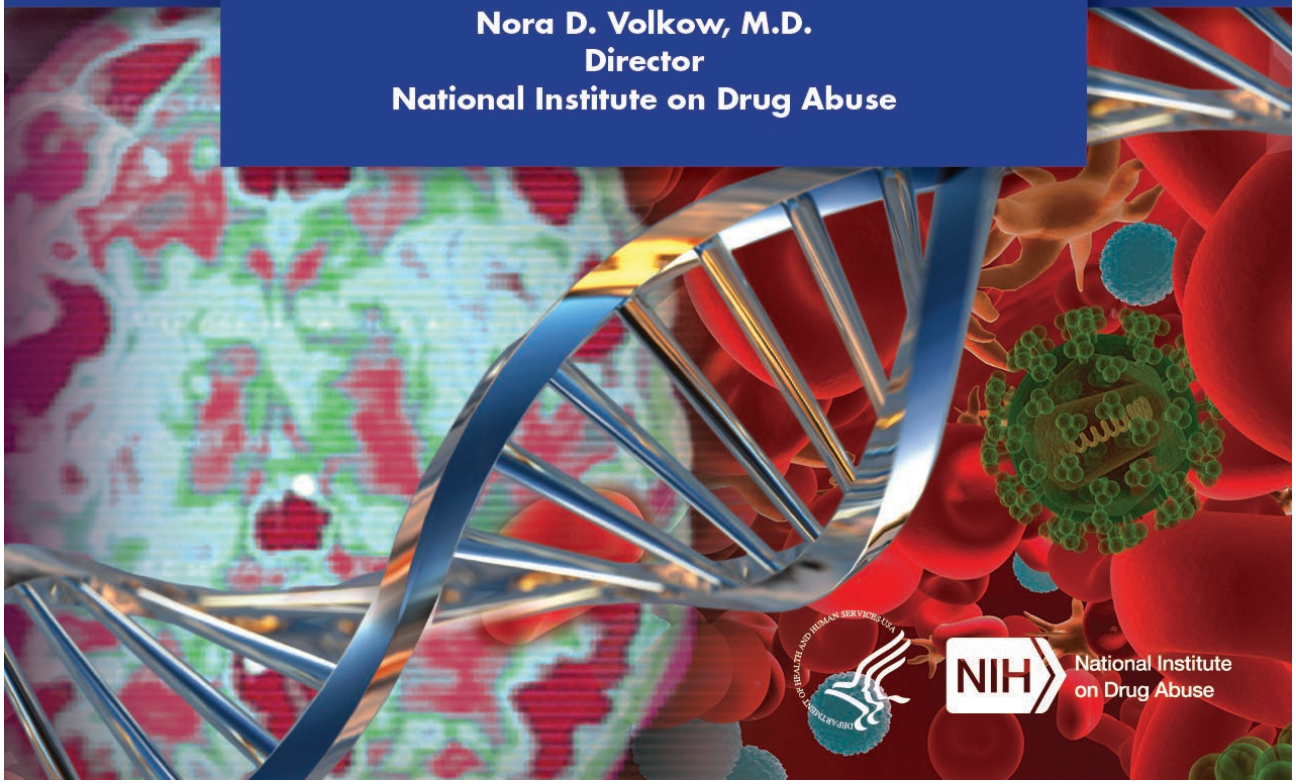
DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

February 2019

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse



NIH National Institute on Drug Abuse

TABLE OF CONTENTS

RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Adolescent Exposure To Δ9-Tetrahydrocannabinol Alters the Transcriptional Trajectory and Dendritic Architecture of Prefrontal Pyramidal Neurons Michael L. Miller, Benjamin Chadwick, Dara L. Dickstein, Immanuel Purushothaman, Gabor Egervari, Tanni Rahman, Chloe Tessereau, Patrick R. Hof, Panos Roussos, Li Shen, Mark G. Baxter, Yasmin L. Hurd; Mol. Psychiatry 2018.

Neuronal circuits within the prefrontal cortex (PFC) mediate higher cognitive functions and emotional regulation that are disrupted in psychiatric disorders. The PFC undergoes significant maturation during adolescence, a period when cannabis use in humans has been linked to subsequent vulnerability to psychiatric disorders such as addiction and schizophrenia. Here, the authors investigated in a rat model the effects of adolescent exposure to Δ^9-tetrahydrocannabinol (THC), a psychoactive component of cannabis, on the morphological architecture and transcriptional profile of layer III pyramidal neurons-using cell type- and layer-specific high-resolution microscopy, laser capture microdissection and next-generation RNA-sequencing. The results confirmed known normal expansions in basal dendritic arborization and dendritic spine pruning during the transition from late adolescence to early adulthood that were accompanied by differential expression of gene networks associated with neurodevelopment in control animals. In contrast, THC exposure disrupted the normal developmental process by inducing premature pruning of dendritic spines and allostatic atrophy of dendritic arborization in early adulthood. Surprisingly, there was minimal overlap of the developmental transcriptomes between THC- and vehicle-exposed rats. THC altered functional gene networks related to cell morphogenesis, dendritic development, and cytoskeleton organization. Marked developmental network disturbances were evident for epigenetic regulators with enhanced co-expression of chromatin- and dendrite-related genes in THC-treated animals. Dysregulated PFC co-expression networks common to both the THC-treated animals and patients with schizophrenia were enriched for cytoskeletal and neurite development. Overall, adolescent THC exposure altered the morphological and transcriptional trajectory of PFC pyramidal neurons, which could enhance vulnerability to psychiatric disorders.

Estrogen Regulation of GRK2 Inactivates Kappa Opioid Receptor Signaling Mediating Analgesia, But Not Aversion Antony D. Abraham, Selena S. Schattauer, Kathryn L. Reichard, Joshua H. Cohen, Harrison M. Fontaine, Allisa J. Song, Salina D. Johnson, Benjamin B. Land, Charles Chavkin; J Neurosci. 2018; 38(37): 8031-8043.

Activation of κ opioid receptors (KORs) produces analgesia and aversion via distinct intracellular signaling pathways, but whether G protein-biased KOR agonists can be designed to have clinical utility will depend on a better understanding of the signaling mechanisms involved. The authors found that KOR activation produced conditioned place aversion and potentiated CPP for cocaine in male and female C57BL/6N mice. Consistent with this, males and females both showed arrestin-mediated increases in phospho-p38 MAPK following KOR activation. Unlike in males, however, KOR activation had inconsistent analgesic effects in females and KOR increased Gβγ-mediated ERK phosphorylation in males, but not females. KOR desensitization was not responsible for the lack of response in females because neither *Grk3* nor *Pdyn* gene knock-out enhanced analgesia. Instead, responsiveness was estrous cycle dependent because KOR analgesia was evident during low estrogen phases of the cycle and in ovariectomized (OVX) females. Estradiol treatment of OVX females suppressed KOR-mediated analgesia, demonstrating that estradiol was sufficient to blunt

Gβγ-mediated KOR signals. G protein-coupled receptor kinase 2 (GRK2) is known to regulate ERK activation, and the authors found that the inhibitory, phosphorylated form of GRK2 was significantly higher in intact females. GRK2/3 inhibition by CMPD101 increased KOR stimulation of phospho-ERK in females, decreased sex differences in KOR-mediated inhibition of dopamine release, and enhanced mu opioid receptor and KOR-mediated analgesia in females. In OVX females, estradiol increased the association between GRK2 and Gβγ. These studies suggest that estradiol, through increased phosphorylation of GRK2 and possible sequestration of Gβγ by GRK2, blunts G protein-mediated signals. SIGNIFICANCE STATEMENT: Chronic pain disorders are more prevalent in females than males, but opioid receptor agonists show inconsistent analgesic efficacy in females. κ opioid receptor (KOR) agonists have been tested in clinical trials for treating pain disorders based on their analgesic properties and low addictive potential. However, the molecular mechanisms underlying sex differences in KOR actions were previously unknown. These studies identify an intracellular mechanism involving estradiol regulation of G protein-coupled receptor kinase 2 that is responsible for sexually dimorphic analgesic responses following opioid receptor activation. Understanding this mechanism will be critical for developing effective nonaddictive opioid analgesics for use in women and characterizing sexually dimorphic effects in other inhibitory G protein-coupled receptor signaling responses.

Connectome-Based Prediction of Cocaine Abstinence Sarah W. Yip, Dustin Scheinost, Marc N. Potenza, Kathleen M. Carroll; Am J Psychiatry, January 4, 2019.
The authors sought to identify a brain-based predictor of cocaine abstinence by using connectome-based predictive modeling (CPM), a recently developed machine learning approach. CPM is a predictive tool and a method of identifying networks that underlie specific behaviors ("neural fingerprints"). Fifty-three individuals participated in neuroimaging protocols at the start of treatment for cocaine use disorder, and again at the end of 12 weeks of treatment. CPM with leave-one-out cross-validation was conducted to identify pretreatment networks that predicted abstinence (percent cocaine-negative urine samples during treatment). Networks were applied to posttreatment functional MRI data to assess changes over time and ability to predict abstinence during follow-up. The predictive ability of identified networks was then tested in a separate, heterogeneous sample of individuals who underwent scanning before treatment for cocaine use disorder (N=45). CPM predicted abstinence during treatment, as indicated by a significant correspondence between predicted and actual abstinence values (r=0.42, df=52). Identified networks included connections within and between canonical networks implicated in cognitive/executive control (frontoparietal, medial frontal) and in reward responsiveness (subcortical, salience, motor/sensory). Connectivity strength did not change with treatment, and strength at posttreatment assessment also significantly predicted abstinence during follow-up (r=0.34, df=39). Network strength in the independent sample predicted treatment response with 64% accuracy by itself and 71% accuracy when combined with baseline cocaine use. These data demonstrate that individual differences in large-scale neural networks contribute to variability in treatment outcomes for cocaine use disorder, and they identify specific abstinence networks that may be targeted in novel interventions.

(R)- N-(1-Methyl-2-hydroxyethyl)-13-(S)-methyl-arachidonamide (AMG315): A Novel Chiral Potent Endocannabinoid Ligand with Stability to Metabolizing Enzymes Liu Y1, Ji L, Eno M, Kudalkar S, Li AL, Schimpgen M, Benchama O, Morales P, Xu S, Hurst D, Wu S, Mohammad KA, Wood JT, Zvonok N, Papahatjis DP, Zhou H, Honrao C, Mackie K, Reggio P, Hohmann AG, Marnett LJ, Makriyannis A, Nikas SP.J. Med. Chem. 2018; 61: 8639−8657.
The synthesis of potent metabolically stable endocannabinoids is challenging. Here the authors report a chiral arachidonoyl ethanolamide (AEA) analogue, namely, (13S,1′R)-dimethyl-

anandamide (AMG315, 3a), a high affinity ligand for the CB1 receptor (Ki of 7.8 ± 1.4 nM) that behaves as a potent CB1 agonist in vitro (EC50 = 0.6 ± 0.2 nM). (13S,1′R)-Dimethylanandamide is the first potent AEA analogue with significant stability for all endocannabinoid hydrolyzing enzymes as well as the oxidative enzymes COX-2. When tested in vivo using the CFA-induced inflammatory pain model, 3a behaved as a more potent analgesic when compared to endogenous AEA or its hydrolytically stable analogue AM356. This novel analogue will serve as a very useful endocannabinoid probe.

Association Studies Of Up To 1.2 Million Individuals Yield New Insights Into the Genetic Etiology Of Tobacco and Alcohol Use Mengzhen Liu, Yu Jiang, Robbee Wedow, Yue Li, David M. Brazel, et al., Nature Genetics January 14, 2019. https://www.nature.com/articles/s41588-018-0307-5#article-info.

Tobacco and alcohol use are leading causes of mortality that influence risk for many complex diseases and disorders. They are heritable and etiologically related behaviors that have been resistant to gene discovery efforts. In sample sizes up to 1.2 million individuals, the authors discovered 566 genetic variants in 406 loci associated with multiple stages of tobacco use (initiation, cessation, and heaviness) as well as alcohol use, with 150 loci evidencing pleiotropic association. Smoking phenotypes were positively genetically correlated with many health conditions, whereas alcohol use was negatively correlated with these conditions, such that increased genetic risk for alcohol use is associated with lower disease risk. The authors report evidence for the involvement of many systems in tobacco and alcohol use, including genes involved in nicotinic, dopaminergic, and glutamatergic neurotransmission. The results provide a solid starting point to evaluate the effects of these loci in model organisms and more precise substance use measures.

EPIDEMIOLOGY, PREVENTION AND SERVICES RESEARCH

Electronic Nicotine Delivery System (ENDS) Use In Relation To Mental Health Conditions, Past-month Serious Psychological Distress and Cigarette Smoking Status, 2017 Spears, Claire Adams; Jones, Dina M; Weaver, Scott R; Yang, Bo; Pechacek, Terry F; Eriksen, Michael P. Addiction. 2018.

Adults with mental health conditions (MHC) exhibit disproportionately high smoking prevalence and experience profound tobacco-related disparities. US nationally representative surveys from 2012 to 2015 found relatively high usage of electronic nicotine delivery systems (ENDS; e.g. e-cigarettes) among adults with MHC. However, research has not examined these associations specifically among never smokers. The aims of this study were to examine associations among MHC diagnosis, serious psychological distress (SPD) and ENDS use and to test whether associations varied by cigarette smoking status. This was a cross-sectional US nationally representative survey conducted in the United States in 2017 among participants comprising a total of 5762 adults (52.0% female; 64.8% non-Hispanic white, 11.4% non-Hispanic black, 15.9% Hispanic, 7.9% non-Hispanic other). Outcomes were lifetime, current and current daily ENDS use. Predictors were lifetime MHC, past-month SPD and cigarette smoking status, and covariates were gender, age, race/ethnicity, education and annual household income. Lifetime MHC and past-month SPD were each associated with higher likelihood of having ever used ENDS ($P \leq 0.001$), currently using ENDS ($P \leq 0.001$) and currently using ENDS daily ($P < 0.05$). There were interactions between MHC and smoking status in predicting ENDS use, such that MHC status predicted higher lifetime and current ENDS use specifically among never and current smokers. Never smokers with MHC had 2.62 higher odds [95% confidence interval, (CI) = 1.54, 4.45] of current ENDS use than

those without MHC. Among never smokers, those with MHC indicated higher expectations that ENDS would improve relaxation and concentration ($P < 0.05$). In 2017, US adults with versus without mental health conditions (MHC) were more likely to use electronic nicotine delivery systems (ENDS). In particular, both never and current smokers with MHC reported disproportionately high rates of current ENDS use.

Risks Of Fatal Opioid Overdose During The First Year Following Nonfatal Overdose
Olfson, Mark; Wall, Melanie; Wang, Shuai; Crystal, Stephen; Blanco, Carlos. Drug Alcohol Depend. 2018; 190: 112-119.
Little is known about risk factors for repeated opioid overdose and fatal opioid overdose in the first year following nonfatal opioid overdose. The authors identified a national retrospective longitudinal cohort of patients aged 18-64 years in the Medicaid program who received a clinical diagnosis of nonfatal opioid overdose. Repeated overdoses and fatal opioid overdoses were measured with the Medicaid record and the National Death Index. Rates of repeat overdose per 1000 person-years and fatal overdose per 100,000 person-years were determined. Hazard ratios of repeated opioid overdose and fatal opioid overdose were estimated by Cox proportional hazards. Nearly two-thirds (64.8%) of the patients with nonfatal overdoses (total n = 75,556) had filled opioid prescriptions in the 180 days before initial overdose. During the 12 months after nonfatal overdose, the rate of repeat overdose was 295.0 per 1000 person-years and that of fatal opioid overdose was 1154 per 100,000 person-years. After controlling for age, sex, race/ethnicity, and region, the hazard of fatal opioid overdose was increased for patients who had filled a benzodiazepine prescription in the 180 days prior to their initial overdose (HR = 1.71, 95%CI: 1.46-1.99), whose initial overdose involved heroin (HR = 1.57, 95%CI:1.30-1.89), or who required mechanical ventilation at the initial overdose (HR = 1.86, 95%CI = 1.50-2.31). Adults treated for opioid overdose frequently have repeated opioid overdoses in the following year. They are also at high risk of fatal opioid overdose throughout this period, which underscores the importance of efforts to engage and maintain patients in evidence-based opioid treatments following nonfatal overdose.

Cannabis Decriminalization: A Study Of Recent Policy Change In Five U.S. States
Grucza, Richard A; Vuolo, Mike; Krauss, Melissa J; Plunk, Andrew D; Agrawal, Arpana; Chaloupka, Frank J; Bierut, Laura J. Int J Drug Policy. 2018; 59: 67-75.
A number of public health professional organizations support the decriminalization of cannabis due to adverse effects of cannabis-related arrests and legal consequences, particularly on youth. The authors sought to examine the associations between cannabis decriminalization and both arrests and youth cannabis use in five states that passed decriminalization measures between the years 2008 and 2014: Massachusetts (decriminalized in 2008), Connecticut (2011), Rhode Island (2013), Vermont (2013), and Maryland (2014). Data on cannabis possession arrests were obtained from federal crime statistics; data on cannabis use were obtained from state Youth Risk Behavior Survey (YRBS) surveys, years 2007-2015. Using a "difference in difference" regression framework, the authors contrasted trends in decriminalization states with those from states that did not adopt major policy changes during the observation period. Decriminalization was associated with a 75% reduction in the rate of drug-related arrests for youth (95% CI: 44%, 89%) with similar effects observed for adult arrests. Decriminalization was not associated with any increase in the past-30 day prevalence of cannabis use overall (relative change=-0.2%; 95% CI: -4.5%, 4.3%) or in any of the individual decriminalization states. Decriminalization of cannabis in Massachusetts, Connecticut, Rhode Island, Vermont, and Maryland resulted in large decreases in cannabis possession arrests for both youth and adults, suggesting that the policy change had its intended consequence. This analysis did not find any increase in the prevalence of youth cannabis use during the observation period.

