability in substance use disorder is attributed to persistent cue-induced drug seeking that intensifies (or "incubates") during drug abstinence. Incubated cocaine seeking has been observed in both humans with cocaine use disorder and in preclinical relapse models. This persistent relapse vulnerability is mediated by neuroadaptations in brain regions involved in reward and motivation. The dorsal hippocampus (DH) is involved in context-induced reinstatement of cocaine seeking but the role of the DH in cocaine seeking during prolonged abstinence has not been investigated. Here we found that transforming growth factor-β (TGF-β) superfamily member activin A is increased in the DH on abstinence day (AD) 30 but not AD1 following extended access cocaine self-administration compared to saline controls. Moreover, activin A does not affect cocaine seeking on AD1 but regulates cocaine seeking on AD30 in a bidirectional manner. Next, we found that activin A regulates phosphorylation of NMDA receptor (NMDAR) subunit GluN2B and that GluN2B-containing NMDARs also regulate expression of cocaine seeking on AD30. Activin A and GluN2B-containing NMDARs have both previously been implicated in hippocampal synaptic plasticity. Therefore, we examined synaptic strength in the DH during prolonged abstinence and observed an increase in moderate long-term potentiation (LTP) in cocaine-treated rats compared to saline controls. Lastly, we examined the role of DH projections to the lateral septum (LS), a brain region implicated in cocaine seeking and found that DH projections to the LS govern cocaine seeking on AD30. Taken together, this study demonstrates a role for the DH in relapse behavior following prolonged abstinence from cocaine self-administration.

Valuation Of Peers' Safe Choices Is Associated With Substance-Naivete In Adolescents Chung D, Orloff MA, Lauharatanahirun N, Chiu PH, King-Casas B. Proc. Natl. Acad. Sci. U.S.A. 2020; 117 (50): 31729-31737.
Social influences on decision-making are particularly pronounced during adolescence and have both protective and detrimental effects. To evaluate how responsiveness to social signals may be linked to substance use in adolescents, we used functional neuroimaging and a gambling task in which adolescents who have and have not used substances (substance-exposed and substance-naïve, respectively) made choices alone and after observing peers' decisions. Using quantitative model-based analyses, we identify behavioral and neural evidence that observing others' safe choices increases the subjective value and selection of safe options for substance-naïve relative to substance-exposed adolescents. Moreover, the effects of observing others' risky choices do not vary by substance exposure. These results provide neurobehavioral evidence for a role of positive peers (here, those who make safer choices) in guiding adolescent real-world risky decision-making.

A Non-Hallucinogenic Psychedelic Analogue With Therapeutic Potential Cameron LP, Tombari RJ, Lu J, Pell AJ, Hurley ZQ, Ehinger Y, Vargas MV, McCarroll MN, Taylor JC, Myers-Turnbull D, Liu T, Yaghoobi B, Laskowski LJ, Anderson EI, Zhang G, Viswanathan J, Brown BM, Tjia M, Dunlap LE, Rabow ZT, Fiehn O, Wulff H, McCorvy JD, Lein PJ, Kokel D, Ron D, Peters J, Zuo Y, Olson DE. Nature. 2021; 589(7842): 474-479.
The psychedelic alkaloid ibogaine has anti-addictive properties in both humans and animals. Unlike most medications for the treatment of substance use disorders, anecdotal reports suggest that ibogaine has the potential to treat addiction to various substances, including opiates, alcohol and psychostimulants. The effects of ibogaine—like those of other psychedelic compounds—are long-

lasting, which has been attributed to its ability to modify addiction-related neural circuitry through the activation of neurotrophic factor signaling. However, several safety concerns have hindered the clinical development of ibogaine, including its toxicity, hallucinogenic potential and tendency to induce cardiac arrhythmias. Here we apply the principles of function-oriented synthesis to identify the key structural elements of the potential therapeutic pharmacophore of ibogaine, and we use this information to engineer tabernanthalog—a water-soluble, non-hallucinogenic, non-toxic analogue of ibogaine that can be prepared in a single step. In rodents, tabernanthalog was found to promote structural neural plasticity, reduce alcohol- and heroin-seeking behaviour, and produce antidepressant-like effects. This work demonstrates that, through careful chemical design, it is possible to modify a psychedelic compound to produce a safer, non-hallucinogenic variant that has therapeutic potential.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Clinical Outcomes Of A COVID-19 Vaccine: Implementation Over Efficacy Paltiel AD, Schwartz JL, Zheng A, Walensky RP. Health Aff (Millwood). 2020; 101377 hlthaff202002054.
The global effort to develop a coronavirus disease 2019 (COVID-19) vaccine is likely to soon produce one or more authorized vaccines. We examine how different definitions and thresholds of vaccine efficacy, coupled with different levels of implementation effectiveness and background epidemic severity, translate into outcomes including cumulative infections, hospitalizations, and deaths. Using a mathematical simulation of vaccination, we find that factors related to implementation will contribute more to the success of vaccination programs than a vaccine's efficacy as determined in clinical trials. The benefits of a vaccine will decline substantially in the event of manufacturing or deployment delays, significant vaccine hesitancy, or greater epidemic severity. Our findings demonstrate the urgent need for health officials to invest greater financial resources and attention to vaccine production and distribution programs, to redouble efforts to promote public confidence in COVID-19 vaccines, and to encourage continued adherence to other mitigation approaches, even after a vaccine becomes available.

Longitudinal Analysis Of Associations Between Reasons for Electronic Cigarette Use And Change In Smoking Status Among Adults In The Population Assessment Of Tobacco And Health Study Soule EK, Plunk AD, Harrell PT, Hayes RB, Edwards KC. Nicotine Tob Res. 2020; 22(5): 663-671.
Introduction: Electronic cigarette (ECIG) use and changes in cigarette smoking status may be influenced by self-reported reasons for using ECIGs. Methods: We analyzed adult current and former cigarette smokers who were also current or former ECIG users at wave 1 (n = 3044) using wave 1 and wave 2 Population Assessment of Tobacco and Health Study data (2013–2015). Prevalence of reporting 13 reasons for ECIG use at wave 1 was examined and weighted logistic regressions were conducted predicting smoking status changes from wave 1 to wave 2. Results: Reasons for ECIG use ranged from 18.1% (people in the media or public figures use them) to 82.5% (they might be less harmful to people around me than cigarettes). From wave 1 to wave 2, 27.2% of former smokers (n = 249) became current smokers and 11.6% of current smokers (n = 246) became former smokers. Among wave 1 former smokers, using ECIGs because of the availability of flavors (AOR = 0.57, 95% CI = 0.39–0.85) or because they don't smell (AOR = 0.64, 95% CI = 0.42–0.97) was associated with lower odds of relapse to smoking, but using ECIGs because using them helps people quit smoking (AOR = 1.55, 95% CI = 1.01–2.38) was associated

with greater odds of relapse. Among wave 1 current smokers, using ECIGs because they can be used where smoking is not allowed (AOR = 0.56, 95% CI = 0.38–0.85) was associated with reduced odds of quitting cigarettes. Conclusions: Some reasons for ECIG use are associated with changes in self-reported smoking status. Researchers should examine ECIG user characteristics when assessing associations between ECIG use and smoking status transitions. Implications: Given that certain reasons for ECIG use, such as using ECIGs in locations are where smoking is not allowed, may inhibit smoking reduction, policies may be developed to prevent ECIG use in locations where smoking is banned. In addition, because certain reasons for ECIG use may aid in relapse prevention, such as availability of desired flavors, efforts should be made to identify ECIG device characteristics that are appealing to smokers but not youth or nontobacco users. These results provide support for future research on reasons for ECIG use to inform regulatory policies.

Treatment Of Opioid Use Disorder Among Commercially Insured Patients In The Context Of The COVID-19 Pandemic Huskamp HA, Busch AB, Uscher-Pines L, Barnett ML, Riedel L, Mehrotra A. JAMA. 2020; 324(23): 2440-2442.
This study uses commercial and Medicare Advantage claims data to compare medication fills, outpatient visits, and urine tests for opioid use disorder in January-May 2020 vs 2019.

Racial Disparities In Overdose Prevention Among People Who Inject Drugs Dayton L, Tobin K, Falade-Nwulia O, Davey-Rothwell M, Al-Tayyib A, Saleem H, Latkin C. J Urban Health. 2020; 97(6): 823-830. *No abstract available*

Marijuana Legalization And Youth Marijuana, Alcohol, And Cigarette Use And Norms Bailey JA, Epstein M, Roscoe JN, Oesterle S, Kosterman R, Hill KG. Am J Prev Med. 2020; 59(3): 309-316.
Introduction: Rates of adolescent substance use have decreased in recent years. Knowing whether nonmedical marijuana legalization for adults is linked to increases or slows desirable decreases in marijuana and other drug use or pro-marijuana attitudes among teens is of critical interest to inform policy and promote public health. This study tests whether nonmedical marijuana legalization predicts a higher likelihood of teen marijuana, alcohol, or cigarette use or lower perceived harm from marijuana use in a longitudinal sample of youth aged 10-20 years. **Methods:** Data were drawn from the Seattle Social Development Project-The Intergenerational Project, an accelerated longitudinal study of youth followed both before (2002-2011) and after nonmedical marijuana legalization (2015-2018). Analyses included 281 youth surveyed up to 10 times and living in a state with nonmedical marijuana legalization between 2015 and 2018 (51% female; 33% white, 17% African American, 10% Asian/Pacific Islander, and 40% mixed race or other). **Results:** Multilevel modeling in 2019 showed that nonmedical marijuana legalization predicted a higher likelihood of self-reported past-year marijuana (AOR=6.85, p=0.001) and alcohol use (AOR 3.38, p=0.034) among youth when controlling birth cohort, sex, race, and parent education. Nonmedical marijuana legalization was not significantly related to past-year cigarette use (AOR=2.43, p=0.279) or low perceived harm from marijuana use (AOR=1.50, p=0.236) across youth aged 10-20 years. **Conclusions:** It is important to consider recent broad declines in youth substance use when evaluating the impact of nonmedical marijuana legalization. States that legalize nonmedical marijuana for adults should increase resources for the prevention of underage marijuana and alcohol use.