Mediating Pathways From Childhood ADHD To Adolescent Tobacco and Marijuana Problems: Roles Of Peer Impairment, Internalizing, Adolescent ADHD Symptoms, and Gender Elkins, Irene J; Saunders, Gretchen R B; Malone, Stephen M; Wilson, Sylia; McGue, Matt; Iacono, William G. J Child Psychol Psychiatry. 2018; 59(10): 1083-1093.
The authors examined whether increased risk for adolescent tobacco and marijuana problems associated with childhood ADHD is explained by key intermediary influences during adolescence and differs by gender. Longitudinal structural equation models examined mediating effects on problems with both substances (or each substance separately) through age-14 peer impairment, internalizing, and adolescent ADHD symptoms in two twin samples, prospectively assessed since age 11 (N = 2,164). Whether these mediators contributed beyond mediating effects of early-adolescent substance use was also considered. Twin difference analyses further illuminated which mediators might be potentially causal. Direct effects of childhood ADHD on age-17 tobacco and marijuana problems (i.e., independent of included mediators) as well as effects of adolescent ADHD symptoms were significant only for females. By contrast, mediation by peer impairment, evident particularly for marijuana, was relatively stronger for males than females. Depression and anxiety were not prospectively associated with age-17 substance problems when earlier substance problems were considered. Consistent with causal influence of early substance use on later problems, monozygotic twins with more severe tobacco or marijuana problems at age 14 than their co-twins were also more likely to have substance problems later in adolescence. Mediation through peer impairment, continued presence of ADHD symptoms, and early substance use may alter development so that childhood ADHD indirectly contributes to problems with tobacco and marijuana. Targeting gender-sensitive interventions prior to mid-adolescence, before these patterns become established, is essential.

Developmental Trajectories Of the Orbitofrontal Cortex and Anhedonia In Middle Childhood and Risk For Substance Use In Adolescence In A Longitudinal Sample Of Depressed and Healthy Preschoolers Luby, Joan L; Agrawal, Arpana; Belden, Andy; Whalen, Diana; Tillman, Rebecca; Barch, Deanna M. Am J Psychiatry. 2018; 175(10): 1010-1021.
Deficits in reward processing are established in mood and substance use disorders and are known risk factors for these disorders. Volume reductions of the orbitofrontal cortex and the striatum, regions that subserve neural response to reward, have been shown to be related to anhedonia in depressive and substance use disorders. The authors sought to investigate how structural maturation of these regions in childhood varies with level of anhedonia and predicts later substance use. The study employed data from a sample of depressed and healthy preschoolers studied longitudinally that included three waves of neuroimaging from school age to adolescence. Three years after scan 3, at ages 13-18, participants underwent a comprehensive behavioral and substance use assessment. Multilevel modeling was used to investigate the relationship between anhedonia and the growth trajectories of the striatum and orbitofrontal cortex. Zero-inflated Poisson regression models were then used to determine whether the intercepts and slopes of these trajectories predicted later alcohol and marijuana use frequency in adolescence. The anhedonia-by-age interaction was significant in the multilevel modeling of orbitofrontal cortical but not striatal volume. Higher anhedonia ratings were significantly associated with steeper decline in orbitofrontal cortical volume with age. Orbitofrontal cortical volume and thickness at age 12 and trajectory over time significantly and negatively predicted subsequent alcohol and marijuana use frequency but not depression during adolescence. The findings suggest that the development of the orbitofrontal cortex during childhood is strongly linked to experiences of anhedonia and that these growth trajectories predict substance use during a developmentally critical period.

Among Whom Is Cigarette Smoking Declining In The United States? The Impact Of Cannabis Use Status, 2002-2015 Pacek, Lauren R; Copeland, Jan; Dierker, Lisa; Cunningham, Chinazo O; Martins, Silvia S; Goodwin, Renee D. Drug Alcohol Depend. 2018; 191: 355-360.
The objectives of this study are 1) estimate changes in the prevalence of daily and non-daily cigarette smoking among current (past 30-day) daily, non-daily, and non-cannabis users in the United States (U.S.) population; 2) examine time trends in current (past 30-day) cigarette smoking in daily, non-daily, and non-cannabis users ages 12+ from 2002 to 2015. Data collected annually from the 2002 to 2015 National Survey on Drug Use and Health (NSDUH) were employed. Linear time trends of daily and non-daily cigarette smoking were assessed using logistic regression with year as the predictor. In 2015, the prevalence of current (past 30-day) cigarette smoking was highest among daily (54.57%), followed by non-daily (40.17%) and non-cannabis users (15.06%). The prevalence of non-daily cigarette smoking increased among daily cannabis users from 2002 to 2015, whereas non-daily cigarette smoking declined among non-daily cannabis users and non-cannabis users from 2002 to 2015. Daily cigarette smoking declined among both cannabis users and non-users; the most rapid decline was observed among daily cannabis users, followed by non-daily and then by non-cannabis users. However, the relative magnitude of the change in prevalence of daily cigarette smoking was similar across the three cannabis groups. Despite ongoing declines in cigarette smoking in the U.S., non-daily cigarette smoking is increasing among current cannabis users, a growing proportion of the U.S. Daily and non-daily cigarette smoking continue to decline among those who do not use cannabis. Efforts to further tobacco control should consider novel co-use-oriented intervention strategies and outreach for the increasing population of cannabis users.

Marijuana Use By Middle-aged and Older Adults In The United States, 2015-2016 Han, Benjamin H; Palamar, Joseph J. Drug Alcohol Depend. 2018; 191: 374-381.
Marijuana use is increasing among middle-aged and older adults in the US, but little is understood of its pattern of use by this population. The authors performed a cross-sectional analysis of responses from 17,608 adults aged ≥50 years from the 2015 and 2016 administrations of the National Survey on Drug Use and Health. Prevalence of past-year marijuana use was estimated and compared between middle-aged adults (age 50-64) and older adults (≥65). Characteristics of past-year marijuana users including demographics, substance use, chronic disease, and emergency room use, were compared to non-marijuana users and stratified by age group. Marijuana use characteristics were also compared between middle-aged and older adults. The authors used multivariable logistic regression to determine correlates of past-year marijuana use. Prevalence of past-year marijuana use was 9.0% among adults aged 50-64 and 2.9% among adults aged ≥65. Prevalence of past-year alcohol use disorder (AUD), nicotine dependence, cocaine use, and misuse of prescription medications (i.e., opioids, sedatives, tranquilizers) were higher among marijuana users compared to non-users. In adjusted models, initiation of marijuana use <19 years of age [adjusted odds ratio (AOR) = 13.43, 95% confidence interval (CI) 9.60, 18.78)], AUD (AOR = 2.11, 95% CI 1.51, 2.94), prescription opioid misuse (AOR 2.49, 95% CI 1.61, 3.85), nicotine dependence (AOR = 1.90, 95% CI 1.59, 2.26), and cocaine use (AOR 7.43, 95% CI 4.23, 13.03), were all associated with increased odds of past-year marijuana use. Marijuana use is becoming more prevalent in this population and users are also at high risk for other drug use.

Psychosocial Functioning Among Regular Cannabis Users With and Without Cannabis Use Disorder Foster, Katherine T; Arterberry, Brooke J; Iacono, William G; McGue, Matt; Hicks, Brian M. Psychol Med. 2018; 48(11): 1853-1861.
In the United States, cannabis accessibility has continued to rise as the perception of its harmfulness has decreased. Only about 30% of regular cannabis users develop cannabis use disorder (CUD), but

it is unclear if individuals who use cannabis regularly without ever developing CUD experience notable psychosocial impairment across the lifespan. Therefore, psychosocial functioning was compared across regular cannabis users with or without CUD and a non-user control group during adolescence (age 17; early risk) and young adulthood (ages 18-25; peak CUD prevalence). Weekly cannabis users with CUD (n = 311), weekly users without CUD (n = 111), and non-users (n = 996) were identified in the Minnesota Twin Family Study. Groups were compared on alcohol and illicit drug use, psychiatric problems, personality, and social functioning at age 17 and from ages 18 to 25. Self-reported cannabis use and problem use were independently verified using co-twin informant report. In both adolescence and young adulthood, non-CUD users reported significantly higher levels of substance use problems and externalizing behaviors than non-users, but lower levels than CUD users. High agreement between self- and co-twin informant reports confirmed the validity of self-reported cannabis use problems. Even in the absence of CUD, regular cannabis use was associated with psychosocial impairment in adolescence and young adulthood. However, regular users with CUD endorsed especially high psychiatric comorbidity and psychosocial impairment. The need for early prevention and intervention - regardless of CUD status - was highlighted by the presence of these patterns in adolescence.

A Family Focused Intervention Influences Hippocampal-Prefrontal Connectivity Through Gains In Self-Regulation Hanson, Jamie L; Gillmore, Alysha D; Yu, Tianyi; Holmes, Christopher J; Hallowell, Emily S; Barton, Allen W; Beach, Steven R H; Galván, Adrianna; MacKillop, James; Windle, Michael; Chen, Edith; Miller, Gregory E; Sweet, Lawrence H; Brody, Gene H. Child Dev. 2018 Oct 8.

The stressors associated with poverty increase the risks for externalizing psychopathology; however, specific patterns of neurobiology and higher self-regulation may buffer against these effects. This study leveraged a randomized control trial, aimed at increasing self-regulation at ~11 years of age. As adults, these same individuals completed functional MRI scanning (M age = 24.88 years; intervention n = 44; control n = 49). Functional connectivity between the hippocampus and ventromedial prefrontal cortex was examined in relation to the intervention, gains in self-regulation, and present-day externalizing symptoms. Increased connectivity between these brain areas was noted in the intervention group compared to controls. Furthermore, individual gains in self-regulation, instilled by the intervention, statistically explained this brain difference. These results begin to connect neurobiological and psychosocial markers of risk and resiliency.

Prospective Predictors Of Flavored E-cigarette Use: A One-year Longitudinal Study Of Young Adults In The U.S. Chen, Julia Cen; Green, Kerry M; Arria, Amelia M; Borzekowski, Dina L G. Drug Alcohol Depend. 2018; 191: 279-285.

E-cigarettes with fruit and candy flavors are appealing among young adults. This study examined the prospective predictors of young adult's flavored e-cigarette use to inform regulation and prevention efforts. The authors used the wave 1 (2013-2014) and wave 2 (2014-2015) data of the Population Assessment of Tobacco and Health (PATH) Study, a nationally representative cohort study of U.S. youth and adults. They analyzed a sample of young adults aged 18-34 (n = 12,383) to identify wave 1 prospective predictors (i.e., socio-demographic characteristics, mental health symptoms, marijuana use, tobacco use, and e-cigarette harm perceptions) of wave 2 flavored e-cigarette use. At wave 2, 8.0% of young adults used e-cigarettes, and 2.5% and 5.5% used tobacco and menthol (TM) and non-tobacco and non-menthol flavors (NTM) flavors, respectively. In the multivariable model, significant prospective predictors (wave 1) of NTM flavored e-cigarette use compared to TM flavored e-cigarette use (wave 2) were younger age (18-24 years) (AOR = 1.82, $p < 0.001$), female gender (AOR=1.81, $p < 0.001$), education attainment of high school graduate and

higher (AOR=1.60, p = 0.024), marijuana use (AOR=1.96, p < 0.001), ever but non-past-month cigarette smoking (AOR=2.75, p < 0.001), never cigarette smoking (AOR=5.08, p = 0.016), and lower harm perception of e-cigarettes (AOR=1.59, p = 0.005). This study highlights high rates of NTM flavor use and specific predictors of NTM flavored e-cigarettes use among young adults in the U.S. Regulation and prevention efforts for curbing flavored e-cigarette use among young adults should focus on these risk factors and high-risk groups (e.g., 18-24 years, female, and never cigarette smokers).

The Cascading Effects Of Multiple Dimensions Of Implementation On Program Outcomes: A Test Of A Theoretical Model Berkel, Cady; Mauricio, Anne M; Sandler, Irwin N; Wolchik, Sharlene A; Gallo, Carlos G; Brown, C Hendricks. Prev Sci. 2018; 19(6): 782-794.
This study tests a theoretical cascade model in which multiple dimensions of facilitator delivery predict indicators of participant responsiveness, which in turn lead to improvements in targeted program outcomes. An effectiveness trial of the 10-session New Beginnings Program for divorcing families was implemented in partnership with four county-level family courts. This study included 366 families assigned to the intervention condition who attended at least one session. Independent observers provided ratings of program delivery (i.e., fidelity to the curriculum and process quality). Facilitators reported on parent attendance and parents'competence in home practice of program skills. At pretest and posttest, children reported on parenting and parents reported child mental health. The authors hypothesized effects of quality on attendance, fidelity and attendance on home practice, and home practice on improvements in parenting and child mental health. Structural Equation Modeling with mediation and moderation analyses were used to test these associations. Results indicated quality was significantly associated with attendance, and attendance moderated the effect of fidelity on home practice. Home practice was a significant mediator of the links between fidelity and improvements in parent-child relationship quality and child externalizing and internalizing problems. Findings provide support for fidelity to the curriculum, process quality, attendance, and home practice as valid predictors of program outcomes for mothers and fathers. Future directions for assessing implementation in community settings are discussed.

Different Kinds Of Lonely: Dimensions Of Isolation and Substance Use In Adolescence Copeland, Molly; Fisher, Jacob C; Moody, James; Feinberg, Mark E. J Youth Adolesc. 2018; 47(8): 1755-1770**.**
Social isolation is broadly associated with poor mental health and risky behaviors in adolescence, a time when peers are critical for healthy development. However, expectations for isolates' substance use remain unclear. Isolation in adolescence may signal deviant attitudes or spur self-medication, resulting in higher substance use. Conversely, isolates may lack access to substances, leading to lower use. Although treated as a homogeneous social condition for teens in much research, isolation represents a multifaceted experience with structurally distinct network components that present different risks for substance use. This study decomposes isolation into conceptually distinct dimensions that are then interacted to create a systematic typology of isolation subtypes representing different positions in the social space of the school. Each isolated position's association with cigarette, alcohol, and marijuana use is tested among 9th grade students (n = 10,310, 59% female, 83% white) using cross-sectional data from the PROSPER study. Different dimensions of isolation relate to substance use in distinct ways: unliked isolation is associated with lower alcohol use, whereas disengagement and outside orientation are linked to higher use of all three substances. Specifically, disengagement presents risks for cigarette and marijuana use among boys, and outside orientation is associated with cigarette use for girls. Overall, the adolescents disengaged from their school network who also identify close friends outside their

grade are at greatest risk for substance use. This study indicates the importance of considering the distinct social positions of isolation to understand risks for both substance use and social isolation in adolescence.

Co-Occurring Psychosocial Problems Predict HIV Status and Increased Health Care Costs and Utilization Among Sexual Minority Men O'Cleirigh, C, Pantalone, DW, Batchelder, AW, Hatzenbuehler,ML, Marquez SM, Grasso,C, Safren, SA and Mayer, KH. J Behav Med. 2018 Aug; 41(4): 450–457.
Sexual orientation related health disparities are well documented. Sexual minority men appear to be at risk for mental health problems due to the stress they experience in establishing and maintaining a minority sexual identity. These mental health issues may combine synergistically and lead to higher medical costs to society. The authors examine whether sexual minority specific syndemic indicators were associated with higher health care costs, health care utilization, or the risk of being HIV-infected. Health care consumers at a community health center (N = 1211) completed a brief screening questionnaire collected over 12 months. Self-reported data were linked with participants' clinical billing records. Adjusted logistic regression models identified that four syndemic indicators (suicidality, substance use, childhood sexual abuse, and intimate partner violence) were each significantly related to each other. Multiple syndemics significantly predicted higher medical care utilization and cost, and were associated with 2.5 times the risk of being HIV-infected (OR 2.49, 95% CI 1.45–4.25). Syndemic indicators did not significantly predict the number of mental health visits or costs per patient. These results confirm and extend earlier findings by relating syndemics to health services use and costs for sexual minority men.

Buprenorphine Use and Spending For Opioid Use Disorder Treatment: Trends From 2003 To 2015 Roberts, Andrew W; Saloner, Brendan; Dusetzina, Stacie B. Psychiatr Serv. 2018; 69(7): 832-835.
This study examined buprenorphine prescription uptake and expenditure trends among privately insured adults from 2003 to 2015 to inform efforts to expand opioid use disorder treatment. A study with a repeated cross-sectional design using MarketScan prescription claims data was conducted to describe trends in total and new buprenorphine use and median total, plan, and out-of-pocket expenditures for a 30-day buprenorphine prescription among privately insured adults from 2003 to 2015. New and total buprenorphine users increased dramatically from 2003 to 2013 and plateaued. Total buprenorphine spending was stable from 2003 to 2008, increased from 2009 to 2013, and declined from 2013 to 2015. Out-of-pocket expenditures steadily decreased from $67 in 2003 to $32 in 2015 for a 30-day prescription. Buprenorphine treatment costs were stable for health plans and declined for privately insured adults since 2003. Identifying remaining barriers to addressing the opioid addiction treatment gap is a priority.