An Evaluation Of Assumptions Underlying Respondent-Driven Sampling And The Social Contexts Of Sexual And Gender Minority Youth Participating In HIV Clinical Trials In The United States Wirtz AL, Iyer J, Brooks D, Hailey-Fair K, Galai N, Beyrer C, Celentano D, Arrington-Sanders R. medRxiv. 2020; 2020.11.02.20222489.
Introduction: Respondent-driven sampling has been an effective sampling strategy for HIV research in many settings but has had limited success among some youth in the United States. We evaluated a modified RDS approach for sampling Black and Latinx sexual and gender minority youth (BLSGMY) and evaluates how lived experiences and social contexts of BLSGMY youth may impact traditional RDS assumptions. **Methods:** RDS was implemented in three cities to engage BLSGMY in HIV prevention or care intervention trials. RDS was modified to include targeted seed recruitment from venues, internet, and health clinics, and provided options for electronic or paper coupons. Qualitative interviews were conducted among a sub-sample of RDS participants to explore their experiences with RDS. Interviews were coded using RDS assumptions as an analytic framework. **Results:** Between August 2017 and October 2019, 405 participants were enrolled, 1,670 coupons were distributed, with 133 returned, yielding a 0.079 return rate. The maximum recruitment depth was 4 waves among seeds that propagated. Self-reported median network size was 5 (IQR 2-10) and reduced to 3 (IQR 1-5) when asked how many peers were seen in the past 30 days. Qualitative interviews (n=27) revealed that small social networks, peer trust, and targeted referral of peers with certain characteristics challenged network, random recruitment, and reciprocity assumptions of RDS. HIV stigma and research hesitancy were barriers to participation and peer referral. **Conclusions:** Small social networks and varying relationships with peers among BLSGMY challenge assumptions that underlie traditional RDS. Modified RDS approaches, including those that incorporate social media, may support recruitment for community-based research but may challenge assumptions of reciprocal relationships. Research hesitancy and situational barriers must be addressed in recruitment and study designs.

"That Person Stopped Being Human": Intersecting HIV And Substance Use Stigma Among Patients And Providers In South Africa Regenauer KS, Myers B, Batchelder AW, Magidson JF. Drug Alcohol Depend. 2020; 216: 108322.
Background: South Africa has the largest number of people living with HIV in the world. Concurrently, problematic alcohol and other drug use (AOD) is prevalent in the country and associated with poor HIV treatment outcomes. Further, the high rates of stigma surrounding HIV and AOD contribute to poor HIV outcomes. Yet, how HIV stigma and AOD stigma together may affect HIV care has not been extensively studied in this context. Thus, we explored HIV and AOD providers' and patients' experiences of HIV and AOD stigma. **Methods:** We conducted 30 semi-structured interviews with patients living with HIV who were struggling with HIV medication adherence and problematic AOD use (n = 19), and providers involved in HIV or AOD treatment (n = 11) in Cape Town, South Africa to assess how HIV and AOD stigmas manifest and relate to HIV care. **Findings:** Two main themes around the intersection of HIV and AOD and their related stigmas were identified: (1) how patients use AOD to cope with HIV stigma; and (2) enacted/anticipated AOD stigma from HIV care providers, which acts as a barrier to HIV care. **Conclusions:** Intersecting HIV and AOD stigmas exist at multiple levels and increase barriers to HIV care in this setting. Accordingly, it is important that future interventions address both these stigmas at multiple levels.

TREATMENT RESEARCH

Subtherapeutic Acetazolamide Doses As A Noninvasive Method For Assessing Medication Adherence Hampson AJ, Schroeder JR, Ellefsen KN, Yammine L, Epstein DH, Preston KL, Huestis MA, Verrico CD. Clin Pharmacol Ther. 2020;108(6): 1203-1212.
Adherence monitoring is a vital component of clinical efficacy trials, as the regularity of medication consumption affects both efficacy and adverse effect profiles. Pill-counts do not confirm consumption, and invasive plasma assessments can only assist post hoc assessments. We previously reported on the pharmacokinetics of a potential adherence marker to noninvasively monitor dosage consumption during a trial without breaking a blind. We reported that consumption cessation of subtherapeutic 15 mg acetazolamide (ACZ) doses showed a predictable urinary excretion decay that was quantifiable for an extended period. The current study describes the clinical implementation of 15 mg ACZ doses as an adherence marker excipient in distinct cohorts taking ACZ for different "adherence" durations. We confirm that ACZ output did not change (accumulate) during 18-20 days of adherence and developed and assessed urinary cutoffs as nonadherence indicators. We demonstrate that whereas an absolute concentration cutoff (989 ng/mL) lacked sensitivity, a creatinine normalized equivalent (1,376 ng/mg ACZ) was highly accurate at detecting nonadherence. We also demonstrate that during nonadherent phases of three trials, creatinine-normalized urinary ACZ elimination was reproducible within and across trials with low variability. Excretion was first order, with a decay half-life averaging ~ 2.0 days. Further, excretion remained quantifiable for 14 days, providing a long period during which the date of last consumption might be determined. We conclude that inclusion of 15 mg ACZ as a dosage form adherence marker excipient, provides a reliable and sensitive mechanism to confirm medication consumption and detect nonadherence during clinical efficacy trials.

Novel Vaccine That Blunts Fentanyl Effects And Sequesters Ultrapotent Fentanyl Analogues Barrientos RC, Bow EW, Whalen C, Torres OB, Sulima A, Beck Z, Jacobson AE, Rice KC, Matyas GR. Mol Pharm. 2020; 17(9): 3447-3460.
Active immunization is an emerging potential modality to combat fatal overdose amid the opioid epidemic. In this study, we described the design, synthesis, formulation, and animal testing of an efficacious vaccine against fentanyl. The vaccine formulation is composed of a novel fentanyl hapten conjugated to tetanus toxoid (TT) and adjuvanted with liposomes containing monophosphoryl lipid A adsorbed on aluminum hydroxide. The linker and hapten N-phenyl-N-(1-(4-(3-(tritylthio)propanamido)phenethyl)piperidin-4-yl)propionamide were conjugated sequentially to TT using amine-N-hydroxysuccinimide-ester and thiol-maleimide reaction chemistries, respectively. Conjugation was facile, efficient, and reproducible with a protein recovery of >98% and a hapten density of 30-35 per carrier protein molecule. In mice, immunization induced high and robust antibody endpoint titers in the order of >106 against the hapten. The antisera bound fentanyl, carfentanil, cyclopropyl fentanyl, para-fluorofentanyl, and furanyl fentanyl in vitro with antibody-drug dissociation constants in the range of 0.36-4.66 nM. No cross-reactivity to naloxone, naltrexone, methadone, or buprenorphine was observed. In vivo, immunization shifted the antinociceptive dose-response curve of fentanyl to higher doses. Collectively, these preclinical results showcased the desired traits of a potential vaccine against fentanyl and demonstrated the feasibility of immunization to combat fentanyl-induced effects.

Evaluation Of The Rewarding Effects Of Mitragynine And 7-hydroxymitragynine In An Intracranial Self-stimulation Procedure In Male And Female Rats

Behnood-Rod A, Chellian R, Wilson R, Hiranita T, Sharma A, Leon F, McCurdy CR, McMahon LR, Bruijnzeel AW. Drug Alcohol Depend. 2020; 215: 108235.

Kratom (Mitragyna speciosa Korth) has been used in Southeast Asia for hundreds of years to increase energy, for relaxation, and to diminish opioid withdrawal. Kratom use has recently spread to Western countries. Kratom could potentially be used for the treatment of opioid withdrawal and pain, but more insight is needed into its abuse potential. Therefore, we investigated the rewarding properties of the primary kratom alkaloid mitragynine and its active metabolite 7-hydroxymitragynine, and morphine as a reference drug in male and female rats. These compounds have agonist activity at mu-opioid receptors. The compounds were tested in an intracranial self-stimulation (ICSS) procedure, which allows for the evaluation of the rewarding/aversive and sedative effects of drugs. Rewarding doses of drugs decrease the brain reward thresholds, and aversive drug doses have the opposite effect. Mitragynine, 7-hydroxymitragynine, and morphine affected the brain reward thresholds. A high dose of 7-hydroxymitragynine (3.2 mg/kg) increased the brain reward thresholds, whereas an intermediate dose of morphine (10 mg/kg) decreased the reward thresholds. 7-Hydroxymitragynine and morphine affected the response latencies. Five mg/kg of morphine increased response latencies. 7-Hydroxymitragynine tended to increase the response latencies, but the post hoc analyses did not reveal a significant effect. There were no sex differences in the effects of mitragynine, 7-hydroxymitragynine, and morphine on the reward thresholds and the response latencies. These initial findings indicate that mitragynine and 7-hydroxymitragynine are not rewarding in the ICSS procedure. The present results suggest that these kratom alkaloids do not have abuse potential.

The Kappa-Opioid Receptor Agonist, Nalfurafine, Blocks Acquisition Of Oxycodone Self-administration And Oxycodone's Conditioned Rewarding Effects In Male Rats

Zamarripa CA, Patel TR, Williams BC, Pareek T, Schrock HM, Prisinzano TE, Freeman KB. Behav Pharmacol. 2020; 31(8): 792-797.

Mu-opioid receptor (MOR) agonists are highly efficacious for the treatment of pain but have significant abuse liability. Recently, we reported that nalfurafine, when combined with oxycodone at a certain ratio, reduced the reinforcing effects of oxycodone in rats while producing additive antinociceptive effects. Questions remain, however, including if the combination will function as a reinforcer in drug-naïve rats, and if the combination produces aversive effects that could explain nalfurafine's ability to reduce oxycodone self-administration? In the present study, we investigated nalfurafine's ability to reduce acquisition of oxycodone self-administration when the two were self-administered as a mixture in drug-naïve rats and nalfurafine's ability to attenuate a conditioned place preference (CPP) induced by oxycodone. In the self-administration study, male Sprague-Dawley rats self-administered intravenous injections of oxycodone (0.056 mg/kg/injection), an oxycodone/nalfurafine combination (0.056/0.0032 mg/kg/injection), or saline under fixed-ratio schedules of reinforcement for 20 days to compare rates of acquisition of drug taking. In the CPP assay, male Sprague-Dawley rats received subcutaneous injections of either saline, oxycodone (3.2 mg/kg), nalfurafine (0.18 mg/kg), or an oxycodone/nalfurafine combination at the same ratio used in the self-administration study (3.2 mg/kg/0.18 mg/kg). All subjects self-administering oxycodone alone met acquisition criteria. However, only 13% of subjects self-administering oxycodone/nalfurafine met criteria, and no subjects acquired self-administration of saline.

Oxycodone, but not nalfurafine alone or the oxycodone/nalfurafine combination, produced rewarding effects in rats in the CPP test. These findings suggest that the combination of oxycodone and nalfurafine will be less habit forming in opioid-naïve patients than oxycodone alone.

Combining A Candidate Vaccine For Opioid Use Disorders With Extended-Release Naltrexone Increases Protection Against Oxycodone-Induced Behavioral Effects And Toxicity
Raleigh MD, Accetturo C, Pravetoni M. J Pharmacol Exp Ther. 2020; 374(3): 392-403.
Opioid use disorders (OUDs) and opioid-related fatal overdoses are a significant public health concern in the United States and worldwide. To offer more effective medical interventions to treat or prevent OUD, antiopioid vaccines are in development that reduce the distribution of the targeted opioids to brain and subsequently reduce the associated behavioral and toxic effects. It is of critical importance that antiopioid vaccines do not interfere with medications that treat OUD. Hence, this study tested the preclinical proof of concept of combining a candidate oxycodone vaccine [oxycodone-keyhole limpet hemocyanin (OXY-KLH)] with an FDA-approved extended-release naltrexone (XR-NTX) depot formulation in rats. The effects of XR-NTX on oxycodone-induced motor activity and antinociception were first assessed in nonvaccinated naïve rats to establish a baseline for subsequent studies. Next, OXY-KLH and XR-NTX were coadministered to determine whether the combination would affect the efficacy of each individual treatment, and it was found that the combination of OXY-KLH and XR-NTX offered greater efficacy in reducing oxycodone-induced motor activity, thigmotaxis, antinociception, and respiratory depression over a range of repeated or escalating oxycodone doses in rats. These data support the feasibility of combining antibody-based therapies with opioid receptor antagonists to provide greater or prolonged protection against opioid-related toxicity or overdose. Combining antiopioid vaccines with XR-NTX may provide prophylactic measures to subjects at risk of relapse and accidental or deliberate exposure. Combination therapy may extend to other biologics (e.g., monoclonal antibodies) and medications against substance use disorders. SIGNIFICANCE STATEMENT: Opioid use disorders (OUDs) remain a major problem worldwide, and new therapies are needed. This study reports on the combination of an oxycodone vaccine [oxycodone-keyhole limpet hemocyanin (OXY-KLH)] with a currently approved OUD therapy, extended-release naltrexone (XR-NTX). Results demonstrated that XR-NTX did not interfere with OXY-KLH efficacy, and combination of low doses of XR-NTX with vaccine was more effective than each individual treatment alone to reduce behavioral and toxic effects of oxycodone, suggesting that combining OXY-KLH with XR-NTX may improve OUD outcomes.

Enhancement Of A Heroin Vaccine Through Hapten Deuteration Belz TF, Bremer PT, Zhou B, Ellis B, Eubanks LM, Janda KD. J Am Chem Soc. 2020; 142(31): 13294-13298.
The United States is in the midst of an unprecedented epidemic of opioid substance use disorder, and while pharmacotherapies including opioid agonists and antagonists have shown success, they can be inadequate and frequently result in high recidivism. With these challenges facing opioid use disorder treatments immunopharmacotherapy is being explored as an alternative therapy option and is based upon antibody-opioid sequestering to block brain entry. Development of a heroin vaccine has become a major research focal point; however, producing an efficient vaccine against heroin has been particularly challenging because of the need to generate not only a potent immune response but one against heroin and its multiple psychoactive molecules. In this study, we explored the consequence of regioselective deuteration of a heroin hapten and its impact upon the immune response against heroin and its psychoactive metabolites. Deuterium (HdAc) and cognate protium

heroin (HAc) haptens were compared head to head in an inclusive vaccine study. Strikingly the HdAc vaccine granted greater efficacy in blunting heroin analgesia in murine behavioral models compared to the HAc vaccine. Binding studies confirmed that the HdAc vaccine elicited both greater quantities and equivalent or higher affinity antibodies toward heroin and 6-AM. Blood-brain biodistribution experiments corroborated these affinity tests. These findings suggest that regioselective hapten deuteration could be useful for the resurrection of previous drug of abuse vaccines that have met limited success in the past.

A Plant-Derived Cocaine Hydrolase Prevents Cocaine Overdose Lethality And Attenuates Cocaine-Induced Drug Seeking Behavior Larrimore KE, Kannan L, Kendle RP, Jamal T, Barcus M, Stefanko K, Kilbourne J, Brimijoin S, Zhan CG, Neisewander J, Mor TS. Prog Neuropsychopharmacol Biol Psychiatry. 2020; 102: 109961.
Cocaine use disorders include short-term and acute pathologies (e.g. overdose) and long-term and chronic disorders (e.g. intractable addiction and post-abstinence relapse). There is currently no available treatment that can effectively reduce morbidity and mortality associated with cocaine overdose or that can effectively prevent relapse in recovering addicts. One recently developed approach to treat these problems is the use of enzymes that rapidly break down the active cocaine molecule into inactive metabolites. In particular, rational design and site-directed mutagenesis transformed human serum recombinant butyrylcholinesterase (BChE) into a highly efficient cocaine hydrolase with drastically improved catalytic efficiency toward (-)-cocaine. A current drawback preventing the clinical application of this promising enzyme-based therapy is the lack of a cost-effective production strategy that is also flexible enough to rapidly scale-up in response to continuous improvements in enzyme design. Plant-based expression systems provide a unique solution as this platform is designed for fast scalability, low cost and the advantage of performing eukaryotic protein modifications such as glycosylation. A Plant-derived form of the Cocaine Super Hydrolase (A199S/F227A/S287G/A328W/Y332G) we designate PCocSH protects mice from cocaine overdose, counters the lethal effects of acute cocaine overdose, and prevents reinstatement of extinguished drug-seeking behavior in mice that underwent place conditioning with cocaine. These results demonstrate that the novel PCocSH enzyme may well serve as an effective therapeutic for cocaine use disorders in a clinical setting.

HIV/AIDS RELATED RESEARCH

Distinct Viral Reservoirs In Individuals With Spontaneous Control Of HIV-1 Jiang C, Lian X, Gao C, Sun X, Einkauf KB, Chevalier JM, Chen SMY, Hua S, Rhee B, Chang K, Blackmer JE, Osborn M, Peluso MJ, Hoh R, Somsouk M, Milush J, Bertagnolli LN, Swee SE, Varriale JA, Burbelo PD, Chus T-W, Laird GM, Serrao E, Engelman AN, Carrington M, Siliciano RF, Siliciano JM, Deeks SG, Walker BD, Lichterfeld M, Yu XG. Nature. 2020; 585(7824): 261-267.
Sustained, drug-free control of HIV-1 replication is naturally achieved in less than 0.5% of infected individuals (here termed 'elite controllers'), despite the presence of a replication-competent viral reservoir1. Inducing such an ability to spontaneously maintain undetectable plasma viraemia is a major objective of HIV-1 cure research, but the characteristics of proviral reservoirs in elite controllers remain to be determined. Here, using next-generation sequencing of near-full-length single HIV-1 genomes and corresponding chromosomal integration sites, we show that the proviral reservoirs of elite controllers frequently consist of oligoclonal to

nearmonoclonal clusters of intact proviral sequences. In contrast to individuals treated with long-term antiretroviral therapy, intact proviral sequences from elite controllers were integrated at highly distinct sites in the human genome and were preferentially located in centromeric satellite DNA or in Krüppel-associated box domain containing zinc finger genes on chromosome 19, both of which are associated with heterochromatin features. Moreover, the integration sites of intact proviral sequences from elite controllers showed an increased distance to transcriptional start sites and accessible chromatin of the host genome and were enriched in repressive chromatin marks. These data suggest that a distinct configuration of the proviral reservoir represents a structural correlate of natural viral control, and that the quality, rather than the quantity, of viral reservoirs can be an important distinguishing feature for a functional cure of HIV-1 infection. Moreover, in one elite controller, we were unable to detect intact proviral sequences despite analysing more than 1.5 billion peripheral blood mononuclear cells, which raises the possibility that a sterilizing cure of HIV-1 infection, which has previously been observed only following allogeneic haematopoietic stem cell transplantation2,3, may be feasible in rare instances.

Bivalent Ligand Aiming Putative Mu Opioid Receptor And Chemokine Receptor CXCR4 Dimers in Opioid Enhanced HIV-1 Entry Ma H, Wang H, Li M, Barreto-de-Souza V, Reinecke BA, Gunta R, Zheng Y, Kang G, Nassehi N, Zhang H, An J, Selley DE, Hauser KF, Zhang Y. ACS Med Chem Lett. 2020; 11(11): 2318-2324.
A bivalent compound 1a featuring both a mu opioid receptor (MOR) and a CXCR4 antagonist pharmacophore (naltrexone and IT1t) was designed and synthesized. Further binding and functional studies demonstrated 1a acting as a MOR and a CXCR4 dual antagonist with reasonable binding affinities at both receptors. Furthermore, compound 1a seemed more effective than a combination of IT1t and naltrexone in inhibiting HIV entry at the presence of morphine. Additional molecular modeling results suggested that 1a may bind with the putative MOR-CXCR4 heterodimer to induce its anti-HIV activity. Collectively, bivalent ligand 1a may serve as a promising lead to develop chemical probes targeting the putative MOR-CXCR4 heterodimer in comprehending opioid exacerbated HIV-1 invasion.

Concurrent Initiation Of Hepatitis C And Opioid Use Disorder Treatment In People Who Inject Drugs
Rosenthal ES, Silk R, Mathur P, Gross C, Eyasu R, Nussdorf L, Hill K, Brokus C, D'Amore A, Sidique N, Bijole P, Jones M, Kier R, McCullough D, Sternberg D, Stafford K, Sun J, Masur H, Kottilil S, Kattakuzhy S. Clin Infect Dis. 2020; 71(7): 1715-1722.
People who inject drugs have a high prevalence of hepatitis C virus (HCV) and significant disease associated with drug use; however, HCV treatment often occurs in absence of interventions to address opioid use disorder and drug use-related harms. The impact of concurrent initiation of opioid agonist therapy (OAT) on HCV treatment and drug use outcomes is unknown. In this prospective, open-label, observational trial at a harm reduction organizations drop-in center in Washington, DC, 100 patients with chronic HCV infection, opioid use disorder, and ongoing injection drug use were treated with sofosbuvir-velpatasvir for 12-weeks and offered buprenorphine initiation. The primary end point was sustained virologic response (SVR), and secondary end points included uptake of and retention in OAT, change in risk behavior, and determinants of SVR. Eighty-two patients (82%) achieved SVR, which was not associated with baseline OAT status ($P = .33$), on-treatment drug use ($P > .99$), or imperfect daily adherence ($P = .35$) but was significantly associated with completing 2 or more 28-pill bottles of sofosbuvir-velpatasvir ($P < .001$) and

receiving OAT at week 24 (P = .01). Of 67 patients not already receiving OAT at baseline, 53 (79%) started OAT. At week 24, 68 (68%) patients were receiving OAT. Receipt of OAT was associated with fewer opiate-positive urine drug screens (P = .003), lower human immunodeficiency virus risk-taking behavior scores (P < .001), and lower rates of opioid overdose (P = .04).The Novel Model of Hepatitis C Treatment as an Anchor to Prevent HIV, Initiate Opioid Agonist Therapy, and Reduce Risky Behavior study demonstrates high uptake of buprenorphine collocated with HCV treatment, and it shows that concurrent initiation of OAT with HCV treatment can result in high rates of SVR while reducing risks associated with drug use.NCT03221309.