Legislators' Sources Of Behavioral Health Research and Preferences For Dissemination: Variations By Political Party Purtle, Jonathan; Dodson, Elizabeth A; Nelson, Katherine; Meisel, Zachary F; Brownson, Ross C. Psychiatr Serv. 2018; 69(10): 1105-1108.
This study sought to characterize primary sources of behavioral health research and dissemination preferences of state legislators and assess differences by political party. A 2017 cross-sectional survey of state legislators (N=475) assessed where legislators seek, and the most important features of, behavioral health research. Bivariate analyses and multivariate logistic regression were conducted. Advocacy organizations (53%), legislative staff (51%), and state agencies (48%) were identified most frequently as sources of behavioral health research. Universities were identified by

significantly more Democrats than Republicans (34% versus 19%; adjusted odds ratio=1.79). Data about budget impact and cost-effectiveness were most frequently rated as very important, but by significantly fewer Democrats than Republicans (77% versus 87% and 76% versus 89%, respectively). To reach legislators and satisfy their information preferences, behavioral health researchers should target diverse audiences, partner with intermediary organizations, and craft messages that include economic evaluation data.

Interim Buprenorphine Treatment During Delays To Comprehensive Treatment: Changes In Psychiatric Symptoms Streck, Joanna M. Ochalek, Taylor A. Badger, Gary J. Sigmon, Stacey C. Exp Clin Psychopharmacol. July 2018; 26(4): 403-409.
Prevalence of depression, anxiety, and mood disorders among individuals with opioid use disorder far exceeds that of the general population. While psychiatric symptoms often improve upon entry into opioid treatment, this has typically been seen with treatments involving psychosocial counseling. In this secondary analysis, the authors examined changes in psychiatric symptoms during a randomized clinical trial evaluating an interim buprenorphine treatment without counseling among individuals awaiting entry into comprehensive treatment. Waitlisted adults with opioid use disorder (N = 50) were randomized to one of two 12-week conditions: interim buprenorphine treatment (IBT; n = 25) consisting of buprenorphine maintenance using a computerized medication dispenser, with bimonthly clinic visits and technology-assisted monitoring, or waitlist control (WLC; n = 25), wherein participants remained on the waitlist of their local clinic. All participants completed assessments of psychiatric symptoms at intake and Study Weeks 4, 8, and 12. The authors examined changes on the Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), Brief Symptom Inventory (BSI), and Psychiatric subscale of the Addiction Severity Index (ASI). Significant group-by-time interactions were observed for all measures of psychiatric severity examined: BAI ($p < .05$), BDI-II ($p < .01$), 5 BSI subscales (ps < .05), and the ASI Psychiatric subscale ($p < .05$). On all measures, IBT participants reported significantly reduced psychiatric severity at the 4-, 8-, and 12-week assessments relative to baseline. In contrast, there were no significant changes in psychiatric symptoms among WLC participants. IBT without counseling may improve psychiatric distress among waitlisted individuals with opioid use disorder.

Computer-Facilitated 5A's For Smoking Cessation: A Randomized Trial Of Technology To Promote Provider Adherence Satterfield, Jason M; Gregorich, Steven E; Kalkhoran, Sara; Lum, Paula J; Bloome, Jessica; Alvarado, Nicholas; Muñoz, Ricardo F; Vijayaraghavan, Maya. Am J Prev Med. July 2018; 55(1): 35-43.
Although evidence-based, the 5A's (Ask, Advise, Assess, Assist, and Arrange) for smoking cessation are often incompletely delivered by primary care providers. This study examines whether a computer tablet 5A's intervention improves primary care provider adherence to the 5A's. Cluster RCT. All primary care providers in three urban, adult primary care clinics were randomized for participation. Any English- or Spanish-speaking patient with a primary care appointment who had smoked >100 lifetime cigarettes and at least one cigarette in the past week was eligible. A cluster RCT comparing computer-facilitated 5A's with usual care assessed effects on provider adherence to each of the 5A's as determined by patient report. Intervention subjects used a computer tablet to complete the 5A's immediately before a primary care appointment. A tailored, patient handout and a structured, clinician guide were generated. Data were collected in 2014-2015 and analyzed in 2016-2017.Provider adherence to the 5A's. Providers (N=221) saw 961 patients (n=412 intervention, n=549 control) for a total of n=1,340 encounters with n=1,011 completed post-visit interviews (75.4% completion). Intervention providers had significantly higher odds of completing Assess (AOR=1.32, 95% CI=1.02, 1.73) and Assist (AOR=1.45, 95% CI=1.08, 1.94). When

looking at first study visits only, intervention providers had higher odds for Arrange (AOR=1.72, 95% CI=1.23, 2.40) and all 5A's (AOR=2.04, 95% CI=1.35, 3.07) but study visit did not influence receipt of the other 5A's. A computer-facilitated 5A's delivery model was effective in improving the fidelity of provider-delivered 5A's to diverse primary care patients. This relatively low-cost, time-saving intervention has great potential for smoking cessation and other health behaviors. Future studies should identify ways to promote and sustain technology implementation. This study is registered at www.clinicaltrials.gov NCT02046408.

A Family Focused Intervention Influences Hippocampal-Prefrontal Connectivity Through Gains In Self-Regulation Hanson, Jamie L; Gillmore, Alysha D; Yu, Tianyi; Holmes, Christopher J; Hallowell, Emily S; Barton, Allen W; Beach, Steven R H; Galván, Adrianna; MacKillop, James; Windle, Michael; Chen, Edith; Miller, Gregory E; Sweet, Lawrence H; Brody, Gene H. Child Dev. 2018 Oct 8.

The stressors associated with poverty increase the risks for externalizing psychopathology; however, specific patterns of neurobiology and higher self-regulation may buffer against these effects. This study leveraged a randomized control trial, aimed at increasing self-regulation at ~11 years of age. As adults, these same individuals completed functional MRI scanning (M age = 24.88 years; intervention n = 44; control n = 49). Functional connectivity between the hippocampus and ventromedial prefrontal cortex was examined in relation to the intervention, gains in self-regulation, and present-day externalizing symptoms. Increased connectivity between these brain areas was noted in the intervention group compared to controls. Furthermore, individual gains in self-regulation, instilled by the intervention, statistically explained this brain difference. These results begin to connect neurobiological and psychosocial markers of risk and resiliency. The Strong African American Families (SAAF) program is a preventive intervention targeting parent-child relationships that has previously demonstrated long-term effects on child self-regulation and substance use, showing major reductions in conduct problems and lessened alcohol use after participation in the program. Findings from this analysis identify malleable neural systems involved in self-regulation; the SAAF intervention impacted parenting practices which led to changes in self-regulation, and the changes in self-regulation impacted neurobiology. These results provide initial evidence that a family oriented intervention can influence brain connectivity, in part, by improving self-regulatory abilities.

Association Of Pharmaceutical Industry Marketing Of Opioid Products To Physicians With Subsequent Opioid Prescribing Hadland, Scott E; Cerdá, Magdalena; Li, Yu; Krieger, Maxwell S; Marshall, Brandon D L. JAMA Intern Med. 2018; 178(6): 861-863.

Despite the increasing contribution of heroin and illicitly manufactured fentanyl to opioid-related overdose deaths in the United States, 40% of deaths involve prescription opioids. Prescription opioids are commonly the first opioid encountered in a trajectory toward illicit consumption. Although opioid prescribing has declined nationally, rates in 2015 were triple those in 1999 and remain elevated in regions of the country with higher numbers of overdoses. Pharmaceutical industry marketing to physicians is widespread, but it is unclear whether marketing of opioids influences prescribing. The authors studied the extent to which pharmaceutical industry marketing of opioid products to physicians during 2014 was associated with opioid prescribing during 2015.

All-Cause Mortality Among People With HIV Released From An Integrated System Of Jails and Prisons In Connecticut, USA, 2007-14: A Retrospective Observational Cohort Study Loeliger, Kelsey B; Altice, Frederick L; Ciarleglio, Maria M; Rich, Katherine M; Chandra, Divya K; Gallagher, Colleen; Desai, Mayur M; Meyer, Jaimie P. The Lancet 2018.

People transitioning from prisons or jails have high mortality, but data are scarce for people with HIV and no studies have integrated data from both criminal justice and community settings. The authors aimed to assess all-cause mortality in people with HIV released from an integrated system of prisons and jails in Connecticut, USA. They linked pharmacy, custodial, death, case management, and HIV surveillance data from Connecticut Departments of Correction and Public Health to create a retrospective cohort of all adults with HIV released from jails and prisons in Connecticut between 2007 and 2014. The authors compared the mortality rate of adults with HIV released from incarceration with the general US and Connecticut populations, and modelled time-to-death from any cause after prison release with Cox proportional hazard models. The authors identified 1350 people with HIV who were released after 24 h or more of incarceration between 2007 and 2014, of whom 184 (14%) died after index release; median age was 45 years (IQR 39-50) and median follow-up was 5·2 years (IQR 3·0-6·7) after index release. The crude mortality rate for people with HIV released from incarceration was 2868 deaths per 100 000 person-years, and the standardized mortality ratio showed that mortality was higher for this cohort than the general US population (6·97, 95% CI 5·96-7·97) and population of Connecticut (8·47, 7·25-9·69). Primary cause of death was reported for 170 individuals; the most common causes were HIV/AIDS (78 [46%]), drug overdose (26 [15%]), liver disease (17 [10%]), cardiovascular disease (16 [9%]), and accidental injury or suicide (13 [8%]). Black race (adjusted hazard ratio [HR] 0·52, 95% CI 0·34-0·80), having health insurance (0·09, 0·05-0·17), being re-incarcerated at least once for 365 days or longer (0·41, 0·22-0·76), and having a high percentage of re-incarcerations in which antiretroviral therapy was prescribed (0·08, 0·03-0·21) were protective against mortality. Positive predictors of time-to-death were age (≥50 years; adjusted HR 3·65, 95% CI 1·21-11·08), lower CD4 count (200-499 cells per μL, 2·54, 1·50-4·31; <200 cells per μL, 3·44, 1·90-6·20), a high number of comorbidities (1·86, 95% CI 1·23-2·82), virological failure (2·76, 1·94-3·92), and unmonitored viral load (2·13, 1·09-4·18). To reduce mortality after release from incarceration in people with HIV, resources are needed to identify and treat HIV, in addition to medical comorbidities, psychiatric disorders, and substance use disorders, during and following incarceration. Policies that reduce incarceration and support integrated systems of care between prisons and communities could have a substantial effect on the survival of people with HIV.

Potential Impact Of Implementing and Scaling Up Harm Reduction and Antiretroviral Therapy On HIV Prevalence and Mortality and Overdose Deaths Among People Who Inject Drugs In Two Russian Cities: A Modelling Study Cepeda, Javier A; Eritsyan, Ksenia; Vickerman, Peter; Lyubimova, Alexandra; Shegay, Marina; Odinokova, Veronika; Beletsky, Leo; Borquez, Annick; Hickman, Matthew; Beyrer, Chris; Martin, Natasha K. Lancet HIV. 2018 Oct;5(10)

Most new HIV infections among people who inject drugs (PWID) in eastern Europe and central Asia occur in Russia, where PWID have a high risk of overdose. In Russia, use of opioid agonist therapy (OAT) is prohibited, and coverage of needle and syringe programmes (NSPs) and antiretroviral therapy (ART) is poor. The authors aimed to assess the effects that scaling up harm reduction (i.e, use of OAT and coverage of NSPs) and use of ART might have on HIV incidence and the frequency of fatal overdoses among PWID in two cities in the Ural Federal District and Siberian Federal District, where the prevalence of HIV is high or increasing in PWID. In this modelling study, the authors developed a dynamic deterministic model that simulated transmission

of HIV through injection drug use and sex among PWID. They calibrated this model to HIV prevalence data among PWID in two Russian cities: Omsk (which has high but increasing prevalence of HIV among PWID) and Ekaterinburg (which has very high but stable prevalence of HIV). The source data were from research studies supported by the Global Fund to Fight AIDS, Tuberculosis, and Malaria and US Centers for Disease Control and Prevention and surveillance studies from WHO and regional AIDS centres. The authors modelled the effects of no intervention scale-up (no use of harm reduction measures and 30% of HIV-positive PWID receiving ART) versus combinations of scaling up of OAT, receipt of high coverage of NSPs, and use of ART on the incidence of HIV infections, mortality from HIV, and the frequency of fatal overdoses from 2018 to 2028. Without intervention, HIV prevalence among PWID in Omsk could increase from 30% in 2018 to 36% (2·5-97·5 percentile interval 22-52) in 2028 and remain high in Ekaterinburg, estimated at 60% (57-67) in 2028. Scaling up OAT to 50% coverage for a duration of 2 years could prevent 35% of HIV infections and 19% of deaths associated with HIV in Omsk and 20% (11-29) of HIV infections and 10% (4-14) of deaths associated with HIV in Ekaterinburg. Further, this scaling up could prevent 33% of overdose deaths over the next 10 years. Scaling up of NSPs and OAT to 50% coverage and tripling recruitment to ART (reaching about 65% of HIV-positive PWID) could prevent 58% (46-69) of HIV infections and 45% (36-54) of deaths associated with HIV in Omsk and 38% (26-50) of HIV infections and 32% (23-41) of deaths associated with HIV in Ekaterinburg by 2028. Legalization of OAT and increased use of ART and NSPs for PWID are urgently needed to prevent HIV and fatal overdose among PWID in Russia.

TREATMENT RESEARCH

Effects Of Lorcaserin On Reinstatement Of Responding Previously Maintained By Cocaine Or Remifentanil In Rhesus Monkeys Gerak, Lisa R; Collins, Gregory T; Maguire, David R; France, Charles P. Exp Clin Psychopharmacol. 2018.
Drug abuse remains a serious public health issue, underscoring the need for additional treatment options. Agonists at serotonin (5-HT)2C receptors, particularly lorcaserin, are being considered as pharmacotherapies for abuse of a variety of drugs, including cocaine and opioids. The current study compared the capacity of lorcaserin to attenuate reinstatement of extinguished responding previously maintained by either cocaine or an opioid; this type of procedure is thought to model relapse, an important aspect of drug abuse. Six rhesus monkeys responded under a fixed-ratio schedule for cocaine (0.032 mg/kg/infusion) or remifentanil (0.00032 mg/kg/infusion). Reinstatement of extinguished responding was examined following administration of noncontingent infusions of cocaine (0.32 mg/kg) or heroin (0.0032-0.1 mg/kg) combined with response-contingent presentations of the drug-associated stimuli, or heroin alone without presentation of drug-associated stimuli. When combined with drug-associated stimuli, cocaine and heroin increased extinguished responding. On average, monkeys emitted fewer reinstated responses following 0.32 mg/kg cocaine, compared with the number of responses emitted when cocaine was available for self-administration or when extinguished responding was reinstated by 0.032 mg/kg heroin. When drug-associated stimuli were not presented, heroin did not increase responding. Lorcaserin dose dependently attenuated reinstated responding, and its potency was similar regardless of whether cocaine or heroin was given before reinstatement sessions. The generality of this effect of lorcaserin across pharmacological classes of abused drugs might make it particularly useful for reducing relapse-related behaviors in polydrug abusers.

Lorcaserin Decreases The Reinforcing Effects Of Heroin, But Not Food, In Rhesus Monkeys
Kohut, Stephen J; Bergman, Jack. Eur J Pharmacol. 2018; 840: 28-32.
Preclinical studies indicate that lorcaserin (Belviq®), an FDA-approved serotonin 2 C receptor agonist, may be a promising medication for the treatment of stimulant addiction. However, few studies have investigated its effects on self-administration of drugs of abuse from other pharmacological classes, including opioids. Here, adult male rhesus macaques (N = 3) responded under a fixed ratio 30 schedule of food (1-g banana-flavored pellets) and IV heroin delivery. Following stable self-administration of a range of heroin doses (0.32-32 μg/kg/inj, IV), the effects of acute pretreatment with lorcaserin (0.32-1.0 mg/kg, IM) on heroin- and food-maintained responding was determined. The ability of repeated treatment with lorcaserin (1.0 mg/kg) to produce sustained decreases in heroin and/or food intake and reinforcing strength were then analyzed using behavioral economic demand procedures. Results show that self-administration of intravenous heroin was dose-dependent, with peak responding maintained, on average, by the unit dose of 3.2 μg/kg/inj. Lorcaserin pretreatment produced a dose-dependent flattening of the dose-response function for heroin self-administration in each subject. On the other hand, lorcaserin did not decrease food-maintained responding. Repeated lorcaserin treatment reduced heroin intake by selectively decreasing its reinforcing strength, as evidenced by a leftward shift in the demand curves for heroin and the absence of comparable changes in the reinforcing strength of food. These results indicate that serotonin 2 C receptor agonists, such as lorcaserin, have behaviorally selective effects on IV self-administration behavior, and deserve further consideration as candidates for the management of opioid use disorder.

The Novel M-opioid Receptor Agonist PZM21 Depresses Respiration and Induces Tolerance To Antinociception Hill, Rob; Disney, Alex; Conibear, Alex; Sutcliffe, Katy; Dewey, William; Husbands, Stephen; Bailey, Chris; Kelly, Eamonn; Henderson, Graeme. Br J Pharmacol. 2018; 175(13): 2653-2661.
PZM21 is a novel μ-opioid receptor ligand that has been reported to induce minimal arrestin recruitment and be devoid of the respiratory depressant effects characteristic of classical μ receptor ligands such as morphine. He authors have re-examined the signalling profile of PZM21 and its ability to depress respiration.G protein (Gi) activation and arrestin-3 translocation were measured in vitro, using BRET assays, in HEK 293 cells expressing μ receptors. Respiration (rate and tidal volume) was measured in awake, freely moving mice by whole-body plethysmography, and antinociception was measured by the hot plate test.PZM21 (10-9 - 3 × 10-5 M) produced concentration-dependent Gi activation and arrestin-3 translocation. Comparison with responses evoked by morphine and DAMGO revealed that PZM21 was a low efficacy agonist in both signalling assays. PZM21 (10-80 mg·kg-1) depressed respiration in a dose-dependent manner. The respiratory depression was due to a decrease in the rate of breathing not a decrease in tidal volume. On repeated daily administration of PZM21 (twice daily doses of 40 mg·kg-1), complete tolerance developed to the antinociceptive effect of PZM21 over 3 days but no tolerance developed to its respiratory depressant effect.These data demonstrate that PZM21 is a low efficacy μ receptor agonist for both G protein and arrestin signalling. Contrary to a previous report, PZM21 depresses respiration in a manner similar to morphine, the classical opioid receptor agonist.