Changes In Gastrointestinal Microbial Communities Influence HIV-specific CD8+ T-cell Responsiveness To Immune Checkpoint Blockade
SahBandar IN, Chew GM, Corley MJ, Pang APS, Tsai N, Hanks N, Khadka VS, Klatt NR, Hensley-McBain T, Somsouk M, Vujkovic-Cvijin I, Chow DC, Shikuma CM, Ndhlovu LC. AIDS. 2020; 34(10): 1451-1460.
The aim of this study was to examine the relationship between gut microbial communities in HIV-infected individuals on suppressive antiretroviral therapy (cART), and the peripheral HIV-Gag-specific CD8 T-cell responses before and after ex-vivo immune checkpoint blockade (ICB).Thirty-four HIV-seropositive, 10 HIV-seronegative and 12 HIV-seropositive receiving faecal microbiota transplant (FMT) participants were included. Gut microbial communities, peripheral and gut associated negative checkpoint receptors (NCRs) and peripheral effector functions were assessed. Bacterial 16s rRNA sequencing for gut microbiome study and flow-based assays for peripheral and gut NCR and their cognate ligand expression, including peripheral HIV-Gag-specific CD8 T-cell responses before and after ex-vivo anti-PD-L1 and anti-TIGIT ICB were performed. Fusobacteria abundance was significantly higher in HIV-infected donors compared to uninfected controls. In HIV-infected participants receiving Fusobacteria-free FMT, Fusobacteria persisted up to 24 weeks in stool post FMT. PD-1 TIGIT and their ligands were expanded in mucosal vs. peripheral T cells and dendritic cells, respectively. PD-L1 and TIGIT blockade significantly increased the magnitude of peripheral anti-HIV-Gag-specific CD8 T-cell responses. Higher gut Fusobacteria abundance was associated with lower magnitude of peripheral IFN-γ+ HIV-Gag-specific CD8 T-cell responses following ICB. The gut colonization of Fusobacteria in HIV infection is persistent and may influence anti-HIV T-cell immunity to PD-1 or TIGIT blockade. Strategies modulating Fusobacteria colonization may elicit a favourable mucosal immune landscape to enhance the efficacy of ICB for HIV cure.

Dental Care Utilization Of Hospitalized Persons Living With HIV And Substance Use Santella AJ, Parish C, Dan R, Feaster DJ, Rodriguez AE, del Rio C, Armstrong WS, Jacobs, P, Metsch LR. J Community Health 2020 Aug 5. Online ahead of print.
People living with HIV (PLWH) who use drugs experience worse health outcomes than their non-using counterparts. Little is known about how often they seek dental care and the factors that influence their utilization. PLWH with substance use disorders who were inpatients at 11 urban hospitals (n = 801) participated in a National Institute on Drug Abuse Clinical Trials Network study to improve engagement in HIV outcomes. Dental care utilization at each time point during the study period (baseline, 6 months and/or 12 months) was assessed (n = 657). Univariate analysis and logistic regression were used to examine factors associated with dental care utilization. Over half (59.4%) reported not having received any dental care at any timepoint. Participants with less than high school education had lower odds of reporting dental care utilization than those with more than

education (aOR = 0.60 [95% CI 0.37-0.99], p = 0.0382). Participants without health insurance also had lower odds of reporting dental care utilization than those with insurance (aOR = 0.50 [95% CI 0.331-0.76], p = 0.0012). Higher food insecurity was associated with having recent dental care utilization (OR = 1.03 [95% CI 1.00, 1.05], p = 0.0359). Additionally, those from Southern states were less likely to report dental care utilization (aOR = 0.55 [95% CI 0.38, 0.79], p = 0.0013). Having health insurance and education are key factors associated with use of dental care for PLWH with substance use disorders. The association between food insecurity and dental care utilization among this population suggests the need for further exploration.

CLINICAL TRIALS NETWORK RESEARCH

Bupropion And Naltrexone In Methamphetamine Use Disorder Trivedi MH, Walker R, Ling W, dela Cruz A, Sharma G, Carmody T, Ghitza UE, Wahle A, Kim M, Shores-Wilson K, Sparenborg S, Coffin P, Schmitz J, Wiest K, Bart G, Sonne SC, Wakhlu S, Rush AJ, Nunes EV, and Shoptaw S. N Engl J Med. 2021; 384: 140-53.
Background: the use of naltrexone plus bupropion to treat methamphetamine use disorder has not been well studied. **Methods:** we conducted this multisite, double-blind, two-stage, placebo-controlled trial with the use of a sequential parallel comparison design to evaluate the efficacy and safety of extended-release injectable naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg per day) in adults with moderate or severe methamphetamine use disorder. in the first stage of the trial, participants were randomly assigned in a 0.26:0.74 ratio to receive naltrexone–bupropion or matching injectable and oral placebo for 6 weeks. those in the placebo group who did not have a response in stage 1 underwent rerandomization in stage 2 and were assigned in a 1:1 ratio to receive naltrexone–bupropion or placebo for an additional 6 weeks. urine samples were obtained from participants twice weekly. the primary outcome was a response, defined as at least three methamphetamine negative urine samples out of four samples obtained at the end of stage 1 or stage 2, and the weighted average of the responses in the two stages is reported. the treatment effect was defined as the between-group difference in the overall weighted responses. **Results:** a total of 403 participants were enrolled in stage 1, and 225 in stage 2. in the first stage, 18 of 109 participants (16.5%) in the naltrexone–bupropion group and 10 of 294 (3.4%) in the placebo group had a response. in the second stage, 13 of 114 (11.4%) in the naltrexone–bupropion group and 2 of 111 (1.8%) in the placebo group had a response. the weighted average response across the two stages was 13.6% with naltrexone–bupropion and 2.5% with placebo, for an overall treatment effect of 11.1 percentage points (wald z-test statistic, 4.53; p<0.001). adverse events with naltrexone–bupropion included gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia. serious adverse events occurred in 8 of 223 participants (3.6%) who received naltrexone–bupropion during the trial. **Conclusions:** among adults with methamphetamine use disorder, the response over a period of 12 weeks among participants who received extended-release injectable naltrexone plus oral extended-release bupropion was low but was higher than that among participants who received placebo. (funded by the national institute on drug abuse and others; adapt-2 clinicaltrials.gov number, nct03078075.)

Emergency Department Patients With Untreated Opioid Disorder: A Comparison Of Those Seeking Versus Not Seeking Referral To Substance Use Treatment Coupet E Jr, D'Onofrio G, Chawarski M, Edelman EJ, O'Connor PG, Owens P, Martel S, Fiellin DA, Cowan E, Richardson L,

Huntley K, Whiteside LK, Lyons MS, Rothman RE, Pantalon M, Hawk K. Drug Alcohol Depend. 2021; 219: 108428.
Background: Little is known regarding the sociodemographic and clinical characteristics of emergency department (ED) patients with untreated opioid use disorder (OUD) and the relationship of those characteristics with whether they were seeking a referral to substance use treatment at the time of their ED visit. **Methods:** Using data collected from 2/2017-1/2019 from participants enrolled in Project ED Health (CTN-0069), we conducted a cross-sectional analysis of patients with untreated moderate to severe OUD presenting to one of four EDs in Baltimore, New York City, Cincinnati, or Seattle. Sociodemographic and clinical correlates, and International Classification of Diseases Tenth Revision (ICD-10) diagnosis codes related to opioid withdrawal, injection-related infection, other substance use, overdose, and OUD of those seeking and not seeking a referral to substance use treatment on presentation were compared using univariate analyses. **Results:** Among 394 study participants, 15.2 % (60/394) came to the ED seeking a referral to substance use treatment. No differences in age, gender, education, health insurance status or housing stability were detected between those seeking and not seeking referral to substance use treatment. Those seeking a referral to substance use treatment were less likely to have urine toxicology testing positive for amphetamine [17 % (10/60) vs 31 % (104/334), p = 0.023] and methamphetamine [23 % (14/60) vs 40 % (132/334), p = 0.017] compared to those not seeking a referral. **Conclusion:** Most patients with untreated OUD seen in the EDs were not seeking a referral to substance use treatment. Active identification, treatment initiation, and coding may improve ED efforts to address untreated OUD.

Impact Of 12 Step Mutual Help Groups On Drug Use Disorder Patients Across Six Clinical Trials Humphreys K, Barreto NB, Alessi SM, Carroll KM, Crits-Christoph P, Donovan DM, Kelly JF, Schottenfeld RS, Timko C, Wagner TH. Drug Alcohol Depend. 2020; 215: 108213.
Background: 12 step mutual help groups are widely accessed by people with drug use disorder but infrequently subjected to rigorous evaluation. Pooling randomized trials containing a condition in which mutual help group attendance is actively facilitated presents an opportunity to assess the effectiveness of 12 step groups in large, diverse samples of drug use disorder patients.
Methods: Data from six federally-funded randomized trials were pooled (n = 1730) and subjected to two-stage instrumental variables modelling, and, fixed and random effects regression models. All trials included a 12 step group facilitation condition and employed the Addiction Severity Index as a core measure. **Results:** The ability of 12 step facilitation to increase mutual help group participation among drug use disorder patients was minimal, limiting ability to employ two-stage instrumental variable models that correct for selection bias. However, traditional fixed and random effect regression models found that greater 12 step mutual help group attendance by drug use disorder patients predicted reduced use of and problems with illicit drugs and also with alcohol. **Conclusion:** Facilitating significant and lasting involvement in 12 step groups may be more challenging for drug use disorder patients than for alcohol use disorder patients, which has important implications for clinical work and for effectiveness evaluations. Though selection bias could explain part of the results of traditional regression models, the finding that participation in 12 step mutual help groups predicts lower illicit drug and alcohol use and problems in a large, diverse, sample of drug use disorder patients is encouraging.

Buprenorphine Physician–Pharmacist Collaboration In The Management Of Patients With Opioid Use Disorder: Results From A Multisite Study Of The National Drug Abuse Treatment Clinical Trials Network Wu L, John WS, Ghitza UE, Wahle A, Matthews AG, Lewis

M, Hart B, Hubbard Z, Bowlby LA, Greenblatt LH, Mannelli P, and Pharm-OUD-Care Collaborative Investigators. Addiction. 11 January 2021. Online ahead of print.
Background and Aims: Physician and pharmacist collaboration may help address the shortage of buprenorphine-waivered physicians and improve care for patients with opioid use disorder (OUD). This study investigated the feasibility and acceptability of a new collaborative care model involving buprenorphine-waivered physicians and community pharmacists. **Design:** Nonrandomized, single-arm, open-label feasibility trial. **Setting:** Three office-based buprenorphine treatment (OBBT) clinics and three community pharmacies in the United States.
Participants: Six physicians, six pharmacists, and 71 patients aged ≥18 years with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) OUD on buprenorphine maintenance. **Intervention:** After screening, eligible patients' buprenorphine care was transferred from their OBBT physician to a community pharmacist for 6 months. **Measurements:** Primary outcomes included recruitment, treatment retention and adherence, and opioid use. Secondary outcomes were intervention fidelity, pharmacists' use of prescription drug monitoring program (PDMP), participant safety, and satisfaction with treatment delivery.
Findings: A high proportion (93.4%, 71/76) of eligible participants enrolled into the study. There were high rates of treatment retention (88.7%) and adherence (95.3%) at the end of the study. The proportion of opioid-positive urine drug screens (UDSs) among complete cases (i.e. those with all six UDSs collected during 6 months) at month 6 was (4.9%, 3/61). Intervention fidelity was excellent. Pharmacists used PDMP at 96.8% of visits. There were no opioid-related safety events. Over 90% of patients endorsed that they were "very satisfied with their experience and the quality of treatment offered," that "treatment transfer from physician's office to the pharmacy was not difficult at all," and that "holding buprenorphine visits at the same place the medication is dispensed was very or extremely useful/convenient." Similarly, positive ratings of satisfaction were found among physicians/pharmacists. **Conclusions:** A collaborative care model for people with opioid use disorder that involves buprenorphine-waivered physicians and community pharmacists appears to be feasible to operate in the United States and have high acceptability to patients.

Use Of Amphetamine-Type Stimulants Among Emergency Department Patients With Untreated Opioid Use Disorder Chawarski MC, Hawk K, Edelman EJ, O'Connor P, Owens P, Marlet S, Coupet E Jr, Whiteside L, Tsui JL, Rothman R, Cowan E, Richardson L, Lyons MS, Fiellin DA, D'Onofrio G. Ann Emerg Med. 2020; 76(6): 782-787.
Study objective: Concurrent use of amphetamine-type stimulants among individuals with opioid use disorder can exacerbate social and medical harms, including overdose risk. The study evaluated rates of amphetamine-type stimulant use among patients with untreated opioid use disorder presenting at emergency departments in Baltimore, MD; New York, NY; Cincinnati, OH; and Seattle, WA. **Methods:** Emergency department (ED) patients with untreated opioid use disorder (N=396) and enrolled between February 2017 and January 2019 in a multisite hybrid type III implementation science study were evaluated for concurrent amphetamine-type stimulant use. Individuals with urine tests positive for methamphetamine, amphetamine, or both were compared with amphetamine-type stimulant-negative patients. **Results:** Overall, 38% of patients (150/396) were amphetamine-type stimulant positive; none reported receiving prescribed amphetamine or methamphetamine medications. Amphetamine-type stimulant-positive versus -negative patients were younger: mean age was 36 years (SD 10 years) versus 40 years (SD 12 years), 69% (104/150) versus 46% (114/246) were white, 65% (98/150) versus 54% (132/246) were unemployed, 67% (101/150) versus 49 (121/246) had unstable housing, 47% (71/150) versus 25% (61/245) reported

an incarceration during 1 year before study admission, 60% (77/128) versus 45% (87/195) were hepatitis C positive, 79% (118/150) versus 47% (115/245) reported drug injection during 1 month before the study admission, and 42% (62/149) versus 29% (70/244) presented to the ED for an injury. Lower proportions of amphetamine-type stimulant-positive patients had cocaine-positive urine test results (33% [50/150] versus 52% [129/246]) and reported seeking treatment for substance use problems as a reason for their ED visit (10% [14/148] versus 19% [46/246]). All comparisons were statistically significant at P<.05 with the false discovery rate correction. **Conclusion:** Amphetamine-type stimulant use among ED patients with untreated opioid use disorder was associated with distinct sociodemographic, social, and health factors. Improved ED-based screening, intervention, and referral protocols for patients with opioid use disorder and amphetamine-type stimulant use are needed.

Cannabis Use, Other Drug Use, And Risk Of Subsequent Acute Care In Primary Care Patients Matson TE, Lapham GT, Bobb JF, Johnson E, Richards JE, Lee AK, Bradley KA, Glass JE. Drug Alcohol Depend. 2020; 216: 108227.
Background: Cannabis and other drug use is associated with adverse health events, but little is known about the association of routine clinical screening for cannabis or other drug use and acute care utilization. This study evaluated whether self-reported frequency of cannabis or other drug use was associated with subsequent acute care. **Method:** This retrospective cohort study used EHR and claims data from 8 sites in Washington State that implemented annual substance use screening. Eligible adult primary care patients (N = 47,447) completed screens for cannabis (N = 45,647) and/or other drug use, including illegal drug use and prescription medication misuse, (N = 45,255) from 3/3/15-10/1/2016. Separate single-item screens assessed frequency of past-year cannabis and other drug use: never, less than monthly, monthly, weekly, daily/almost daily. An indicator of acute care utilization measured any urgent care, emergency department visits, or hospitalizations ≤19 months after screening. Adjusted Cox proportional hazards models estimated risk of acute care. **Results:** Patients were predominantly non-Hispanic White. Those reporting cannabis use less than monthly (Hazard Ratio [HR] = 1.12, 95 % CI = 1.03-1.21) or daily (HR = 1.24; 1.10-1.39) had greater risk of acute care during follow-up than those reporting no use. Patients reporting other drug use less than monthly (HR = 1.34; 1.13-1.59), weekly (HR = 2.21; 1.46-3.35), or daily (HR = 2.53; 1.86-3.45) had greater risk of acute care than those reporting no other drug use. **Conclusion:** Population-based screening for cannabis and other drug use in primary care may have utility for understanding risk of subsequent acute care. It is unclear whether findings will generalize to U.S. states with broader racial/ethnic diversity.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

Nucleus Accumbens Cytoarchitecture Predicts Weight Gain In Children Rapuano KM, Laurent JS, Hagler Jr. DJ, Hatton SN, Thompson WK, Jernigan TL, Dale AM, Casey BJ, Watts R. Proc Natl Acad Sci U S A. 2020; 117(43): 26977-26984.
The prevalence of obesity in children and adolescents worldwide has quadrupled since 1975 and is a key predictor of obesity later in life. Previous work has consistently observed relationships between macroscale measures of reward-related brain regions (e.g., the nucleus accumbens [NAcc]) and unhealthy eating behaviors and outcomes; however, the mechanisms underlying these associations remain unclear. Recent work has highlighted a potential role of neuroinflammation in the NAcc in

animal models of diet-induced obesity. Here, we leverage a diffusion MRI technique, restriction spectrum imaging, to probe the microstructure (cellular density) of subcortical brain regions. More specifically, we test the hypothesis that the cell density of reward-related regions is associated with obesity-related metrics and early weight gain. In a large cohort of nine- and ten-year-olds enrolled in the Adolescent Brain Cognitive Development (ABCD) study, we demonstrate that cellular density in the NAcc is related to individual differences in waist circumference at baseline and is predictive of increases in waist circumference after 1 y. These findings suggest a neurobiological mechanism for pediatric obesity consistent with rodent work showing that high saturated fat diets increase gliosis and neuroinflammation in reward-related brain regions, which in turn lead to further unhealthy eating and obesity.

Behavioral And Brain Signatures Of Substance Use Vulnerability In Childhood Rapuano KM, Rosenberg MD, Maza MT, Dennis NJ, Dorji M, Greene AS, Horien C, Scheinost D, Todd Constable R, Casey BJ. Dev Cogn Neurosci. 2020; 46: 100878.
The prevalence of risky behavior such as substance use increases during adolescence; however, the neurobiological precursors to adolescent substance use remain unclear. Predictive modeling may complement previous work observing associations with known risk factors or substance use outcomes by developing generalizable models that predict early susceptibility. The aims of the current study were to identify and characterize behavioral and brain models of vulnerability to future substance use. Principal components analysis (PCA) of behavioral risk factors were used together with connectome-based predictive modeling (CPM) during rest and task-based functional imaging to generate predictive models in a large cohort of nine- and ten-year-olds enrolled in the Adolescent Brain & Cognitive Development (ABCD) study (NDA release 2.0.1). Dimensionality reduction (n = 9,437) of behavioral measures associated with substance use identified two latent dimensions that explained the largest amount of variance: risk-seeking (PC1; e.g., curiosity to try substances) and familial factors (PC2; e.g., family history of substance use disorder). Using cross-validated regularized regression in a subset of data (Year 1 Fast Track data; n>1,500), functional connectivity during rest and task conditions (resting-state; monetary incentive delay task; stop signal task; emotional n-back task) significantly predicted individual differences in risk-seeking (PC1) in held-out participants (partial correlations between predicted and observed scores controlling for motion and number of frames [rp]: 0.07-0.21). By contrast, functional connectivity was a weak predictor of familial risk factors associated with substance use (PC2) (rp: 0.03-0.06). These results demonstrate a novel approach to understanding substance use vulnerability, which-together with mechanistic perspectives-may inform strategies aimed at early identification of risk for addiction.