Pharmacological Comparisons Between Cannabidiol and KLS-13019 Brenneman, Douglas E; Petkanas, Dean; Kinney, William A. J Mol Neurosci. 2018; 66(1): 121-134.
Cannabidiol (CBD) exhibits neuroprotective properties in many experimental systems. However, development of CBD as a drug has been confounded by the following: (1) low potency; (2) a large number of molecular targets; (3) marginal pharmacokinetic properties; and (4) designation as a

schedule 1 controlled substance. The present work compared the properties of CBD with a novel molecule (KLS-13019) that has structural similarities to CBD. The design strategy for KLS-13019 was to increase hydrophilicity while optimizing neuroprotective potency against oxidative stress toxicity relevant to hepatic encephalopathy. The protective responses of CBD and KLS-13019 were compared in dissociated rat hippocampal cultures co-treated with toxic levels of ethanol and ammonium acetate. This comparison revealed that KLS-13019 was 31-fold more potent than CBD in preventing neuronal toxicity from the combined toxin treatment, while both compounds exhibited complete protective efficacy back to control values. In addition, treatment with KLS-13019 alone was 5-fold less toxic (TC50) than CBD. Previous studies suggested that CBD targeted the Na+-Ca2+ exchanger in mitochondria (mNCX) to regulate intracellular calcium levels, an important determinant of neuronal survival. After treatment with an inhibitor of mNCX (CGP-37157), no detectable neuroprotection from ethanol toxicity was observed for either CBD or KLS-13019. Furthermore, AM630 (CB2 antagonist) significantly attenuated CBD-mediated neuroprotection, while having no detectable effect on neuroprotection from KLS-13019. Our studies indicated KLS-13019 was more potent and less toxic than CBD. Both compounds can act through mNCX. KLS-13019 may provide an alternative to CBD as a therapeutic candidate to treat diseases associated with oxidative stress.

A Bifunctional Nociceptin and Mu Opioid Receptor Agonist Is Analgesic Without Opioid Side Effects In Nonhuman Primates Ding, Huiping; Kiguchi, Norikazu; Yasuda, Dennis; Daga, Pankaj R; Polgar, Willma E; Lu, James J; Czoty, Paul W; Kishioka, Shiroh; Zaveri, Nurulain T; Ko, Mei-Chuan. Sci Transl Med. 2018; 10(456).

Misuse of prescription opioids, opioid addiction, and overdose underscore the urgent need for developing addiction-free effective medications for treating severe pain. Mu opioid peptide (MOP) receptor agonists provide very effective pain relief. However, severe side effects limit their use in the clinical setting. Agonists of the nociceptin/orphanin FQ peptide (NOP) receptor have been shown to modulate the antinociceptive and reinforcing effects of MOP agonists. The authors report the discovery and development of a bifunctional NOP/MOP receptor agonist, AT-121, which has partial agonist activity at both NOP and MOP receptors. AT-121 suppressed oxycodone's reinforcing effects and exerted morphine-like analgesic effects in nonhuman primates. AT-121 treatment did not induce side effects commonly associated with opioids, such as respiratory depression, abuse potential, opioid-induced hyperalgesia, and physical dependence. These results in nonhuman primates suggest that bifunctional NOP/MOP agonists with the appropriate balance of NOP and MOP agonist activity may provide a dual therapeutic action for safe and effective pain relief and treating prescription opioid abuse.

The G-protein Biased Mu-opioid Agonist, TRV130, Produces Reinforcing and Antinociceptive Effects That Are Comparable To Oxycodone In Rats Austin Zamarripa, C; Edwards, Shelley R; Qureshi, Hina N; Yi, John N; Blough, Bruce E; Freeman, Kevin B. Drug Alcohol Depend. 2018; 192: 158-162.

Mu-opioid agonists (e.g., oxycodone) are highly effective therapeutics for pain. However, they also produce reinforcing effects that increase their likelihood of abuse. Recent strategies in drug development have focused on opioids with biased receptor-signaling profiles that favor activation of specific intracellular pathways over others with the aim of increasing therapeutic selectivity. TRV130, a mu agonist biased towards G-protein signaling, produces antinociceptive effects comparable to the mu agonist, morphine, but exhibits reduced side effects. However, in terms of abuse potential, the authors know of no published preclinical data investigating the effects of

TRV130 as a reinforcer. In the present study, they assessed the relative reinforcing effects of TRV130 and oxycodone, a commonly-prescribed mu agonist, in rats self-administering the drugs under a progressive-ratio (PR) schedule of reinforcement. In addition, they assessed the relative potency and efficacy of TRV130 and oxycodone in rats in a test of thermal antinociception (Hot Plate). For self-administration, male Sprague-Dawley rats (n = 7) self-administered intravenous infusions of TRV130 or oxycodone (0.01-0.32 mg/kg/inj) under a PR schedule of reinforcement. For the Hot-Plate test, male rats (n = 7) received subcutaneous injections of TRV130 (0.1-3.2 mg/kg/inj) or oxycodone (0.1-5.6 mg/kg/inj), and nociceptive response latencies were measured. TRV130 and oxycodone were equi-potent and equi-effective in self-administration and thermal antinociception. This study demonstrates that TRV130 produces reinforcing and antinociceptive effects that are quantitatively similar to oxycodone, and that a biased-signaling profile does not necessarily reduce abuse potential.

Effects Of Lorcaserin and Buspirone, Administered Alone and As A Mixture, On Cocaine Self-administration In Male and Female Rhesus Monkeys Collins, Gregory T; France, Charles P. Exp Clin Psychopharmacol. 2018; 26(5): 488-496.
Cocaine use disorder is a serious public health issue for which there is no effective pharmacotherapy. One strategy to speed development of medications for cocaine use disorder is to repurpose drugs already approved for use in humans based on their ability to interact with targets known to be important for addiction. Two such drugs, lorcaserin (Belviq; a drug with serotonin [5-HT]2C receptor agonist properties) and buspirone (Buspar; a drug with 5-HT1A receptor partial agonist and dopamine D3/D4 receptor antagonist properties) can produce modest decreases in cocaine self-administration in rhesus monkeys. The current study evaluated the effectiveness of mixtures of lorcaserin and buspirone (at fixed dose ratios of 3:1, 1:1, and 1:3 relative to each drug's ID50) to reduce responding for 0.032 mg/kg/inf cocaine under a progressive ratio schedule of reinforcement in 2 male and 2 female rhesus monkeys. Dose addition analyses were used to determine if the effects of the drug mixtures differed from those predicted for an additive interaction between lorcaserin and buspirone. Dose-dependent reductions of cocaine self-administration were observed when lorcaserin and buspirone were administered alone, as well as when they were administered as 3:1, 1:1, and 1:3 fixed ratio mixtures of lorcaserin + buspirone. The effects of the 1:1 mixture of lorcaserin + buspirone on cocaine self-administration were supraadditive, whereas the effects of 3:1 and 1:3 mixtures were additive. Together, these results indicate that a combination therapy containing a mixture of lorcaserin and buspirone might be more effective than either drug alone at treating cocaine use disorder.

A Sub-set Of Psychoactive Effects May Be Critical To The Behavioral Impact Of Ketamine On Cocaine Use Disorder: Results From A Randomized, Controlled Laboratory Study Dakwar, E; Nunes, E V; Hart, C L; Hu, M C; Foltin, R W; Levin, F R. Neuropharmacology. 2018; 142: 270-276.
Efforts to translate sub-anesthetic ketamine infusions into widespread clinical use have centered around developing medications with comparable neurobiological activity, but with attenuated psychoactive effects so as to minimize the risk of behavioral toxicity and abuse liability. Converging lines of research, however, suggest that some of the psychoactive effects of sub-anesthetic ketamine may have therapeutic potential. Here, the authors assess whether a subset of these effects - the so-called mystical-type experience - mediates the effect of ketamine on craving and cocaine use in cocaine dependent research volunteers. They found that ketamine leads to significantly greater acute mystical-type effects (by Hood Mysticism Scale: HMS), dissociation (by Clinician Administered Dissociative States Scale: CADSS), and near-death experience phenomena

(by the Near-Death Experience Scale: NDES), relative to the active control midazolam. HMS score, but not the CADSS or NDES score, was found to mediate the effect of ketamine on global improvement (decreased cocaine use and craving) over the post-infusion period. This is the first controlled study to show that mystical-type phenomena, long considered to have therapeutic potential, may work to impact decision-making and behavior in a sustained manner. These data suggest that an important direction for medication development is the identification of ketamine-like pharmacotherapy that is selectively psychoactive (as opposed to free of experiential effects entirely), so that mystical-type perspectival shifts are more reliably produced and factors lending to abuse or behavioral impairment are minimized. Future research can further clarify the relationship between medication-occasioned mystical-type effects and clinical benefit for different disorders. This article is part of the Special Issue entitled 'Psychedelics: New Doors, Altered Perceptions'.

Effects Of Electronic Cigarette Liquid Solvents Propylene Glycol and Vegetable Glycerin On User Nicotine Delivery, Heart Rate, Subjective Effects, and Puff Topography Spindle, Tory R; Talih, Soha; Hiler, Marzena M; Karaoghlanian, Nareg; Halquist, Matthew S; Breland, Alison B; Shihadeh, Alan; Eissenberg, Thomas. Drug Alcohol Depend. 2018; 188: 193-199.
Electronic cigarettes (ECIGs) are a class of tobacco products that produce different effects (e.g., nicotine delivery), depending on the device, liquid, and behavioral factors. However, the influence of the two primary ECIG liquid solvents, propylene glycol (PG) and vegetable glycerin (VG), on ECIG acute effects is unknown. Thirty ECIG-experienced, ≥12-h nicotine- abstinent participants completed four conditions consisting of two ECIG-use bouts (10 puffs, 30 s interpuff-interval) differing only by liquid PG:VG ratio (2PG:98VG, 20PG:80VG, 55PG:45VG, 100PG). Device power (7.3 W) and liquid nicotine concentration (18 mg/ml) remained constant. Nicotine delivery, subjective effects, heart rate (HR), and puff topography were assessed. In the 100PG condition, participants took shorter and smaller puffs but obtained significantly more nicotine relative to the two VG-based conditions. Total nicotine exposure (i.e., area under the curve) was also significantly higher during use of the two PG-based liquids. However, participants reported that the 100 PG liquid was significantly less "pleasant" and "satisfying" relative to the other liquids (all ps < .05). Increases in HR and decreases in abstinence symptoms (e.g., "craving") did not differ across conditions. PG:VG ratio influenced nicotine delivery, some subjective effects, and puff topography. Lower overall product satisfaction associated with the 100PG liquid suggests factors other than nicotine delivery (e.g., aerosol visibility) may play a role in maintaining ECIG use. Regulating ECIG acute effects such as nicotine delivery and subjective effects may require simultaneous attention to liquid PG:VG ratio as well as device, liquid, and behavioral factors known to influence these outcomes.

Emerging Trends In Cannabis Administration Among Adolescent Cannabis Users Knapp, Ashley A; Lee, Dustin C; Borodovsky, Jacob T; Auty, Samantha G; Gabrielli, Joy; Budney, Alan J. J Adolesc Health. 2018.
The legal landscape of cannabis availability and use in the United States is rapidly changing. As the heterogeneity of cannabis products and methods of use increases, more information is needed on how these changes affect use, especially in vulnerable populations such as youth. A national sample of adolescents aged 14-18 years (N = 2,630) were recruited online through advertisements displayed on Facebook and Instagram to complete a survey on cannabis. The survey assessed patterns of edible use, vaping, and smoking cannabis, and the associations among these administration routes and use of other substances. The most frequent and consistent route of cannabis use was smoking (99% lifetime), with substantial numbers reporting vaping (44% lifetime) and edible use (61%

lifetime). The majority of those who had experimented with multiple routes of cannabis administration continued to prefer smoking, and the most common pattern of initiation was smoking, followed by edibles and then vaping. In addition to cannabis use, adolescents reported high rates of nicotine use and substantial use of other substances. Adolescents who used more cannabis administration routes tended to also report higher frequency of other substances tried. Additional work is needed to determine whether the observed adolescent cannabis administration patterns are similar across different samples and sampling methods as well as how these trends change over time with extended exposure to new products and methods. The combined knowledge gained via diverse sampling strategies will have important implications for the development of regulatory policy and prevention and intervention efforts.

Associations Between Marijuana Use and Tobacco Cessation Outcomes In Young Adults
Erin A. Vogela, Mark L. Rubinsteinb, Judith J. Prochaskac, Danielle E. Ramoa. J Subst Abuse Treat. 2018; 94: 69-73.
Marijuana and tobacco co-use is common among young adults, and findings are mixed regarding the association between marijuana use and smoking cessation outcomes. This study examined the longitudinal relationships between marijuana use and smoking cessation outcomes among young adults (aged 18-25 years; N = 500) enrolled in a 3-month smoking cessation intervention on Facebook. At baseline and 3, 6, and 12 months, participants reported their marijuana use and their smoking behaviors (seven-day point prevalence abstinence from smoking, cigarettes per day, quit attempts) and readiness to quit. Longitudinal analyses controlled for experimental condition and adjusted for baseline stage of change, baseline average cigarettes per day, sex, alcohol use, and age participants began smoking regularly. Use of marijuana by young adult smokers was associated with a lower likelihood of reduced smoking (OR = 0.71, 95% CI [0.51, 0.98], p = .036) and a lower likelihood of abstaining from smoking (OR = 0.56, 95% CI [0.35, 0.90], p = .017) in the past seven days, as assessed over 12 months of follow-up. Use of marijuana was not significantly associated with perceptions of or engagement in the smoking cessation intervention, stage of change for quitting smoking, or tobacco quit attempts (all p > 0.08). Study findings indicate that while marijuana use is unrelated to motivation to quit tobacco and engage in cessation interventions, marijuana use is associated with less success in reducing and abstaining from tobacco. Additional support and targeted tobacco cessation strategies to address challenges associated with marijuana co-use may be needed.

Buprenorphine Medication-assisted Treatment During Pregnancy: An Exploratory Factor Analysis Associated With Adherence Coker, Jessica L; Catlin, David; Ray-Griffith, Shona; Knight, Bettina; Stowe, Zachary N. Drug Alcohol Depend. 2018; 192: 146-149.
The treatment of pregnant women with opioid use disorder is challenging due to the myriad of physical, mental, and social complications. Factors influencing adherence to buprenorphine during pregnancy have not been identified. Pregnant women with opioid use disorder followed in a tertiary clinic were included in a retrospective chart review from buprenorphine induction through delivery. All women who had been evaluated and treated with buprenorphine from January 1, 2014, to September 31, 2016, were included. Adherence was defined as follows: 1) adherent: attended follow up visits, negative urine toxicology screens, and phase advancement; 2) moderately adherent: attended follow up visits until delivery, had not completed six negative urine toxicology screens, or had positive urine toxicology screens (i.e., no phase advancement); 3) non-adherent: missed follow up visits and did not stay in treatment until delivery. Sociodemographic characteristics, family psychiatric history, current and lifetime psychiatric and childhood trauma along with treatment factors were compared by category of adherence. Sixty-four women met

criteria for inclusion in this study with 41 (64%) adherent; eight (13%) moderately adherent; and 15 (23%) non-adherent. In the non-adherent group compared to the adherent group, the clinician-rated opioid withdrawal scale score was significantly higher, and the daily buprenorphine dose at last visit was significantly lower. Women who were non-adherent to buprenorphine during pregnancy had higher severity of opioid withdrawal symptoms and lower doses of buprenorphine. These findings should be further explored with the goal of optimizing care without increasing risk for neonates.

Reduction In Cannabis Use and Functional Status In Physical Health, Mental Health, and Cognition Mooney, Larissa J; Zhu, Yuhui; Yoo, Caroline; Valdez, Jonathan; Moino, Kevin; Liao, Jung-Yu; Hser, Yih-Ing. J Neuroimmune Pharmacol. 2018; 13(4): 479-487.
Treatment for substance use disorders has traditionally been abstinence-oriented, but evaluating the merits of low-level cannabis use as potential treatment endpoint may identify benefits that are clinically relevant for treatment-seeking individuals who do not attain abstinence. This study explores if reduction in cannabis use to a lower level of use is related to improved physical health, mental health, and perceived cognitive functions. Study participants with a history of problematic cannabis use (n = 111) completed assessments. Regression models were used to explore the relationship between past 30-day cannabis use levels (abstinent [57%], low use [22%] defined as less than or equal to 3 days per week, and heavy use [22%] defined as 4 or more days of use per week) and functional status in physical health, mental health, and cognition. Compared to heavy users, both abstinent and low-use individuals were similarly associated with better global health, appetite, and depression outcomes. Abstinent users also reported improved sleep, anxiety, and self-reported cognitive functioning relative to heavy users. Thus, reduction in cannabis use to lower levels is associated with beneficial outcomes important to health and other areas of functioning in individuals with problematic cannabis use.

Methadone Maintenance Treatment Among Patients Exposed To Illicit Fentanyl In Rhode Island: Safety, Dose, Retention, and Relapse At 6 Months Stone, Andrew C; Carroll, Jennifer J; Rich, Josiah D; Green, Traci C. Drug Alcohol Depend. 2018; 192: 94-97.
Illicitly manufactured fentanyl (IMF) is a potent synthetic opioid that has been contributing to overdose deaths in the United States. This study examined intake toxicology and six-month treatment outcomes for patients newly admitted to a single methadone maintenance treatment program (MMTP) in Rhode Island with a high prevalence of illicit fentanyl. The authors conducted a retrospective chart review of patients admitted to a single MMTP between November 1st, 2016 and August 31st, 2017 followed for six months. Outcomes measured included: 1) retention in treatment at 6 months; 2) evidence of sustained abstinence; 3) relapse; 4) methadone dosage required to achieve sustained abstinence; and 5) the number of days required to achieve abstinence. The authors observed 154 unique intake events (representing 147 patients). 80% (n = 123) tested positive for fentanyl at intake. During the six-month follow up period, 32% (n = 49) left treatment before six months, two individuals died within five weeks of discontinuation. No deaths were seen among those remaining in treatment. The majority (89%) who remained in treatment at six months achieved abstinence. No significant difference was seen for dose or time to achieve abstinence. Relapse was common (57%). Repeated exposure to fentanyl was seen frequently (71%) while in MMT before and after achieving abstinence. While there is concern that the potency of IMF may reduce the effectiveness of MAT, this study suggests that MMT is safe, abstinence achievable, and MMT is protective against death among fentanyl-exposed patients.

Blocking Drug Activation As A Therapeutic Strategy To Attenuate Acute Toxicity and Physiological Effects Of Heroin Zhang, Ting; Zheng, Xirong; Kim, Kyungbo; Zheng, Fang; Zhan, Chang-Guo. Sci Rep. 2018; 8(1): 16762.
Heroin is a growing national crisis in America. There is an increasing frequency of heroin overdoses. All of the currently used therapeutic approaches to treatment of heroin abuse and other opioid drugs of abuse focus on antagonizing a brain receptor (particularly μ-opiate receptors). However, it has been known that the therapeutic use of certain μ-opiate receptor antagonist may actually increase heroin overdose. Once overdosed, heroin addicts may continue to get overdosed again and again until fatal. Here the authors report their design and validation of a novel therapeutic strategy targeting heroin activation based on their analysis of the chemical transformation and functional change of heroin in the body. An effective blocker of heroin activation, such as ethopropazine tested in this study, may be used as a standalone therapy or in combination with a currently available, traditional medications targeting μ-opiate receptors (e.g. naltrexone or its extended-release formulation Vivitrol). The combination therapy would be ideal for heroin abuse treatment as the effects of two therapeutic agents targeting two independent mechanisms are cooperative.

Methamphetamine-associated Dysregulation Of The Hypothalamic-pituitary-thyroid Axis Jones, Deborah L; Carrico, Adam W; Babayigit, Suat; Rodriguez, Violeta J; Aguila, Carlos; Kumar, Mahendra. J Behav Med. 2018; 41(6): 792-797.
Methamphetamine and HIV impair thyroid function, but few studies have investigated their combined effects on thyroid dysregulation. This study examined the associations of methamphetamine use alone and in combination with HIV on thyroid function among men in South Florida. Measures of thyroid function in methamphetamine-using, HIV-infected (METH+HIV+; n = 127) and HIV-negative (METH+HIV-; n = 46) men who have sex with men (MSM) were compared to non-methamphetamine-using, HIV-negative men (METH-HIV-; n = 136). Thyroid function was dysregulated in methamphetamine-using MSM, irrespective of HIV status. Both meth-using groups had greater odds of abnormal thyroid stimulating hormone levels and significantly higher mean free triiodothyronine (T3) levels. Elevated free T3 was associated with greater depressive symptoms. Overall, outcomes have important implications for assessment of thyroid function in methamphetamine users, particularly among those presenting with depression.

Kinetic Characterization Of Cholinesterases and A Therapeutically Valuable Cocaine Hydrolase For Their Catalytic Activities Against Heroin and Its Metabolite 6-monoacetylmorphine Kim, Kyungbo; Yao, Jianzhuang; Jin, Zhenyu; Zheng, Fang; Zhan, Chang-Guo. Chem Biol Interact. 2018; 293: 107-114.
As the most popularly abused one of opioids, heroin is actually a prodrug. In the body, heroin is hydrolyzed/activated to 6-monoacetylmorphine (6-MAM) first and then to morphine to produce its toxic and physiological effects. It has been known that heroin hydrolysis to 6-MAM and morphine is accelerated by cholinesterases, including acetylcholinesterase (AChE) and/or butyrylcholine-esterase (BChE). However, there has been controversy over the specific catalytic activities and functional significance of the cholinesterases, which requires for the more careful kinetic characterization under the same experimental conditions. Here the authors report the kinetic characterization of AChE, BChE, and a therapeutically promising cocaine hydrolase (CocH1) for heroin and 6-MAM hydrolyses under the same experimental conditions. It has been demonstrated that AChE and BChE have similar kcat values (2100 and 1840 min-1, respectively) against heroin, but with a large difference in KM (2170 and 120 μM, respectively). Both AChE and BChE can catalyze 6-MAM hydrolysis to morphine, with relatively lower catalytic efficiency compared to the

heroin hydrolysis. CocH1 can also catalyze hydrolysis of heroin (kcat = 2150 min-1 and KM = 245 μM) and 6-MAM (kcat = 0.223 min-1 and KM = 292 μM), with relatively larger KM values and lower catalytic efficiency compared to BChE. Notably, the KM values of CocH1 against both heroin and 6-MAM are all much larger than previously reported maximum serum heroin and 6-MAM concentrations observed in heroin users, implying that the heroin use along with cocaine will not drastically affect the catalytic activity of CocH1 against cocaine in the CocH1-based enzyme therapy for cocaine abuse.

Vaccination Reduces Fentanyl Distribution To The Brain and Fentanyl-induced Toxicity In Mice and Rats: A Potential Role For A Prophylactic Vaccine Against Fentanyl-induced Overdose Raleigh, Michael D; Baruffaldi, Federico; Peterson, Samantha J; Le Naour, Morgan; Harmon, Theresa M; Vigliaturo, Jennifer R; Pentel, Paul R; Pravetoni, Marco. J Pharmacol Exp Ther. 2018.

Fentanyl is an extremely potent synthetic opioid that has been increasingly used to adulterate heroin, cocaine and counterfeit prescription pills leading to an increase in opioid-induced fatal overdoses in the US, Canada, and Europe. A vaccine targeting fentanyl could offer protection against fatal overdoses in both recreational drug users and others in professions at risk of accidental exposure. This study focuses on the development of a vaccine consisting of a fentanyl hapten (F) conjugated to keyhole limpet hemocyanin (KLH) carrier protein or to GMP-grade subunit KLH (sKLH). Immunization with F-KLH in mice and rats reduced fentanyl-induced hotplate antinociception and in rats reduced fentanyl distribution to brain compared to controls. F-KLH did not reduce antinociceptive effects of equianalgesic doses of heroin or oxycodone in rats. To assess vaccine effect on fentanyl toxicity, rats immunized with F-sKLH or unconjugated sKLH were exposed to increasing s.c. doses of fentanyl. Vaccination with F-sKLH shifted the dose-response curves to the right for both fentanyl-induced antinociception and respiratory depression. Naloxone reversed fentanyl effects in both groups, showing that its activity for reversing opioid overdose was preserved. These data demonstrate pre-clinical selectivity and efficacy of a fentanyl vaccine and suggest that vaccines may offer a therapeutic option in reducing fentanyl-induced overdoses.

Preclinical Efficacy and Characterization Of Candidate Vaccines For Treatment Of Opioid Use Disorders Using Clinically Viable Carrier Proteins Baruffaldi, Federico; Kelcher, April Huseby; Laudenbach, Megan; Gradinati, Valeria; Limkar, Ajinkya; Roslawski, Michaela; Birnbaum, Angela; Lees, Andrew; Hassler, Carla; Runyon, Scott; Pravetoni, Marco. Mol Pharm. 2018; 15(11): 4947-4962.

Vaccines may offer a new treatment strategy for opioid use disorders and opioid-related overdoses. To speed translation, this study evaluates opioid conjugate vaccines containing components suitable for pharmaceutical manufacturing and compares analytical assays for conjugate characterization. Three oxycodone-based haptens (OXY) containing either PEGylated or tetraglycine [(Gly)4] linkers were conjugated to a keyhole limpet hemocyanin (KLH) carrier protein via carbodiimide (EDAC) or maleimide chemistry. The EDAC-conjugated OXY(Gly)4-KLH was most effective in reducing oxycodone distribution to the brain in mice. Vaccine efficacy was T cell-dependent. The lead OXY hapten was conjugated to the KLH, tetanus toxoid, diphtheria cross-reactive material (CRM), as well as the E. coli-expressed CRM (EcoCRM) and nontoxic tetanus toxin heavy chain fragment C (rTTHc) carrier proteins. All vaccines induced early hapten-specific B cell expansion and showed equivalent efficacy against oxycodone in mice. However, some hapten-protein conjugates were easier to characterize for molecular weight and size. Finally, heroin vaccines formulated with either EcoCRM or KLH were equally effective in reducing heroin-induced antinociception and

distribution to the brain of heroin and its metabolites in mice. This study identifies vaccine candidates and vaccine components for further development.

HIV/AIDS RELATED RESEARCH

Frontline Science: Buprenorphine Decreases CCL2-mediated Migration Of CD14+ CD16+ Monocytes Jaureguiberry-Bravo, Matias; Lopez, Lillie; Berman, Joan W. J Leukoc Biol. 2018; 104(6): 1049-1059.
HIV infection of the CNS causes neuroinflammation and damage that contributes to the development of HIV-associated neurocognitive disorders (HAND) in greater than 50% of HIV-infected individuals, despite antiretroviral therapy (ART). Opioid abuse is a major risk factor for HIV infection. It has been shown that opioids can contribute to increased HIV CNS pathogenesis, in part, by modulating the function of immune cells. HIV enters the CNS within two weeks after peripheral infection by transmigration of infected monocytes across the blood brain barrier (BBB). CD14+ CD16+ monocytes are a mature subpopulation that is increased in number in the peripheral blood of HIV-infected people. Mature monocytes can be productively infected with HIV, and they transmigrate preferentially across the BBB in response to CCL2, a chemokine elevated in the CNS and CSF of HIV-infected people even with ART. Buprenorphine, an opioid derivate, is an opioid replacement therapy for heroin addiction. It is a partial agonist of μ-opioid receptor and full antagonist of κ-opioid receptor. The effects of buprenorphine on CCL2-mediated CD14+ CD16+ monocytes transmigration across the BBB, a critical mechanism that promotes neuroinflammation and HAND, have not been characterized. The authors showed for the first time that buprenorphine decreases several steps of CCL2-mediated human mature monocyte transmigration. They propose that buprenorphine treatment in the context of HIV infection could serve a dual purpose, to treat opioid addiction and also to reduce neuroinflammation. Additionally, buprenorphine may be used as a treatment for HAND not only in the context of opioid abuse.

Associations Between Cannabis Use, Sexual Behavior, and STIs/HIV In A Cohort Of Young Men Who Have Sex With Men Gorbach, Pamina M; Javanbakht, Marjan; Shover, Chelsea L; Bolan, Robert K; Ragsdale, Amy; Shoptaw, Steven. Sex Transm Dis. 2018.
Among men who have sex with men (MSM) the relationship between sexually transmitted infections (STIs) and cannabis use is not well established. The authors assessed cannabis use, sexual behavior, and STIs including HIV in a diverse cohort of young MSM. In Los Angeles the mSTUDY cohort conducted visits every 6 months with 512 MSM between 2014 and 2017 collecting demographics, sexual behaviors, and reports of frequency of substance use. Each visit conducted testing for gonorrhea, chlamydia and syphilis via blood, urine, and pharyngeal and rectal swabs by PCR, HIV was assessed using rapid tests for HIV negatives and viral load for HIV positives. The authors analyzed the relationship between cannabis use, sexual behaviors and STIs/HIV across 1,535 visits. Significantly fewer participants tested positive for STIs at visits when reporting the previous 6 months use of only cannabis (11.7%) compared to no drugs (16.3%) or other drugs (20.0%), (p=0.01). Fewer MSM reporting only cannabis use than no or other drug use had been incarcerated, had incarcerated partners, experienced interpersonal violence, and were HIV positive. In multivariable analyses visits with positive STIs were associated with other drug use (adjusted odds ratio (AOR) 1.69, 95% CI (1.03-2.78)) but not use of cannabis only or no drug use after controlling for age, HIV status, new sex partners, and number of sex partners. When MSM reported

using cannabis exclusively fewer STIs were detected and lower risk sexual engagements reported than when MSM reported no drug or other drug use.

Measurement Of Current Substance Use In A Cohort Of HIV-Infected Persons In Continuity HIV Care, 2007-2015 Lesko, Catherine R; Keil, Alexander P; Moore, Richard D; Chander, Geetanjali; Fojo, Anthony T; Lau, Bryan. Am J Epidemiol. 2018; 187(9): 1970-1979.
Accurate, routine measurement of recent illicit substance use is challenging. The Johns Hopkins Human Immunodeficiency Virus Clinical Cohort (Baltimore, Maryland) collects 2 imperfect but routine measurements of recent substance use: medical record review and self-interview. The authors used Bayesian latent class modeling to estimate sensitivity and specificity of each measurement as well as prevalence of substance use among 2,064 patients engaged in care during 2007-2015. Sensitivity of medical record review was higher than sensitivity of self-interview for cocaine and heroin use; posterior estimates ranged from 44% to 76% for cocaine use and from 39% to 67% for heroin use, depending on model assumptions and priors. In contrast, sensitivity of self-interview was higher than sensitivity of medical record review for any alcohol use, hazardous alcohol use, and cigarette smoking. Posterior estimates of sensitivity of self-interview were generally above 80%, 85%, and 87% for each substance, respectively. Specificity was high for all measurements. From one model, the authors estimated prevalence of substance use in the cohort to be 12.5% for cocaine, 9.3% for heroin, 48.5% for alcohol, 21.4% for hazardous alcohol, and 55.4% for cigarettes. Prevalence estimates from other models were generally comparable. Measurement error of substance use is nontrivial and should be accounted for in subsequent analyses.

High-Risk Prescription Opioid Use Among People Living With HIV Canan, Chelsea E; Chander, Geetanjali; Monroe, Anne K; Gebo, Kelly A; Moore, Richard D; Agwu, Allison L; Alexander, G Caleb; Lau, Bryan; HIV Research Network. J Acquir Immune Defic Syndr. 2018; 78(3): 283-290.
Prescription opioid use is greater among people living with HIV (PLWH), yet little is known about the prevalence of specific types of high-risk use among these individuals. The authors analyzed clinical and demographic data from the HIV Research Network and prescribing data from Medicaid for noncancer patients seeking HIV treatment at 4 urban clinics between 2006 and 2010. HIV Research Network patients were included in the analytic sample if they received at least one incident opioid prescription. The authors examined 4 measures of high-risk opioid use: (1) high daily dosage; (2) early refills; (3) overlapping prescriptions; and (4) multiple prescribers. Of 4605 eligible PLWH, 1814 (39.4%) received at least one incident opioid prescription during follow-up. The sample was 61% men and 62% African American with a median age of 44.5 years. High-risk opioid use occurred among 30% of incident opioid users (high daily dosage: 7.9%; early refills: 15.9%; overlapping prescriptions: 16.4%; and multiple prescribers: 19.7%). About half of the cumulative incidence of high-risk use occurred within 1 year of receiving an opioid prescription. After adjusting for study site, high-risk opioid use was greater among patients with injection drug use as an HIV risk factor [adjusted hazard ratio (aHR) = 1.39, 95% confidence interval: 1.11 to 1.74], non-Hispanic whites [aHR = 1.61, (1.21 to 2.14)], patients age 35-45 [aHR = 1.94, (1.33 to 2.80)] and 45-55 [aHR = 1.84, (1.27 to 2.67)], and patients with a diagnosis of chronic pain [aHR = 1.32, (1.03 to 1.70)]. A large proportion of PLWH received opioid prescriptions, and among these opioid recipients, high-risk opioid use was common. High-risk use patterns often occurred within the first year, suggesting this is a critical time for intervention.

Network Analysis Of Hippocampal Neurons By Microelectrode Array In The Presence Of HIV-1 Tat and Cocaine Mohseni Ahooyi, Taha; Shekarabi, Masoud; Decoppet, Emilie A; Langford, Dianne; Khalili, Kamel; Gordon, Jennifer. J Cell Physiol. 2018;233(12): 9299-9311.
HIV-associated neurocognitive disorders affecting greater than 30% of patients are caused by HIV-1 infection of the CNS, and in part, include neurotoxic effects of the viral transactivator of transcription, Tat protein. In addition to increasing the risk for becoming HIV infected, cocaine abuse enhances the neuropathogenic impacts of HIV-1. To investigate the outcome of Tat and cocaine interference in the hippocampal neuronal network, cross-rank-corrlation was employed to develop a systematic framework to assess hippocampal neurons behavior cultured on multielectrode arrays. Tat and cocaine differentially disturbed neuronal spiking rates, amplitude, synchronous activity, and oscillations within the hippocampal neuronal network via potentiation of inhibitory neurotransmission. The Tat-mediated impairment of neuronal spiking was reversible by removal of Tat, which restored neuronal activity. The presence of astrocytes co-cultured with neuronal networks diminished the effects of Tat and cocaine on neuron function suggesting a role for astrocytes in stabilizing neuronal behavior and increasing neuronal spontaneous activities such as bursting amplitude, frequency, and wave propagation rate. Taken together, thes studies indicate that the HIV protein Tat and cocaine impair hippocampal neuronal network functioning and that the presence of astrocytes alleviates network dysfunction pointing to a newly discovered pathway through which ionic homeostasis is maintained by neuron-glial crosstalk in the CNS.