Positive Economic, Psychosocial, and Physiological Ecologies Predict Brain Structure And Cognitive Performance In 9–10-Year-Old Children Gonzalez MR, Palmer CE, Uban KA, Jernigan TL, Thompson WK, Sowell ER. Front Hum Neurosci. 2020; 14: 578822.
While low socioeconomic status (SES) introduces risk for developmental outcomes among children, there are an array of proximal processes that determine the ecologies and thus the lived experiences of children. This study examined interrelations between 22 proximal measures in the economic, psychosocial, physiological, and perinatal ecologies of children, in association with brain structure and cognitive performance in a diverse sample of 8,158 9-10-year-old children from the Adolescent Brain Cognitive Development (ABCD) study. SES was measured by the income-to-needs ratio (INR), a measure used by federal poverty guidelines. Within the ABCD study, in what is one of the

largest and most diverse cohorts of children studied in the United States, we replicate associations of low SES with lower total cortical surface area and worse cognitive performance. Associations between low SES (<200% INR) and measures of development showed the steepest increases with INR, with apparent increases still visible beyond the level of economic disadvantage in the range of 200-400% INR. Notably, we found three latent factors encompassing positive ecologies for children across the areas of economic, psychosocial, physiological, and perinatal well-being in association with better cognitive performance and the higher total cortical surface area beyond the effects of SES. Specifically, latent factors encompassing youth perceived social support and perinatal well-being were positive predictors of developmental measures for all children, regardless of SES. Further, we found a general latent factor that explained relationships between 20 of the proximal measures and encompassed a joint ecology of higher social and economic resources relative to low adversity across psychosocial, physiological, and perinatal domains. The association between the resource-to-adversity latent factor and cognitive performance was moderated by SES, such that for children in higher SES households, cognitive performance progressively increased with these latent factor scores, while for lower SES, cognitive performance increased only among children with the highest latent factor scores. Our findings suggest that both positive ecologies of increased access to resources and lower adversity are mutually critical for promoting better cognitive development in children from low SES households. Our findings inform future studies aiming to examine positive factors that influence healthier development in children.

INTRAMURAL RESEARCH

Processing In Lateral Orbitofrontal Cortex Is Required To Estimate Subjective Preference During Initial, But Not Established, Economic Choice Gardner MPH, Sanchez D, Conroy JC, Wikenheiser AM, Zhou J, Schoenbaum G. Neuron. 2020; 108(3): 526-537.
The orbitofrontal cortex (OFC) is proposed to be critical to economic decision making. Yet one can inactivate OFC without affecting well-practiced choices. One possible explanation of this lack of effect is that well-practiced decisions are codified into habits or configural-based policies not normally thought to require OFC. Here, we tested this idea by training rats to choose between different pellet pairs across a set of standard offers and then inactivating OFC subregions during choices between novel offers of previously experienced pairs or between novel pairs of previously experienced pellets. Contrary to expectations, controls performed as well on novel as experienced offers yet had difficulty initially estimating their subjective preference on novel pairs, difficulty exacerbated by lateral OFC inactivation. This pattern of results indicates that established economic choice reflects the use of an underlying model or goods space and that lateral OFC is only required for normal behavior when the established framework must incorporate new information.

Sigma-1 Receptor Chaperones Rescue Nucleocytoplasmic Transport Deficit Seen In Cellular And Drosophila ALS/FTD Models Lee PT, Liévens JC, Wang SM, Chuang JY, Khalil B, Wu HE, Chang WC, Maurice T, Su TP. Nat Commun. 2020; 11(1): 5580.
In a subgroup of patients with amyotrophic lateral sclerosis (ALS)/Frontotemporal dementia (FTD), the (G4C2)-RNA repeat expansion from C9orf72 chromosome binds to the Ran-activating protein (RanGAP) at the nuclear pore, resulting in nucleocytoplasmic transport deficit and accumulation of Ran in the cytosol. Here, we found that the sigma-1 receptor (Sig-

1R), a molecular chaperone, reverses the pathological effects of (G4C2)-RNA repeats in cell lines and in *Drosophila*. The Sig-1R colocalizes with RanGAP and nuclear pore proteins (Nups) and stabilizes the latter. Interestingly, Sig-1Rs directly bind (G4C2)-RNA repeats. Overexpression of Sig-1Rs rescues, whereas the Sig-1R knockout exacerbates, the (G4C2)-RNA repeats-induced aberrant cytoplasmic accumulation of Ran. In *Drosophila*, Sig-1R (but not the Sig-1R-E102Q mutant) overexpression reverses eye necrosis, climbing deficit, and firing discharge caused by (G4C2)-RNA repeats. These results on a molecular chaperone at the nuclear pore suggest that Sig-1Rs may benefit patients with C9orf72 ALS/FTD by chaperoning the nuclear pore assembly and sponging away deleterious (G4C2)-RNA repeats.

VTA Glutamatergic Neurons Mediate Innate Defensive Behaviors Barbano MF, Wang HL, Zhang S, Miranda-Barrientos J, Estrin DJ, Figueroa-González A, Liu B, Barker DJ, Morales M. Neuron. 2020; 107(2): 368-382.e8.
The ventral tegmental area (VTA) has dopamine, GABA, and glutamate neurons, which have been implicated in reward and aversion. Here, we determined whether VTA-glutamate or -GABA neurons play a role in innate defensive behavior. By VTA cell-type-specific genetic ablation, we found that ablation of glutamate, but not GABA, neurons abolishes escape behavior in response to threatening stimuli. We found that escape behavior is also decreased by chemogenetic inhibition of VTA-glutamate neurons and detected increases in activity in VTA-glutamate neurons in response to the threatening stimuli. By ultrastructural and electrophysiological analysis, we established that VTA-glutamate neurons receive a major monosynaptic glutamatergic input from the lateral hypothalamic area (LHA) and found that photoinhibition of this input decreases escape responses to threatening stimuli. These findings indicate that VTA-glutamate neurons are activated by and required for innate defensive responses and that information on threatening stimuli to VTA-glutamate neurons is relayed by LHA-glutamate neurons.

Long-Term Cocaine Self-Administration Produces Structural Brain Changes That Correlate With Altered Cognition Jedema HP, Song X, Aizenstein HJ, Bonner AR, Stein EA, Yang Y, Bradberry CW. Biol Psychiatry. 2021; 89(4): 376-385.
An enduring question from cross-sectional clinical studies is whether the structural and functional differences often observed between cocaine users and healthy control subjects result from a history of drug use or instead reflect preexisting differences. To assess causality from drug exposure, true predrug baseline imaging and neurocognitive assessments are needed. We addressed this fundamental question of causality using longitudinal anatomical magnetic resonance imaging and neurocognitive assessments in rhesus macaques. Cognitive tasks employed were stimulus reversal learning as a measure of cognitive flexibility/inhibitory control and delayed match to sample as a measure of visual working memory. Time points examined were before and following 12 months of chronic cocaine ($n = 8$) or water ($n = 6$) self-administration. A magnetic resonance imaging–only time point was also obtained following 2 years of forced abstinence. We identified localized patterns of gray matter density (GMD) changes that were largely concordant with cross-sectional clinical studies. These included decreases in orbitofrontal cortex, insula, amygdala, and temporal cortex. There was also a prominent increase in GMD in the caudate putamen. GMD decreases were significantly correlated with cognitive impairments across individuals only in select cortical regions. Following abstinence, changes in GMD in some regions, including the orbitofrontal cortex,

insula, and amygdala, were persistent and thus may play an important role in risk of relapse following extended abstinence. Cocaine use is causal in producing regional changes in GMD, and those changes appear to drive cognitive impairments.

Distinct Signaling By Ventral Tegmental Area Glutamate, GABA, And Combinatorial Glutamate-GABA Neurons In Motivated Behavior Root DH, Barker DJ, Estrin DJ, Miranda-Barrientos JA, Liu B, Zhang S, Wang HL, Vautier F, Ramakrishnan C, Kim YS, Fenno L, Deisseroth K, Morales M. Cell Rep. 2020; 32(9): 108094
Ventral tegmental area (VTA) neurons play roles in reward and aversion. We recently discovered that the VTA has neurons that co-transmit glutamate and GABA (glutamate-GABA co-transmitting neurons), transmit glutamate without GABA (glutamate-transmitting neurons), or transmit GABA without glutamate (GABA-transmitting neurons). However, the functions of these VTA cell types in motivated behavior are unclear. To identify the functions of these VTA cell types, we combine recombinase mouse lines with INTRSECT2.0 vectors to selectively target these neurons. We find that VTA cell types have unique signaling patterns for reward, aversion, and learned cues. Whereas VTA glutamate-transmitting neurons signal cues predicting reward, VTA GABA-transmitting neurons signal cues predicting the absence of reward, and glutamate-GABA co-transmitting neurons signal rewarding and aversive outcomes without signaling learned cues related to those outcomes. Thus, we demonstrate that genetically defined subclasses of VTA glutamate and GABA neurons signal different aspects of motivated behavior.

GRANTEE HONORS AND AWARDS

Deanna Barch, **Ph.D., M.A.,** Professor and Chair of the Department of Psychological and Brain Sciences in Arts & Sciences, Gregory B. Couch Professor of Psychiatry and Radiology, and Multiple Principal Investigator (MPI) at the ABCD site at Washington University in St. Louis, was appointed to the National Academy of Medicine. She was selected for helping identify neural and psychological mechanisms that give rise to the symptoms of psychosis and other forms of mental illness that contribute significantly to disability.

Dale Boger, Ph.D., Scripps Research Institute, was awarded the 2020 Tetrahedron Prize for Creativity in Organic Chemistry.

Kathleen Carroll, Ph.D., Albert E. Kent Professor of Psychiatry, Yale University Department of Psychiatry, was selected to be highlighted at the 2020 Office of Behavioral and Social Sciences Research 25th Anniversary Behavioral and Social Sciences Research Festival. NIDA's Division of Therapeutics and Medical Consequences (DTMC) nominated her but unfortunately, she will not be able to accept this selection due to her recent sudden passing. Kathleen had over 35 years of continued NIDA, National Institute of Mental Health (NIMH), National Institute of Alcohol Abuse and Alcoholism funding. Her contributions span many areas of treatment including (1) evaluating the efficacy of a range of behavioral therapies (cognitive behavioral, motivation interviewing, twelve step facilitation, and contingency management), alone and in combination with medication (disulfiram, galantamine, buprenorphine, methadone, and naltrexone), (2) improving the methodological rigor of clinical trials research in the addictions, including identification of clinically meaningful outcome indicators and (3) mentoring junior investigators (including women and underrepresented minorities) in these methods and strategies. She authored or co-authored over 320 articles in peer-reviewed publications, with over 50 chapters in major textbooks and several books and published manuals (Scopus – h-index=75; >19,434 citations; 57 papers cited more than 100 times). Her key contributions to behavioral and social sciences were: Stage Model of Behavioral Therapies Development; Development, Evaluation, and Dissemination of Behavioral Interventions; and Optimal Combinations of Behavioral Therapies and Medication for Addiction.

Damien Fair, Ph.D., Redleaf Endowed Director of the Masonic Institute for the Developing Brain, Professor in the Institute of Child Development and Department of Pediatrics at the University of Minnesota and MPI at the ABCD site at Oregon Health and Sciences University, received a Macarthur Fellowship in 2020. He is a cognitive neuroscientist advancing our understanding of brain functioning during development in typical and atypical contexts. Combining technical advances in functional magnetic resonance imaging (fMRI), advanced mathematical techniques, and expertise in psychology and neuroscience, Fair investigates resting state brain connectivity—the brain's intrinsic or spontaneous neural activity.