Neuroprotective Effects Of Fatty Acid Amide Hydrolase Catabolic Enzyme Inhibition In A HIV Tat Model Of Neuroaids Douglas J. Hermes, Changqing Xu, Justin L. Poklis, Micah J. Niphakis, Benjamin F. Cravatt, Ken Mackie, Aron H. Lichtman, Bogna M. Ignatowska-Jankowska, Sylvia Fitting; Neuropharmacology, 2018;141:55-65.
The HIV-1 transactivator of transcription (Tat) is a neurotoxin involved in the pathogenesis of HIV-1 associated neurocognitive disorders (HAND). The neurotoxic effects of Tat are mediated directly via AMPA/NMDA receptor activity and indirectly through neuroinflammatory signaling in glia. Emerging strategies in the development of neuroprotective agents involve the modulation of the endocannabinoid system. A major endocannabinoid, anandamide (N-arachidonoyl-ethanolamine, AEA), is metabolized by fatty acid amide hydrolase (FAAH). Here the authors demonstrate using a murine prefrontal cortex primary culture model that the inhibition of FAAH, using PF3845, attenuates Tat-mediated increases in intracellular calcium, neuronal death, and dendritic degeneration via cannabinoid receptors (CB_1R and CB_2R). Live cell imaging was used to assess Tat-mediated increases in $[Ca^{2+}]_i$, which was significantly reduced by PF3845. A time-lapse assay revealed that Tat potentiates cell death while PF3845 blocks this effect. Additionally PF3845 blocked the Tat-mediated increase in activated caspase-3 (apoptotic marker) positive neurons. Dendritic degeneration was characterized by analyzing stained dendritic processes using Imaris and Tat was found to significantly decrease the size of processes while PF3845 inhibited this effect. Incubation with CB_1R and CB_2R antagonists (SR141716A and AM630) revealed that PF3845-mediated calcium effects were dependent on CB_1R, while reduced neuronal death and degeneration was CB_2R-mediated. PF3845 application led to increased levels of AEA, suggesting the observed effects are likely a result of increased endocannabinoid signaling at CB_1R/CB_2R. These findings suggest that modulation of the endogenous cannabinoid system through inhibition of FAAH may be beneficial in treatment of HAND.

CTN-RELATED RESEARCH

Prevalence and Patterns of Opioid Misuse and Opioid Use Disorder Among Primary Care Patients Who Use Tobacco John WS, Zhu H, Mannelli P, Subramaniam GA, Schwartz RP, McNeely J, Wu LT. Drug Alcohol Depend. 2019 Jan 1;194:468-475. doi: 10.1016/j.drugalcdep.2018.11.011. Epub 2018 Nov 26.

Current data suggest that opioid misuse or opioid use disorder (OUD) may be over represented among tobacco users. However, this association remains understudied in primary care settings. A better understanding of the extent of heterogeneity in opioid misuse among primary care patients who use tobacco may have implications for improved primary care-based screening, prevention, and intervention approaches. Data were derived from a sample of 2000 adult (aged ≥18) primary care patients across 5 distinct clinics. Among past-year tobacco users (n = 882), the authors assessed the prevalence of opioid misuse and OUD by sociodemographic characteristics and past-year polysubstance use. Latent class analysis (LCA) was used to identify heterogeneous subgroups of tobacco users according to past-year polysubstance use patterns. Multinomial logistic regression was used to examine variables associated with LCA-defined class membership. Past-year tobacco use was reported by >84% of participants who reported past-year opioid misuse or OUD. Among those reporting past-year tobacco use, the prevalence of past-year opioid misuse and OUD was 14.0% and 9.5%, respectively. The prevalence of opioid misuse or OUD was highest among tobacco users who were male or unemployed. Three LCA-defined classes among tobacco users were identified including a tobacco-minimal drug use group (78.0%), a tobacco-cannabis use group (10.1%), and a tobacco-opioid/polydrug use group (11.9%). Class membership differed by sociodemographic characteristics. Results from this study support the benefit of more comprehensive assessment of and/or monitoring for opioid misuse among primary care patients who use tobacco, particularly for those who are male, unemployed, or polydrug users.

Multicomorbidity of Chronic Diseases and Substance Use Disorders and Their Association with Hospitalization: Results from Electronic Health Records Data Wu LT, Zhu H, Ghitza UE. Drug Alcohol Depend. 2018 Nov 1;192:316-323. doi: 10.1016/j.drugalcdep.2018.08.013. Epub 2018 Oct 2.

Chronic diseases are prevalent and the leading causes of mortality. Comorbidity of substance use disorders (SUDs) and chronic diseases is understudied to inform behavioral healthcare integration. This study leveraged electronic health record (EHR) data of 211,880 adults from a large health system to examine prevalence and correlates of comorbidity of SUDs and nine chronic disease groups and to determine their association with hospitalization. Logistic regression analyses were conducted to estimate associations between chronic diseases and SUDs. To control for severity of diagnosis, analyses of associations between SUD and hospitalization were stratified by the number of chronic conditions. In the sample, 48.3% had ≥1 chronic condition (hypertension 33.7%, arthritis 16.2%, diabetes 13.7%, chronic kidney disease 9.9%, asthma 9.1%, chronic obstructive pulmonary disease 8.9%, ischemic heart disease 8.3%, cancer 4.6%, and hepatitis 1.3%). Prevalence of SUD (overall 13.3%) among patients increased with multiple chronic conditions (14.3% having SUD among patients with one condition; 21.2% having SUD among patients with two to three conditions; and 32.5% having SUD among patients with 4-9 conditions). Chronic conditions were associated with increased odds of SUDs. For all SUD groups, hospitalization was more prevalent among patients with SUD than those without it; prevalence of hospitalization increased with the number of comorbid chronic conditions. Findings reveal a striking pattern of multicomorbidity of SUD and chronic diseases and its positive association with hospitalization. Behavioral healthcare

integration should consider efforts to assess and treat comorbid SUD and chronic diseases, especially among adults with multiple chronic conditions.

Tobacco Use During Cannabis Cessation: Use Patterns and Impact on Abstinence in a National Drug Abuse Treatment Clinical Trials Network Study McClure EA, Baker NL, Sonne SC, Ghitza UE, Tomko RL, Montgomery L, Babalonis S, Terry GE, Gray KM. Drug Alcohol Depend. 2018 Nov 1;192:59-66. doi: 10.1016/j.drugalcdep.2018.07.018. Epub 2018 Aug 25.
It is common for cannabis users to also use tobacco. While data suggest that tobacco users have more difficulty achieving cannabis cessation, secondary analyses of clinical trial data sets may provide insight into the moderating variables contributing to this relationship, as well as changes in tobacco use during cannabis treatment. Those were the aims of this secondary analysis.
The parent study was a multi-site trial of N-acetylcysteine for cannabis dependence conducted within the National Drug Abuse Treatment Clinical Trials Network. Participants were treatment-seeking adults (ages 18-50) who met criteria for cannabis dependence (N = 302). For cigarette smokers (n = 117), tobacco use was assessed via timeline follow-back and nicotine dependence was assessed via the Fagerström Test for Nicotine Dependence (FTND). Outcome measures included: 1) changes in tobacco use based on treatment assignment, nicotine dependence, and concurrent cannabis reduction/abstinence, and 2) independent associations between nicotine dependence and cannabis abstinence. Cigarette smokers accounted for 39% of the sample (117/302), with a median FTND score of 3.0 (10-point scale). Among those with lower baseline nicotine dependence scores, cigarette smoking was reduced in the active treatment group compared to placebo. Those with moderate/high levels of nicotine dependence showed slight increases in smoking following active treatment. Nicotine dependence did not affect cannabis cessation. Cigarette smoking during cannabis treatment was affected, but depended on baseline nicotine dependence severity, though dependence levels did not impact cannabis abstinence. Interventions that address both tobacco and cannabis are needed, especially due to an increasing prevalence of cannabis use.

Cost-Effectiveness of Buprenorphine-Naloxone Versus Extended-Release Naltrexone to Prevent Opioid Relapse Murphy SM, McCollister KE, Leff JA, Yang X, Jeng PJ, Lee JD, Nunes EV, Novo P, Rotrosen J, Schackman BR. Ann Intern Med. 2018 Dec 18. doi: 10.7326/M18-0227. [Epub ahead of print].
Not enough evidence exists to compare buprenorphine-naloxone with extended-release naltrexone for treating opioid use disorder. The objective of this study was to evaluate the cost-effectiveness of buprenorphine-naloxone versus extended-release naltrexone. This was a cost-effectiveness analysis alongside a previously reported randomized clinical trial of 570 adults in 8 U.S. inpatient or residential treatment programs. The sujects studied were adults with opioid use disorder. This was a 24-week intervention with an additional 12 weeks of observation.Interventions employed were buprenorphine-naloxone and extended-release naltrexone. Study outcome measures included incremental costs combined with incremental quality-adjusted life-years (QALYs) and incremental time abstinent from opioids. Use of the health care sector perspective and a willingness-to-pay threshold of $100 000 per QALY showed buprenorphine-naloxone to be preferable to extended-release naltrexone in 97% of bootstrap replications at 24 weeks and in 85% at 36 weeks. Similar results were obtained with incremental time abstinent from opioids as an outcome and with use of the societal perspective. The base-case results were sensitive to the cost of the 2 treatments and the success of randomized treatment initiation. Study limmitations included a relatively short follow-up for a chronic condition, substantial missing data, no information on patient out-of-pocket and social service costs. The authors conclude that buprenorphine-naloxone is preferred to extended-release

naltrexone as first-line treatment when both options are clinically appropriate and patients require detoxification before initiating extended-release naltrexone.

Substance Use Outcomes in Cocaine-dependent Tobacco Smokers: A Mediation Analysis Exploring the Role of Sleep Disturbance, Craving, Anxiety, and Depression Winhusen TM, Theobald J, Lewis DF. J Subst Abuse Treat. 2019 Jan;96:53-57. doi: 10.1016/j.jsat.2018.10.011. Epub 2018 Oct 26. TRIAL REGISTRATION: ClinicalTrials.gov: NCT01077024
Sleep disturbance may play a role in cocaine use outcomes and, hence, may be a potential therapeutic target for cocaine use disorder (CUD). Research in this area, which has largely relied on resource-intensive polysomnography, would be facilitated by identifying a self-report sleep measure predictive of CUD outcomes and by a better understanding of the mechanisms by which sleep may impact CUD outcomes. This study tested the predictive validity of the Pittsburgh Sleep Quality Index (PSQI), a self-report assessment of past-month sleep quality. To better understand potential mechanisms, mediation models relating sleep disturbance to CUD outcomes were evaluated.
This is a secondary analysis of data from cocaine-dependent (n = 290) participants in a multi-site trial evaluating smoking-cessation treatment for stimulant-dependent patients. The PSQI was collected at baseline; the outcomes of interest were cocaine and drug abstinence at end-of-treatment (weeks 9-10). Potential mediators, measured in weeks 1-8, were: cocaine craving (Brief Substance Craving Scale); and anxiety and depression symptoms (Hospital Anxiety and Depression Scale). Mediation techniques were used to evaluate mediation effects separately and jointly. The majority of participants (58.3%) had baseline sleep disturbance. Sleep disturbance was not a significant predictor of end-of-treatment abstinence when regressed without consideration of mediators. Cocaine craving, anxiety, and depression were significant mediators, both separately and jointly, of an effect of baseline sleep disturbance on end-of-treatment abstinence. This exploratory analysis suggests that there may be an indirect relationship between self-reported sleep quality and substance use outcomes in cocaine-dependent patients, mediated by craving, anxiety, and depression.

INTRAMURAL RESEARCH

Medicinal Chemistry Section
Molecular Targets and Medications Discovery Branch

Dopamine D3R Antagonist VK4-116 Attenuates Oxycodone Self-Administration and Reinstatement Without Compromising Its Antinociceptive Effects You Z-B, Bi G-H, Galaj E, Kumar V, Cao J, Gadiano A, Rais R, Slusher BS, Gardner EL, Xi Z-X and Newman AH. Neuropsychopharmacology. 2018 Nov 27.
Prescription opioids such as oxycodone are highly effective analgesics for clinical pain management, but their misuse and abuse have led to the current opioid epidemic in the United States. In order to ameliorate this public health crisis, the development of effective pharmacotherapies for the prevention and treatment of opioid abuse and addiction is essential and urgently required. In this study, the authors evaluated—in laboratory rats—the potential utility of VK4-116, a novel and highly selective dopamine D3 receptor (D3R) antagonist, for the prevention and treatment of prescription opioid use disorders. Pretreatment with VK4-116 (5–25 mg/kg, i.p.) dose-dependently inhibited the acquisition and maintenance of oxycodone self-administration. VK4-116 also lowered the breakpoint (BP) for oxycodone self-administration under a progressive-ratio schedule of reinforcement, shifted the oxycodone dose–response curve downward, and inhibited oxycodone extinction responding and reinstatement of oxycodone seeking behavior. In

addition, VK4-116 pretreatment dose-dependently enhanced the antinociceptive effects of oxycodone and reduced naloxone precipitated conditioned place aversion in rats chronically treated with oxycodone. In contrast, VK4-116 had little effect on oral sucrose self-administration. Taken together, these findings indicate a central role for D3Rs in opioid reward and support further development of VK4-116 as an effective agent for mitigating the development of opioid addiction, reducing the severity of withdrawal and preventing relapse.

Addiction Biology Unit, Medicinal Chemistry Section
Molecular Targets and Medications Discovery Branch

Deletion Of The Type 2 Metabotropic Glutamate Receptor Increases Heroin Abuse Vulnerability In Transgenic Rats Gao J-T, Jordan CJ, Bi GH, He Y, Yang HJ, Gardner EL, Xi Z-X Neuropsychopharmacology. 2018 Dec;43(13):2615-2626.
Opioid abuse is a rapidly growing public health crisis in the USA. Despite extensive research in the past decades, little is known about the etiology of opioid addiction or the neurobiological risk factors that increase vulnerability to opioid use and abuse. Recent studies suggest that the type 2 metabotropic glutamate receptor (mGluR2) is critically involved in substance abuse and addiction. In the present study, the authors evaluated whether low-mGluR2 expression may represent a risk factor for the development of opioid abuse and addiction using transgenic mGluR2-knockout (mGluR2-KO) rats. Compared to wild-type controls, mGluR2-KO rats exhibited higher nucleus accumbens (NAc) dopamine (DA) and locomotor responses to heroin, higher heroin self-administration and heroin intake, more potent morphine-induced analgesia and more severe naloxone-precipitated withdrawal symptoms. In contrast, mGluR2-KO rats displayed lower motivation for heroin self-administration under high price progressive-ratio (PR) reinforcement conditions. Taken together, these findings suggest that mGluR2 may play an inhibitory role in opioid action, such that deletion of this receptor results in an increase in brain DA responses to heroin and in acute opioid reward and analgesia. Low-mGluR2 expression in the brain may therefore be a risk factor for the initial development of opioid abuse and addiction.
Neuroimaging Research Branch

Striatal Activity Correlates With Stimulant-Like Effects Of Alcohol In Healthy Volunteers Weafer J, Ross TJ, O'Connor S, Stein EA, de Wit H, Childs E. Neuropsychopharmacology. 2018 Dec;43(13):2532-2538. doi: 10.1038/s41386-018-0166-x. Epub 2018 Aug 1.
Individuals who experience greater stimulation and less sedation from alcohol are at increased risk for alcohol-related problems. However, little is known regarding the neurobiological mechanisms underlying subjective response to alcohol. The current study examined the degree to which alcohol-induced brain activation correlates with ratings of stimulation and sedation, using a within-subjects, double-blind, placebo-controlled design. Participants (N = 34 healthy adults with no history of alcohol use disorder) completed three sessions: a calibration session to determine the duration of infusion needed to bring the breath alcohol to 80 mg/dl for each subject, and two counterbalanced fMRI sessions with placebo and alcohol administration. During the fMRI sessions, participants underwent 50 min scans, which included a 10 min baseline period, the IV infusion period needed to bring breath alcohol concentration (BrAC) to a peak 80 mg/dl (on the alcohol session), followed by a post-peak decline period. Participants rated their subjective stimulation and sedation at regular intervals throughout the scan. A priori VOI analyses showed that the time course of stimulation correlated with BOLD signal in the striatum. The time course of sedation did not correlate with BOLD signal in any VOIs. There were no correlations in primary visual cortex, which served as a

control. These findings are the first to show that alcohol effects in the striatum are linked to the positive, stimulant-like effects of the drug and advance our understanding of the neurobiological mechanisms underlying individual differences in subjective responses to alcohol, and more broadly, risk for alcohol use disorders.

Molecular Neuropsychiatry Research Branch

Expression Of Immediate Early Genes In Brain Reward Circuitries: Differential Regulation By Psychostimulant and Opioid Drugs Bisagno V, Cadet JL. Neurochem Int. 2018 Dec 14. pii: S0197-0186(18)30516-3.
Although some of the clinical manifestations of substance use disorders might be superficially similar, it is highly likely that different classes of abused drugs including opioids (heroin, morphine, and oxycodone, other opioids) and psychostimulants (cocaine and amphetamines) cause different neuroadaptations in various brain regions dependent in the distribution and concentration of their biochemical sites of actions. In fact, different molecular networks are indeed impacted by acute and chronic administration of addictive substances. Some of the genes whose expression is influenced by the administration of these substances are immediate-early genes (IEGs). IEGs include classes of low expression genes that can become very highly induced within seconds or minutes of activation by endogenous or exogenous stimuli. These IEGs might play important roles in activating target genes that regulate adaptations implicated in the behavioral manifestations diagnosed as addiction. Therefore, the purpose of this review is to provide an overview of recent data on the effects of psychostimulants and opioids on IEG expression in the brain. The review documents some contrasting effects of these classes of drugs on gene expression and indicates that further studies are necessary to identify the specific effects of each drug class when trying to predict clinical responses to therapeutic agents.

Molecular Mechanisms of Cellular Stress and Inflammation

Gesicle-Mediated Delivery Of CRISPR/Cas9 Ribonucleoprotein Complex For Inactivating The HIV Provirus Campbell LA, Coke LM, Richie CT, Fortuno LV, Park AY, Harvey BK. Mol Ther. 2019 Jan 2;27(1):151-163. doi: 10.1016/j.ymthe.2018.10.002. Epub 2018 Oct 11.
Investigators have utilized the CRISPR/Cas9 gene-editing system to specifically target well-conserved regions of HIV, leading to decreased infectivity and pathogenesis in vitro and ex vivo. The authors utilized a specialized extracellular vesicle termed a "gesicle" to efficiently, yet transiently, deliver Cas9 in a ribonucleoprotein form targeting the HIV long terminal repeat (LTR). Gesicles are produced through expression of vesicular stomatitis virus glycoprotein and package protein as their cargo, thus bypassing the need for transgene delivery, and allowing finer control of Cas9 expression. Using both NanoSight particle and western blot analysis, the authors verified production of Cas9-containing gesicles by HEK293FT cells. Application of gesicles to CHME-5 microglia resulted in rapid but transient transfer of Cas9 by western blot, which is present at 1 hr, but is undetectable by 24 hr post-treatment. Gesicle delivery of Cas9 protein preloaded with guide RNA targeting the HIV LTR to HIV-NanoLuc CHME-5 cells generated mutations within the LTR region and copy number loss. Finally, the authors demonstrated that this treatment resulted in reduced proviral activity under basal conditions and after stimulation with pro-inflammatory factors lipopolysaccharide (LPS) or tumor necrosis factor alpha (TNF-α). These data suggest that gesicles are a viable alternative approach to deliver CRISPR/Cas9 technology.

Synaptic Plasticity Section, Cellular Neurobiology Research Branch

Genetic Deletion Of Vesicular Glutamate Transporter In Dopamine Neurons Increases Vulnerability To MPTP-Induced Neurotoxicity In Mice Shen, H., Marino, R.A.M., McDevitt, R.A., Bi, G.-H., Chen, K., Madeo, G., Lee, P.-T., Liang, Y., De Biase, L.M., Su, T.-P., et al. (2018).. Proceedings of the National Academy of Sciences 201800886.
A subset of midbrain dopamine (DA) neurons express vesicular glutamate transporter 2 (VgluT2), which facilitates synaptic vesicle loading of glutamate. Recent studies indicate that such expression can modulate DA-dependent reward behaviors, but little is known about functional consequences of DA neuron VgluT2 expression in neurodegenerative diseases like Parkinson's disease (PD). Here, the authors report that selective deletion of VgluT2 in DA neurons in conditional VgluT2-KO (VgluT2-cKO) mice abolished glutamate release from DA neurons, reduced their expression of brain-derived neurotrophic factor (BDNF) and tyrosine receptor kinase B (TrkB), and exacerbated the pathological effects of exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Furthermore, viral rescue of VgluT2 expression in DA neurons of VglutT2-cKO mice restored BDNF/TrkB expression and attenuated MPTP-induced DA neuron loss and locomotor impairment. Together, these findings indicate that VgluT2 expression in DA neurons is neuroprotective. Genetic or environmental factors causing reduced expression or function of VgluT2 in DA neurons may place some individuals at increased risk for DA neuron degeneration. Therefore, maintaining physiological expression and function of VgluT2 in DA neurons may represent a valid molecular target for the development of preventive therapeutic interventions for PD.

Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section

A Deeper Insight Into How GABA-B Receptor Agonism Via Baclofen May Affect Alcohol Seeking and Consumption: Lessons Learned From A Human Laboratory Investigation
Farokhnia M, Deschaine SL, Sadighi A, Farinelli LA, Lee MR, Akhlaghi F, Leggio L. Molecular Psychiatry. 2018 Oct 31. doi: 10.1038/s41380-018-0287-y. [Epub ahead of print],
Previous studies suggest that GABA-B receptor agonism may represent an effective pharmacological approach to treat addictive disorders. Baclofen is a selective GABA-B receptor agonist which has been investigated as a potential treatment for alcohol use disorder. However, research is needed to understand the biobehavioral mechanisms underlying baclofen's effect on alcohol use. In the present randomized, double-blind, placebo-controlled study, thirty-four alcohol-dependent individuals were randomized to receive baclofen (30 mg/d) or placebo for a week, and then participated in a laboratory experiment consisting of three procedures: alcohol cue-reactivity, priming, and self-administration. During the experiment, craving and other subjective responses to alcohol were assessed, and blood samples were collected for pharmacokinetic measurements. The effects of baclofen on the relationships between different alcohol-related laboratory parameters were investigated. Baclofen pharmacokinetic parameters and their correlations with behavioral measures were also examined. Results showed that baclofen disrupted the link between alcohol priming and self-administration, as indicated by significant interaction effects between drug condition (baclofen vs. placebo) and some of the priming variables (alcohol craving: $F_{3,9} = 6.03$, $p = 0.01$; alcohol sedation: $F_{3,6} = 7.16$, $p = 0.01$) on the total amount of alcohol self-administered. Considerable interindividual variability in baclofen pharmacokinetic parameters was observed. Maximum plasma concentrations of baclofen negatively correlated with cue-induced alcohol craving ($r = -0.57$, $p = 0.03$) and priming-induced ratings of 'like more' ($r = -0.59$, $p = 0.02$). In

conclusion, baclofen may work by dissociating the link between an initial drink (priming) and subsequent alcohol consumption (self-administration). Considerable pharmacokinetic variability is an important factor to take into account when employing baclofen as a treatment for alcohol use disorder.

Designer Drug Research Unit

Comparative Neuropharmacology of N-(2-methoxybenzyl)-2,5-dimethoxyphenethylamine (NBOMe) Hallucinogens and Their 2C Counterparts in Male Rats Elmore JS, Decker AM, Sulima A, Rice KC, Partilla JS, Blough BE, Baumann MH. Neuropharmacology. 2018 Nov; 142:240-250.
2,5-Dimethoxyphenethylamines (2C compounds) are 5-HT2A/2C receptor agonists that induce hallucinogenic effects. N-methoxybenzylation of 2C compounds markedly increases their affinity for 5-HT2A receptors, and two such analogs, 2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25C-NBOMe) and 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe), have emerged in recreational drug markets. Here, the authors investigated the neuropharmacology of 25C-NBOMe and 25I-NBOMe in rats, as compared to their 2C analogs and the prototypical 5-HT2A/2C agonist DOI. Compounds were tested in vitro using 5-HT2A receptor binding and calcium mobilization assays. For in vivo experiments, 25C-NBOMe (0.01-0.3 mg/kg), 25I-NBOMe (0.01-0.3 mg/kg), 2-(4-chloro-2,5-dimethoxyphenyl)ethanamine (2C-C) (0.1-3.0 mg/kg), 2-(4-iodo-2,5-dimethoxyphenyl) ethanamine (2C-I) (0.1-3.0 mg/kg) and DOI (0.03-1.0 mg/kg) were administered subcutaneously (sc) to male rats, and 5-HT2A-mediated behaviors were assessed. NBOMes displayed higher affinity for 5-HT2A receptors than their 2C counterparts but were substantially weaker in functional assays. 25C-NBOMe and 25I-NBOMe were much more potent at inducing wet dog shakes (WDS) and back muscle contractions (BMC) when compared to 2C-C and 2C-I. Pretreatment with the selective 5-HT2A antagonist (R)-(2,3-dimethoxyphenyl){1-[2-(4-fluorophenyl)ethyl]-4-piperidinyl}methanol (M100907) reversed behaviors produced by all agonists. Interestingly, binding affinities at the 5-HT2A receptor were significantly correlated with potencies to induce BMC but not WDS. These findings show that NBOMes are ultrapotent 5-HT2A agonists in rats, similar to effects in mice, and consistent with the reported hallucinogenic effects in human users.

Neuronal Circuits and Behavior Unit, Cellular Neurobiology Research Branch

Electrophysiological Properties and Projections Of Lateral Hypothalamic Parvalbumin Positive Neurons PLoS One 2018; 13(6): e0198991.
Kisner, A., Slocomb, J. E., Sarsfield, S., Zuccoli, M. L., Siemian, J., Gupta, J. F., Kumar, A., and Aponte, Y. (2018) PLoS One 13(6): e0198991.
Cracking the cytoarchitectural organization, activity patterns, and neurotransmitter nature of genetically-distinct cell types in the lateral hypothalamus (LH) is fundamental to develop a mechanistic understanding of how activity dynamics within this brain region are generated and operate together through synaptic connections to regulate circuit function. However, the precise mechanisms through which LH circuits orchestrate such dynamics have remained elusive due to the heterogeneity of the intermingled and functionally distinct cell types in this brain region. Here the authors reveal that a cell type in the mouse LH identified by the expression of the calcium-binding protein parvalbumin (PVALB; LHPV) is fast-spiking, releases the excitatory neurotransmitter

glutamate, and sends long range projections throughout the brain. Thus, these findings challenge long-standing concepts that define neurons with a fast-spiking phenotype as exclusively GABAergic. Furthermore, the authors provide for the first time a detailed characterization of the electrophysiological properties of these neurons. This work identifies LHPV neurons as a novel functional component within the LH glutamatergic circuitry and will serve as a basis for future models of LH circuitry that regulate behaviors essential for survival.

Behavioral Neurophysiology Research Section
Cellular Neurobiology Research Branch

Rethinking Dopamine As Generalized Prediction Error Gardner MPH, Schoenbaum G, Gershman SJ. Proc Biol Sci. 2018 Nov 21; 284(1891): pii:20181645. doi: 10.1098/rspb.2018.1645
Midbrain dopamine neurons are commonly thought to report a reward prediction error (RPE), as hypothesized by reinforcement learning (RL) theory. While this theory has been highly successful, several lines of evidence suggest that dopamine activity also encodes sensory prediction errors unrelated to reward. Here, the authors develop a new theory of dopamine function that embraces a broader conceptualization of prediction errors. By signaling errors in both sensory and reward predictions, dopamine supports a form of RL that lies between model-based and model-free algorithms. This account remains consistent with current canon regarding the correspondence between dopamine transients and RPEs, while also accounting for new data suggesting a role for these signals in phenomena such as sensory preconditioning and identity unblocking, which ostensibly draw upon knowledge beyond reward predictions.

Drug Design and Synthesis Section
Molecular Targets and Medications Discovery Branch

Cocaine Reward Is Reduced By Decreased Expression Of Receptor Type Protein Tyrosinephosphatase D (PTPRD) And By A Novel PTPRD Antagonist Uhl GR, Martinez MJ, Paik P, Sulima A, Bi GH, Iyer MR, Gardner E, Rice KC, Xi ZX. Proc Natl Acad Sci U S A. 2018 Nov 6;115(45):11597-11602
Receptor-type protein tyrosine phosphatase D (PTPRD) is a neuronal cell-adhesion molecule/synaptic specifier that has been implicated in addiction vulnerability and stimulant reward by human genomewide association and mouse cocaine-conditioned place-preference data. However, there have been no reports of effects of reduced expression on cocaine self-administration. There have been no reports of PTPRD targeting by any small molecule. There are no data about behavioral effects of any PTPRD ligand. The authors now report (i) robust effects of heterozygous PTPRD KO on cocaine self-administration (These data substantially extend prior conditioned place-preference data and add to the rationale for PTPRD as a target for addiction therapeutics.); (ii) identification of 7-butoxy illudalic acid analog (7-BIA) as a small molecule that targets PTPRD and inhibits its phosphatase with some specificity; (iii) lack of toxicity when 7-BIA is administered to mice acutely or with repeated dosing; (iv) reduced cocaine-conditioned place preference when 7-BIA is administered before conditioning sessions; and (v) reductions in well-established cocaine self-administration when 7-BIA is administered before a session (in WT, not PTPRD heterozygous KOs). These results add to support for PTPRD as a target for medications to combat cocaine use disorders. 7-BIA provides a lead compound for addiction therapeutics.

RAPT Unit
Clinical Pharmacology and Therapeutics Research Branch

Science-Based Actions Can Help Address The Opioid Crisis Epstein DH, Heilig M, and Shaham Y. Trends in Pharmacological Sciences 39(11): 911-916, 2018.
The epidemic of addiction and overdose is real. Addiction among pain patients accounts for only a small proportion but a large number. Scientific opinion leaders can be most effective on two fronts, each relatively low-tech: dissemination and oversight of empirically established treatments, and promulgation of social-science-based strategies for population-level prevention.

Neuropsychopharmacology Section

Cocaine and Cocaine Expectancy Increase Growth Hormone, Ghrelin, GLP-1, IGF-1, Adiponectin, and Corticosterone While Decreasing Leptin, Insulin, GIP, and Prolactin
You ZB, Wang B, Gardner EL, Wise RA. Pharmacol Biochem Behav. 2019 Jan;176:53-56. doi: 10.1016/j.pbb.2018.11.001. Epub 2018 Nov 7.
The dopamine system-essential for mood and movement-can be activated in two ways: by excitatory inputs that cause burst firing and stamp-in learning or by slow excitatory or inhibitory inputs-like leptin, insulin, ghrelin, or corticosterone-that decrease or increase single-spike (pacemaker) firing rate and that modulate motivation. In the present study the authors monitored blood samples taken prior to and during intravenous cocaine or saline self-administration in rats. During cocaine-taking, growth hormone and acetylated ghrelin increased 10-fold; glucagon-like peptide-1 (GLP-1) doubled; non-acetylated ghrelin, insulin-like growth factor-1 (IGF-1), and corticosterone increased by 50% and adiponectin increased by 17%. In the same blood samples, leptin, insulin, gastric inhibitory polypeptide (GIP), and prolactin decreased by 40-70%. On the first day of testing under extinction conditions-where the animals earned unexpected saline instead of cocaine-5-fold increases were seen for growth hormone and acetylated ghrelin and equal changes-in amplitude and latency-were seen in each of the other cases except for IGF-1 (which increased at a slower rate). Single-spike firing affects the tonic activation level of the dopamine system, involving very different controls than those that drive burst firing; thus, the present data suggest interesting new targets for medications that might be used in the early stages of drug abstinence.

Neurobiology of Relapse Section
Behavioral Neuroscience Branch

Volitional Social Interaction Prevents Drug Addiction In Rat Models Venniro M, Zhang M, Caprioli D, Golden SA, Heins C, Hoots JK, Morales M, Epstein DH, Shaham Y (2018). Nature Neuroscience 21:1520-1529.
Addiction treatment has not been appreciably improved by neuroscientific research. One problem is that mechanistic studies using rodent models do not incorporate volitional social factors, which play a critical role in human addiction. Here, using rats, the authors introduce an operant model of choice between drugs and social interaction. Independent of sex, drug class, drug dose, training conditions, abstinence duration, social housing, or "addiction score" in the DSM-IV-based and intermittent access models, operant social reward prevented drug self-administration. This protection was lessened by delay or punishment of the social reward but neither measure was correlated with the "addiction score." Social choice-induced abstinence also prevented incubation of methamphetamine

craving. This protective effect was associated with activation of central amygdala PKCδ-expressing inhibitory neurons and inhibition of anterior insular cortex activity. These findings highlight the need for incorporating social factors into neuroscience-based addiction research and support the wider implantation of socially based addiction treatments.

Clinical Pharmacology and Therapeutics Research Branch

Craving, Mood, and Background Stress In The Hours Surrounding Drug Use and Stressful Events In Patients With Opioid-Use Disorder Preston KL, Kowalczyk WJ, Phillips KA, Jobes ML, Vahabzadeh M, Lin JL, Mezghanni M, Epstein DH. Psychopharmacology (Berl). 2018 Sep;235(9):2713-2723.
Ecological momentary assessment of specific events usually focuses more on antecedents and concomitants than on aftermaths, potentially missing early consequences of drug use and discrete episodes of stress and drug use. For up to 16 weeks, outpatients on opioid-agonist treatment carried smartphones on which they initiated entries for stressful events (SEs) or lapses to drug use (DUs), and thrice daily when randomly prompted (RPs). Participants rated their stress, opioid craving, cocaine craving, and moods. RP entries within 5 h of an event were analyzed and compared to other RPs. Stress, negative mood, and craving were generally higher before and after DUs and SEs compared to background levels in participants with at least one DU (n = 149) or SE (n = 158). Before DUs, there were increases in negative mood, opioid craving, and cocaine craving, but not background stress. Before SEs, there were increases in background stress, opioid craving, and cocaine craving, but not negative mood. These changes were more variable after events than before. Neither DUs nor SEs were significantly related to positive mood. Stress increased before stressful-event entries, but was less evident before drug use. Craving increased in the hours before drug use and stressful events-and remained elevated in the hours after either event. These results suggest a stronger link between drug use and craving than between drug use and stress. Lapses to drug use did not improve mood or reduce stress, at least not at our 1-h-bin time resolution, suggesting that if such benefits exist, they are brief.