Kenneth Kendler, M.D., has been appointed to the Virginia Commonwealth University's (VCU) Virginia Institute for Psychiatric and Behavioral Genetics (VIPBG) Distinguished Professorship established by an anonymous donor. Named after the VIPBG he launched over 22 years ago, the newly created endowed position honors Kenneth's legacy while further supporting his research endeavors. Kenneth is a respected leader in our department, at VCU and across the globe. The most

cited researcher in psychiatry worldwide, his work in twin studies sheds light on the genetics of mental illness, alcohol and substance abuse. Those contributions were honored at VCU's commencement ceremony, where we were proud to see him receive VCU's Presidential Medallion, established in 1984 to honor outstanding contributions by members of the university community.

John W. McIlveen, Ph.D., a NIDA Clinical Trials Network (CTN) Western State Node investigator, has been honored by the National Association of State Alcohol and Drug Abuse Directors with its 2020 President's Award for his leadership of the State Opioid Treatment Authorities and his coordination of their responses to the SARS-CoV-2 pandemic and the emergency changes in dosing practices in opioid treatment programs.

Michael Neale, Ph.D., has been named to the Virginia Commonwealth University's Rachel Brown Banks Professorship. His design and development of statistical modeling software has dramatically advanced analysis of neuroimaging, substance use and psychiatric outcomes. His open-source computer program—widely used by researchers in modeling data to determine whether genetic variants are linked to outcome variables—has been cited more than 3,000 times in scientific literature.

Kelsey Priest, Ph.D., M.P.H., an early investigator affiliated with the NIDA CTN Western States Node, recently became Oregon Health & Science University's first STAT Wunderkind! STAT recognized Kelsey as an up-and-coming scientific superstar by naming her to the 2020 Wunderkind cohort.

Gordana Vitaliano, M.D., Ph.D., Harvard Medical School, was selected as a World Molecular Imaging Congress (WMIC) 2020 spotlight speaker. The title of his talk was "Novel Antibody-Targeted Clathrin-Based Superparamagnetic Iron Oxide Nanoprobes for MR Imaging of Dopamine Transporters."

The grantees below were selected to be the American Association for the Advancement of Science Fellows:
Abraham Palmer, Ph.D., University of California, San Diego: For distinguished contributions to our understanding of model systems and human genetics of addiction, substance abuse, neuropsychiatric and behavioral traits.

Raymond C. Stevens, Ph.D., University of Southern California: For the development of technologies to significantly accelerate protein structure determination and drug discovery, including G-protein-coupled receptors, that have led to new biological insights and therapeutics.

Rachel Tyndale, Ph.D., Centre for Addiction and Mental Health/University of Toronto (Canada): For outstanding contributions to understanding of the role of drug metabolism in addiction and in particular, how genetic polymorphisms alter behaviors relevant to nicotine addiction.

STAFF HONORS AND AWARDS

Ida Fredriksson, Ph.D., Intramural Research Program (IRP), a postdoctoral fellow in the laboratory of Yavin Shaham, Ph.D., received the 2020 Women Scientist Advisors Scholar Award.

Eliot Gardner, Ph.D., IRP, received the Lifetime Achievement Award from the International Cannabinoid Research Society and the Pioneer Award for his lifetime of work in the field of neuropsychopharmacology by The Winter Conference on Brain Research.

Evan Hart, Ph.D., IRP, a postdoctoral fellow in the laboratory of Geoffrey Schoenbaum, M.D., Ph.D., received the National Institute of General Medical Sciences Postdoctoral Research Associate Program fellowship award.

Margaret Kroen, IRP, received the NIH Clinical Center Chief Executive Officer (CEO) Award for Staff Asymptomatic Testing.

Lorenzo Leggio, M.D., Ph.D., IRP, was presented with the 2020 Jacob P. Waletzky Award from the Society for Neuroscience "given to a young scientist whose independent research has led to significant conceptual and empirical contributions to the understanding of drug addiction".

Yu (Woody) Lin, M.D., Ph.D., and Roger Sorensen, Ph.D., M.P.A., of the Integrative Neuroscience Branch, along with Linda Chang, M.D., M.S., of the University of Maryland School of Medicine, Baltimore, and Johnny He, Ph.D., Rosalind Franklin University, Chicago, edited a special issue of the Journal of Neuroimmune Pharmacology [volume 15(4), December 2020], which contains 10 invited review papers that highlight and extend work presented at the 2019 pre-conference satellite workshop, *Unraveling NeuroAIDS in the Presence of Substance Use Disorders,* held at the 25th Society on NeuroImmune Pharmacology conference, April 10-15, 2019, in Portland, Oregon.

Rajtarun Madangopal, Ph.D., IRP, was awarded a Brain & Behavior Research Foundation Young Investigator National Alliance for Research on Schizophrenia & Depression (NARSAD) Grant.

Marisela Morales, Ph.D., IRP, received the Ruth Kirchstein Mentoring Award for exemplary performance while demonstrating significant leadership, skill, and ability in serving as a mentor.

Karran Phillips, **M.D., M.Sc.,** IRP, received the NIH Clinical Center CEO Award for Staff Asymptomatic Testing.

Ayesha Sengupta, Ph.D., IRP, received the 2020 "Where there's a WIL there's a way" Research Grant.by The Women in Learning Awards Committee designed to honor one outstanding yet underrepresented graduate student or postdoctoral fellow.

Yavin Shaham, Ph.D., IRP, received the NIH Director's Award for the development of novel animal models that have led to a paradigm shift in research on behavior and brain mechanisms of drug addiction.

Rita Valentino, Ph.D., Director of the Division of Neuroscience and Behavior was elected to the position of Secretary of the American College of Neuropsychopharmacology.

Marco Venniro, Ph.D., IRP, was awarded a Brain & Behavior Research Foundation Young Investigator NARSAD Grant.

Jingfeng Zhou, Ph.D., IRP, a postdoctoral fellow in the laboratory of Geoffrey Schoenbaum, M.D., Ph.D., received the NIH Pathway to Independence Grant Award.

The following individuals received a 2020 NIDA IRP Women Scientist Advisors Awards:
Smriti Mongia, Ph.D., – Excellence in Research, Postdoctoral Fellow
Stephanie Gantz, Ph.D., – Excellence in Research, Post-doctoral Fellow
Daria Piacentino, M.D., Ph.D., M.Sc., – Promising Post-doctoral Fellow
Flavia Barbano, Ph.D., – Research Recognition Award, Staff Scientist
Leslie Ramsey, Ph.D., – Research Recognition Award, Staff Scientist

The following individuals were 2020 Fellows Award for Research Excellence winners:
Alessandro Bonifazi, Ph.D.
Ida Fredriksson, Ph.D.
Jeremiah Bertz, Ph.D.
Smriti Mongia, Ph.D.
Qinglei Meng
Chloe Jordan, Ph.D.
Justin Siemian, Ph.D.
Tarun Madangopal, Ph.D.
Jorge Miranda Barrientos, Ph.D.

STAFF CHANGES

New Appointments

Jessica Cotto, M.P.H., a Health Science Policy Administrator, was named Deputy Branch Chief of the Science Policy Branch, Office of Science Policy and Communications. Ms. Cotto joined the Science Policy Branch in 2009 where her primary responsibilities include analyzing data and synthesizing information from disparate sources to identify trends related to substance use and contributing to a variety of science-based materials to inform the public about drug use and addiction. She earned her bachelor's degree in Cellular and Molecular Biology from San Diego State University and a Master of Public Health in Epidemiology and Biostatistics from George Washington University. Prior to NIDA, Ms. Cotto served as a Clinical Research Associate for The Children's National Medical Center, the National Institute of Allergy and Infectious Diseases, and the National Cancer Institute.

Carol Cushing was with the NIH for over 26 years during which she acquired both in-depth knowledge and a unique skill set associated with NIDA Center for Clinical Trials Network (CCTN) and NIDA activities. She returns to NIDA as a Program Analyst after her retirement three years ago. As a re-employed annuitant, Ms. Cushing will utilize her expertise to mentor new staff, provide support for CTN activities, and disseminate current research news and findings to the CCTN/CTN.

New Staff

Allison Adams, M.B.A., joined NIDA's Office of Management's Management Analysis Branch as a Management Analyst on January 3, 2020. Allison comes to NIDA from a position with the National Institute of Allergy and Infectious Diseases.

Sarah Adan joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on October 25, 2020. Sarah comes to NIDA from a position with the city of Alexandria, Virginia.

Nina Bernick joined the Division of Neuroscience and Behavior as an NIH Civic Digital Intern. Nina is a rising senior at Yale University, who is studying Applied Mathematics and Mechanical Engineering. This fall, she worked as a software engineer with Susan Wright, Ph.D., Roger Little, Ph.D., and members of the information technology team with the goal of using artificial intelligence algorithms to automate tasks for various NIDA staff to increase efficiency and productivity for grants management and administration.

Soyoun Cho, Ph.D., has joined NIDA as a Scientific Review Officer. She received her doctorate in neuroscience at the University of Pittsburgh, followed by a postdoctoral fellowship at the Vollum Institute, Oregon Health & Science University. Her postdoctoral work focused on how sensory information is conveyed by neurons through synapses and the key events occurring in synaptic terminals for this transmission. Her research was published in several high-impact journals including *Nature, Neuron* and *Journal of Neuroscience*. She subsequently obtained a faculty

position with the Boys Town National Research Hospital in Omaha, Nebraska, where she developed an independent neuroscience research program. Prior to joining NIDA, she was working as a senior research scientist at Vivozon, Inc. to develop non-opioid analgesics.

Marcy Fitz-Randolph, D.O., M.P.H., joined NIDA's Division of Epidemiology, Prevention and Services Research as a Physician in the Services Research Branch on November 22, 2020. Dr. Fitz-Randolph comes to NIDA from a position in the private sector.

Molly Freimuth, M.B.A., joined NIDA on January 4, 2021, as the Deputy Communications Director, Communications Branch, Office of Science Policy and Communications. Ms. Freimuth was previously with the NIH Clinical Center, where she served as a Senior Public Affairs Officer and Strategic Communications Supervisor. While at the Clinical Center, she led their media relations team for the past 7 years and oversaw coverage of major press stories there, including managing the filming of "First in Human," the Discovery documentary series. Prior to joining NIH, Ms. Freimuth was a Press Officer at the U.S. Environmental Protection Agency. Ms. Freimuth obtained her bachelor's degree from Towson University where she studied Mass Communications, Business Administration and Broadcast Journalism before obtaining her master's degree.

Marisela Garcia-Gomez joined NIDA's Office of Management's Management Analysis Branch as a Management Analyst on December 6, 2020. Marisela comes to NIDA from a position with the Department of the Army.

Renato Gomes joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on November 8, 2020.

Stacie Gutowski, Ph.D., joined NIDA's Office of Translational Initiatives & Program Innovations as a Biomedical Engineer on September 13, 2020. Stacie comes to NIDA from a position with the Food and Drug Administration.

LaToya Harmon joined NIDA's Financial Management Branch as a Budget Analyst on September 13, 2020. LaToya comes to NIDA from a position with the NIH Office of the Director.

Matthew Houle joined NIDA's Office of Mangement as an Ethics Specialist on October 13, 2020. Matthew comes to NIDA from a position with the National Institute on Minority Health and Health Disparities.

Isabela Lopes joined NIDA's Office of Diversity and Health Disparities as a Health Specialist on August 30, 2020. Isabela comes to NIDA from a position with the Department of Health and Human Services.

Barbara Oudekerk, Ph.D., joined NIDA's Division of Epidemiology, Prevention and Services Research in January 2021.

Barbara Maurer, Ph.D., joined NIDA's Division of Epidemiology, Prevention and Services Research as a Social and Behavioral Scientist Administrator in the Prevention Research Branch on January 3, 2021.

Sunila Nair, Ph.D., joined the Division of Neuroscience and Behavior's Integrative Neuroscience Branch as a program official. Sunila completed a Ph.D. in neuropharmacology at the University of Cincinnati followed by postdoctoral fellowships at the Intramural Research Program at NIDA and the University of Washington. Prior to joining the Integrative Neuroscience Branch, Sunila was Assistant Professor in the Department of Psychiatry and Behavioral Sciences at the University of Washington. She directed a research program focused on determining how the functional activity of neurons in the brain—specifically the limbic, cortical and hypothalamic circuitry—is controlled and altered in response to drugs of abuse and non-drug reinforcers. Her research program was funded by the NIH, Brain and Behavior Research Institute (NARSAD Young Investigator Award) and the Alcohol and Drug Abuse Research Institute at the University of Washington. More recently, her research has focused on sex differences in addiction; specifically, on the organizational and activational effects of gonadal hormones, and dimorphism in cell-type specific alterations in neural circuits that drive relapse to drug-seeking behaviors.

Preethy Nayar, MBBS, M.S., Ph.D., has joined NIDA as a Scientific Review Officer (SRO). She previously worked as an SRO at the Center for Scientific Review. After receiving her medical degree, Preethy completed her residency in otorhinolaryngology at the Postgraduate Institute of Medical Education and Research, Chandigarh, India. Preethy her Ph.D. in Health Services Organization and Research from Virginia Commonwealth University. Before joining the NIH, she was a tenured associate professor at the University of Nebraska Medical Center. Her research focused on geographical and racial/ethnic disparities in outcomes and access to health care for patients with chronic conditions. She also investigated patient and health care provider perspectives of the quality of health care services.

Nicholas Niefeld joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on November 8, 2020.

Shivani Patel joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on September 27, 2020. Shivani comes to NIDA from a position with the National Institute of Allergy and Infectious Diseases.

Alexa Romberg, Ph.D., joined NIDA's Division of Epidemiology, Prevention and Services Research as a Social and Behavioral Scientist Administrator in the Prevention Research Branch on December 6, 2020.

Shaun Rostad joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on October 13, 2020.

Matthew Seager, Ph.D., began working at NIDA DTMC on December 7, 2020. He received his Ph.D. in Psychology (Behavioral Neuroscience) from Miami University in Oxford, Ohio, and began his first postdoctoral fellowship as an Intramural Research Training Award Fellow in the Behavioral Neuroscience Unit of the Laboratory of Adaptive Systems at the National Institute of Neurological Disorders and Stroke and continued in the Blanchette Rockefeller Neurosciences Institute at the West Virginia University School of Medicine. Matt entered the pharmaceutical industry as a Postdoctoral Scientist at Eli Lilly in Indianapolis, and eventually led his own laboratories at Merck

and Bristol Myers Squibb, where he focused on behavioral pharmacology support for Alzheimer's disease, schizophrenia, depression, and neuropathic pain programs. Matt joins the Medications Discovery and Toxicology Branch of DTCM as a Health Scientist Administrator and will act as a Contracting Officer's Representative for *in vitro* receptor profiling and safety pharmacology studies, as well as support the Addiction Treatment Discovery Program and the Toxicology Program.

Tamara Slipchenko, Ph.D., joined NIDA's Office of Translational Initiatives and Program Innovations as a Health Scientist Administrator on December 20, 2020. Tamara comes to NIDA from a position in the private sector.

Trishma Smith-Winston joined NIDA's Office of the Director's AIDS Research Program as an Administrative Technician on December 20, 2020. Trishma comes to NIDA from a position in the private sector.

Karen Walls joined NIDA's Division of Epidemiology, Prevention and Services Research in January 2021.

Staff Departures

Steve Brito left his position with NIDA as a Management Analyst in the Office of Management's Management Analysis Branch on December 5, 2020, for a position with the Department of the Navy.

Clark Tung left his position as a Program Support Assistant in NIDA's Division of Epidemiology, Prevention and Services Research on September 12, 2020, for a position with the National Cancer Institute.

Kim DiFonzo, a Press Officer in the Communications Branch, Office of Science Policy and Communications, left NIDA on December 4, 2020, for a position with the Food and Drug Administration.

Chloe Jordan, Ph.D., left her position as a Health Scientist Administrator in NIDA's Division of Extramural Research on October 9, 2020.

Belinda Sims, Ph.D., left NIDA in January 2021 for a new and exciting opportunity as the Training Officer in National Institute of Mental Health's Division of Services & Intervention Research. Belinda had been a part of the DESPR team since 2004 and contributed to NIDA in many capacities, including her work on the NIDA Research Training Committee and the Helping to End Addiction Long-term℠ Prevention Initiative.

Shirley Simson, a Press Officer in the Communications Branch, Office of Science Policy and Communications, left NIDA on December 18, 2020, for a position with the Food and Drug Administration.

Retirements

Moira O'Brien, M.Phil., retired from NIDA in December 2020 after 30 years of public service, all at NIDA. Notably, for more than 10 years starting in 2003, Moira was the Project Officer for the Community Epidemiology Work Group, and subsequently served as the Project Scientist for the National Drug Early Warning System. Both of these projects characterize the nature and extent of emerging and current drug abuse trends within local, national and international contexts, and identify associated health, social and behavioral consequences; enhance the identification and monitoring of emerging trends including use of novel psychoactive substances; elucidate individual, social, cultural and contextual factors influencing the initiation of drug using behaviors; and examine processes influencing the development and diffusion of new drug trends.

Kenzie Preston, Ph.D., Chief, Clinical Pharmacology and Therapeutics Research Branch, retired on December 31, 2020.

Jeff Schulden, M.D., retired from Federal service in October 2020 after more than 20 years of service to our country. Jeff had been a Medical Officer in NIDA's Epidemiology Research Branch since February 2008, where he served as a Medical officer and Deputy Branch Chief. Jeff's career began in the Air Force before attending Harvard Medical School, then following more than 18 years in the United States Public Health Service. Prior to joining NIDA, Jeff worked at the Centers for Disease Control and Prevention as a Medical Epidemiologist in the Division of HIV/AIDS Prevention, and an Epidemic Intelligence Service Officer in the Division of Violence Prevention.

Joyce Williams, a Program Analyst in NIDA's Division of Neuroscience and Behavioral Research, retired from Federal service on October 2, 2020.

In Memoriam

Kathleen (Kathy) M. Carroll, Ph.D., a clinical scientist in the Yale Department of Psychiatry who made seminal contributions to improving treatments for addiction, died unexpectedly after a brief illness on December 28, 2020. She was 62 years old. At the time of her death, Kathy was the Albert E. Kent Professor of Psychiatry, Yale School of Medicine, and the Director of the Psychosocial Research in the Division on Addictions.

Kathy possessed a rare blend of brilliance, generosity, and humility that propelled a career spanning over 30 years in addiction treatment research at Yale. She graduated *summa cum laude* from Duke University, received her Ph.D. in clinical psychology and neuropsychology in 1988 from the University of Minnesota, and completed her pre-doctoral training at the Yale School of Medicine's Division of Substance Abuse. Following a brief stint as Instructor in Neurology at Harvard Medical School, she joined the faculty at Yale in 1989 as Assistant Professor of Psychiatry. Working closely with Bruce Rounsaville, M.D., she helped establish and subsequently led the Psychotherapy Development Center (PDC), NIDA's only funded Center of Excellence devoted to behavioral therapies research. Through Dr. Carroll's leadership, the PDC became one of the most important sources of addiction treatment development and dissemination over the past 25 years, improving the methodological rigor of clinical trials research and leading to multiple clinical innovations that have impacted the lives of many struggling with addiction. Officially ending in 2020, the PDC produced more than 1,500 peer-reviewed publications and launched the careers of dozens of independent investigators. Dr. Carroll also served as a Principal Investigator of NIDA's Clinical Trials Network, a partnership between NIDA, treatment researchers and community providers to work toward new treatment options in community-level clinical practice.

The depths of her contribution to the field of addiction are unparalleled. She has been a Principal Investigator on more than 100 research projects funded through NIH, with funding amounts totaling over $76 million. She authored or co-authored over 330 articles in peer-reviewed publications, with over 50 chapters in major textbooks, along with several books and published manuals. Her Cognitive Behavioral Therapy (CBT) manual for cocaine use disorders has been translated to over 14 languages and implemented worldwide. Among the defining accomplishments of her career has been broader recognition of the efficacy, safety, and durability of behavioral therapies. She helped establish the Stage Model of Behavioral Therapies Development that facilitated important advances by defining stages of science for behavioral therapies development, from pilot testing of novel approaches translated from basic clinical science ("Stage 1") to efficacy testing via randomized clinical trials ("Stage 2") to effectiveness research based in community settings (Stage 3"). This required a set of methodological advances (e.g., systemization of interventions in manuals, development of fidelity rating systems, therapist training strategies) to which she made multiple contributions. She received a NIH Method to Extend Research in Time award for her work which led to the development of an effective web-based version of CBT ("CBT4CBT"), now validated in eight independent trials. CBT4CBT became one of the first evidence-based computerized interventions for a range of substance use disorders and is currently being adapted and implemented for various co-occurring conditions.

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