Neural Engineering Unit, Behavior Neuroscience Research Branch

Distinct and Dynamic ON and OFF Neural Ensembles In the Prefrontal Cortex Code Social Exploration Liang B, Zhang LF, Barbera G, Fang W, Zhang J, Chen X, Chen R, Li Y, and Lin DT. 2018. Neuron 100, 700–714. doi: 10.1016/j.neuron.2018.08.043.
The medial prefrontal cortex (mPFC) is important for social behavior, but the mechanisms by which mPFC neurons code real-time social exploration remain largely unknown. Here the authors utilized miniScopes to record calcium activities from hundreds of excitatory neurons in the mPFC while mice freely explored restrained social targets in the absence or presence of the psychedelic drug phencyclidine (PCP). The authors identified distinct and dynamic ON and OFF neural ensembles that displayed opposing activities to code real-time behavioral information. They further illustrated that ON and OFF ensembles tuned to social exploration carried information of salience and novelty for social targets. Finally, they showed that dysfunctions in these ensembles were associated with abnormal social exploration elicited by PCP. These findings underscore the importance of mPFC ON and OFF neural ensembles for proper exploratory behavior, including social exploration, and pave the way for future studies elucidating neural circuit dysfunctions in psychiatric disorders.

Structural Biology Core

AP-MALDI Mass Spectrometry Imaging of Gangliosides Using 2,6 Dihydroxy-acetophenone
Jackson SN, Muller L, Roux A, Oktem B, Moskovets E, Doroshenko V, Woods AS. JASMS 29, 1463-1472, 2018.
Matrix-assisted laser/desorption ionization (MALDI) mass spectrometry imaging (MSI) is widely used as a unique tool to record the distribution of a large range of biomolecules in tissues. 2,6-Dihydroxyacetophenone (DHA) matrix has been shown to provide efficient ionization of lipids, especially gangliosides. The major drawback for DHA as it applies to MS imaging is that it sublimes under vacuum (low pressure) at the extended time necessary to complete both high spatial and mass resolution MSI studies of whole organs. To overcome the problem of sublimation, the authors used an atmospheric pressure (AP)-MALDI source to obtain high spatial resolution images of lipids in the brain using a high mass resolution mass spectrometer. Additionally, the advantages of atmospheric pressure and DHA for imaging gangliosides are highlighted. The imaging of [M–H]− and [M–H2O–H]− mass peaks for GD1 gangliosides showed different distribution, most likely reflecting the different spatial distribution of GD1a and GD1b species in the brain.

GRANTEE HONORS AND AWARDS

Cliff Brangwynne, Ph.D. of Princeton was the recipient of the 2018 MacArthur award for his work on cellular membraneless compartmentalization through liquid-liquid partitioning.

Byungkook Lim, Ph.D. of UCSD was the recipient of the Freedman Award for work on circuitry dissection of psychiatric disease.

Xiao-Jing Wang, Ph.D. of NYU won the Goldman-Rakic award for his work in Computational Neuroscience.

Michelle Mazei-Robison, Ph.D. from Michigan State University was the recipient of the Early Career Award from the Division of Neuropharmacology of ASPET.

Jun-Xu Li, Ph.D. from the University of Buffalo was the recipient of the JH Woods Early Career Award in Behavioral Pharmacology from ASPET.

Palmer W. Taylor, Ph.D. from UCSD was the recipient of the Robert R. Ruffalo Career Achievement Award in Pharmacology from ASPET.

CTN Northeast Node partners at the New Hampshire Department of Health and Human Services (including Northeast Node Core Investigator Dr. Mary Brunette) were recently awarded a grant from the Substance Abuse and Mental Health Services Administration (SAMHSA) to integrate physical and mental health treatment for young adults with severe mental illness (SMI) or severe emotional disturbance (SED). The project will support 1,100 patients in New Hampshire ages 16-35 with SMI or SED through a program called ProHealth NH. ProHealth will work with three state Community Mental Health and Federally Qualified Health Centers to create health homes with integrated physical and mental health care, with a goal of preventing and/or treating future health conditions.

CTN Pacific Northwest Node's **Dr. Dennis Donovan**, after twenty-five years, retired as the Director of the Alcohol & Drug Abuse Institute (ADAI) at the University of Washington (UW). He will continue his work in the CTN as the Co-PI (with Dr. Mary Hatch-Maillette) of the Pacific Northwest Node, member of the CTN Publications Committee, as well as selected other activities within the CTN, ADAI, and the UW, under his new status as Professor Emeritus. Dennis M. Donovan had been the director of the Alcohol and Drug Abuse Institute since 1993 and a UW faculty member since 1981; he has been a Professor in Psychiatry & Behavioral Sciences and Adjunct Professor in the UW Departments of Psychology, Health Services, and Global Health. He also directed the Substance Abuse and HIV/STI Scientific Working Group within the UW's Center for AIDS Research. Dr. Donovan has been a Principal Investigator of numerous federally funded grants, including NIAAA's Project MATCH, the NIAAA COMBINE Study, and NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN).

STAFF HONORS AND AWARDS

STAFF HONORS

NIDA Director's Award of Merit

Center for the Clinical Trials Network
Ronald Dobbins -- In recognition of your expert fiscal management skills in mapping a comprehensive budget plan for the CTN Opioid Research Enhancement Project.

Division of Extramural Research
Katia Howlett -- In recognition of your multiple outstanding contributions to DER, and to NIDA more broadly during a period of personnel transitions and policy changes affecting the entire Institute.

NIDA Scientific Review Team
Julia Berzhanskaya
Julius Diggs
Lyle Furr
Jason Hill
Angelina Jordan
Susan McGuire
Gerald McLaughlin
Ivan Navarro
Hiromi Ono
Christina Page
Ipolia Ramadan
Natisha Rowe
Tracy Waldeck
In recognition of outstanding service in advancing the science on the causes and consequences of drug use and addiction toward improving individual and public health.

Division of Epidemiology, Services and Prevention Research
Moira O'Brien -- In recognition of your contributions to ensuring NIDA is at the forefront of understanding emerging drug trends.

Division of Neuroscience and Behavior
John Satterlee -- In recognition of extraordinary effort in advancing the neuroscience of pain through the development of the successful Common Fund proposal, Acute to Chronic Pain Signatures.

Myriam Selmane -- In recognition of your leading the charge to present NIDA to the neuroscience community at the Annual Meeting of the Society for Neuroscience.

Division of Therapeutics and Medical Consequences
Philip Krieter -- In recognition of exceptional leadership and initiative in overseeing pharmacokinetic/pharmacodynamic studies for NIDA DTMC and its pharmaceutical company partners.

Tanya Ramey -- In recognition of leadership in developing the plan for opioid and other SUD clinical outcomes assessments as FDA-qualified Drug Development Tools to accelerate drug development.

Intramural Research Program
Kenzie Preston -- In recognition of your contributions to our understanding of opioid pharmacology and to the effective use of contingency management treatments.

Yihong Yang -- In recognition of your outstanding contributions to the development of functional magnetic resonance imaging methodology and its applications to drug addiction.

NIDA Patient Safety and Quality Clinical Care Committee
Debbi Allen
Lois Blue
Janice Carico
Carla Harrison
Kathy Lightfoot
Karen McCullough
Shannon Pfistner
Karran Phillips
Betty Jo Salmeron
Arum Yoo
Stacy Yung
In recognition of efforts to raise awareness of the importance of patient safety and quality clinical care in the clinical research setting.

Office of the Director
NIDA OD Leadership Support Team
Kelley Henry
Ellie Johnson
Hilda Schulke
Maggie Stevenson
In recognition of extraordinary support provided to NIDA Leadership during an unprecedented period of activity driven by the national Opioid Crisis.

OUD Patient Focused Drug Development
Elena Koustova
Anna McCaffrey
Victor Prikhodko
Irina Sazonova
In recognition of dedication to patient-centricity in organizing the Opioid Use Disorder Patient Focused Drug Development meeting with the Food and Drug Administration.

Office of Management
Jagdeep Kathuria -- In recognition of your commitment to NIDA, focused on the assessment, collaboration, design, and implementation of NIDA Application Modernization and Software Redesign projects.

NIDA HQ Hiring Surge Team
Marcus Brown
Montrue Crawford
Gloria Dabbondanza
Shawntay Lewis
Keisha Miller
Chanvadey Nhim
In recognition of outstanding coordination, dedication, and service to the NIDA headquarters/extramural program during the unprecedented 2018 hiring surge.

Office of Acquisitions Management Team
In recognition of successfully closing fiscal year 18 through this group's leadership and management through change, collaboration, and dedication.

Office of Science Policy and Communications
Emily Einstein -- In recognition of your tireless efforts to communicate NIDA science to a variety of stakeholders and Federal partners.

Monitoring the Future Survey Team
Josie Anderson
Ruben Baler
Jessica Cotto
Kimberly DiFonzo
Emily Einstein
Mark Fleming
Tara Garwood
Emily Jones
Carol Krause
Jinhee Lee
Janet Linton
Alexa Lopez
Marsha Lopez
Aaron Martinek
Ann Rea
Shirley Simson
Eric Wargo
In recognition of the consistently rapid analysis and translation of survey data resulting in widespread dissemination.

NIDA Director's Award for Collaboration

Development of Medications to Prevent and Treat Opioid Use Disorders and Overdose Funding Opportunity Announcement Team
Carol Alderson
Jason Hill
Gerald McLaughlin
Iván Montoya
Ivan Navarro
Christina Page
Yvonne Walker
In recognition of the NIDA Program, Administrative and Review staff advancing the funding opportunity announcement for Development of Medications to Prevent and Treat Opioid Use Disorders and Overdose.

2018 NIDA Diversity Consortium
Meyer Glantz
Guifang Lao
Amy Lossie
Vani Pariyadath
Belinda Sims
Shelley Su
Kevin Walton
Ericka Wells
In recognition of superior dedication in reviewing and evaluating NIDA's annual Diversity Supplement applications and for being committed to NIDA's diversity enhancement goals.

NIDA "Risk Myth Breakers@NIH" Team
Josie Anderson
Darius Bickham
Sussana Morales
In recognition of the collaboration between OM and OSPC to produce a unique video promoting Risk Awareness at NIDA and NIH.

NIDA Director's Award for Diversity

NIDA/NIA LGBTQ+ Interest Group
Kristen Alexander
Samantha Cermak
Adam Cornish
Eric Shiroma
Kelsey Wright
In recognition of your efforts to create a space at the IRP to build connections that foster inclusivity and mutual understanding.

NIDA Director's Award for Quality of Worklife

Eliminating Stigma in Addiction and Mental Illness Working Group
Lauren Brick
Megan Dwyer
Reuben Don
Devin Effinger
David Epstein
Holly Hake
Carla Harrison
Stephen Heishman
Michelle Jobes
Louisa Kane
Sherry Lam
Janette Lebron
Michelle Leff
Rolanda Morris
Mary Pfeiffer
Karran Phillips
David Reiner
Sam Stull
In recognition of your efforts to increase our understanding of and sensitivity to addiction and mental illness so that we are empowered to end stigma.

NIDA Director's Rising Star Award
Amy Lossie
Sneha Singh
Leandro Vendruscolo
In recognition of your accomplishments, creativity, energy, and ability to inspire others at NIDA.

NIDA Director's Innovator Award
Hanbing Lu -- In recognition of your work on the development of a novel coil design approach and the implementation of a rodent-specific Transcranial Magnetic Stimulation system.

PHS NIH Commissioned Corps Unit Commendation Award

NIH/NIDA PHS Volunteers for First Annual Health Fair
CAPT Michelle Baker-Bartlett
CAPT Paul Na
CDR John Hubbard
CDR Jeannettee Joyner
LCDR Michael Gwathmey
LCDR James Pitt
LT Tara Lemons
LT Stacy Yung
In recognition of these Public Health Service officers' efforts to plan, coordinate, support and host the 1st Annual Health Fair.

30 Years of Government Service Recognition
Nathan Appel
David McCann
Joellen Austin
Stephen Heishman
Carol Lindsay

40 Years of Government Service Recognition
Tsung Ping Su
Rao Rapaka
Evelyn Anderson

OTHER STAFF HONORS

Miguel Arenivar, IRP, was awarded the NIDA IRP Scientific Director's Fellowship for Diversity in Research, Autumn 2018.

Dr. Chloe Jordan, IRP, received a travel award to speak in a symposium – "In the Pipeline: Innovative Therapeutics to Address the Opioid Crisis," sponsored by ACNP in Hollywood, FL in December 2018. The tile of her talk was "Dopamine D3 Receptor-Based Medication Strategies to Combat Opioid Addiction."

Dr. Lorenzo Leggio, IRP, was awarded tenure by the NIH Central Tenure Committee.

Dr. Lorenzo Leggio was presented with the Eva King Killam Research Award from the American College on Neuropsychopharmacology (ACNP) for "outstanding translational research contributions to neuropsychopharmacology."

Dr. Amy Newman, IRP, received a 2018 NIH Office of the Director Honor Award as a member of the NIH Tenure-Track Mentoring Program and a co-leader of the NIDA-NIA TTI Mentoring Program.

Rao Rapaka, Ph.D., DNB, received the Life Time Achievement Award -2018 from the Society for Personalized Nano-Medicine (SPNM) during their Symposium in Miami, FL on November 2, 2018.

Dr. Kenner Rice, IRP, received a Lifetime Achievement Award at the 3rd Annual Chemistry and Pharmacology of Drug Abuse Conference, held in Boston on August 2-3, 2018.

Dr. Justin Siemian, IRP, received the 2019 Fellows Award for Research Excellence (FARE Award; travel stipend to attend a meeting and present his research findings).

Dave Thomas, Ph.D., DESPR, will be receiving the American Pain Society's 2019 John and Emma Bonica Public Service Award. The Bonica Award recognizes distinguished contributions to the field of pain through public education, dissemination of information, public service, or other efforts that further knowledge about pain.

STAFF CHANGES

Mary Kautz, Ph.D., DNB, stepped aside as Acting Branch Chief of the Behavioral Cognitive Neuroscience Branch to focus on her position as Director of the Tobacco Regulator Science Program for which she serves as our liason to the FDA.

Dr. Anne Leong is volunteering 1 day per week in SRB. Dr. Leong is a Society for Research in Child Development (SRCD)/American Academy for the Advancement of Science (AAAS) fellow with a primary placement at NICHD.

William Longinetti is detailed to SRB on a 6-month rotation as a Presidential Management Fellow from SAMHSA, where he is a public health advisor in the Center for Substance Abuse Treatment.

Lizette Nkongho, M.P.H., who has a MPH from George Mason University will work with Mary Kautz as a contractor in the Tobacco Regulatory Science Program.

Vani Pariyadath, Ph.D., DNB, Integrative Neuroscience Branch will serve as the new Acting Branch Chief of the Behavioral Cognitive Neuroscience Branch.

Shelley Su, Ph.D., DNB, a program officer in the Behavioral Cognitive Neuroscience Branch, moved to the Division of Epidemiology, Services and Prevention Research.

Dr. Agnieszka Sulima was appointed as a Staff Scientist in the Drug Design and Synthesis Section, Molecular Targets and Medications Discovery Branch, IRP.

Dr. Tisha Wiley was selected as the SRB Branch Chief and started at the end of August. Dr. Wiley has directed a portfolio of health services research grants in the Services Research Branch at NIDA since 2012. Dr. Wiley is also the Associate Director for Justice Systems. In this role, Dr. Wiley will be leading NIDA's Justice Community Opioid Innovation Network (JCOIN), one of NIDA's signature HEAL initiatives.

New Staff

Scott Bredow joined NIDA's Office of Management, Office of Acquisitions as a Supervisory Contract Specialist on January 6, 2019. Scott comes to NIDA from a position with NHLBI.

Michelle Cecilia joined NIDA's Office of Management, Office of Acquisitions as a Contract Specialist on January 20, 2019. Michelle comes to NIDA from a position with the private sector.

Dr. Brenda Curtis joined the Clinical Pharmacology and Therapeutics Research Branch of the NIDA IRP on January 7, 2019 as a tenure-track investigator. She will lead the Technology and Translational Science (TTS) Unit. Dr. Curtis' research will focus on the role of digital technology in the identification, treatment, and recovery of those with a substance use disorder. Using "big data" generated from online and handheld devices, she hopes to gain a better understanding of relapse vulnerability in order to translate research findings into clinical interventions.

Andrea Czajowski joined NIDA's Office on AIDS as a Program Analyst on December 9, 2018. Andrea comes to NIDA from a position with the Indian Health Service.

Dr. Minnjuan W. Flournoy Floyd joined SRB as a Program Officer. She has spent the last 5 ½ years at SAMHSA, most recently, as a public health advisor in the Office of the Director in the Center for Substance Abuse Treatment (CSAT), and as a social science analyst (staff fellow) in the Center for Behavioral Health Statistics and Quality (CBHSQ).

Dr. Katrina Foster comes to DTMC from the Department of Veterans Affairs, Office of Research and Development. Dr. Foster is trained as a behavioral neuroscientist and is interested in both pre-clinical and clinical substance abuse research. At the VA, she served as the scientific portfolio manager and scientific expert for 2 highly visible portfolios, mental health and substance abuse. Before her tenure at the VA, she served as the scientific review officer for 2 subcommittees at NIAAA. Dr. Foster received her Doctorate in Psychobiology from Indiana-University-Purdue University-Indianapolis. She completed her post-doctoral fellowship at the Behavioral Pharmacology Research Unit at John's Hopkins University. Her role within CRGB is management of the cocaine and methamphetamine treatment grants.

Dr. Michelle Freund joined NIDA in January as the Project Director for the HEALthy Brain and Child Development (HEALthy BCD) Study. She comes to NIDA from the Office of Technology Development and Coordination at the National Institute of Mental Health where she managed a research portfolio of grants that are focused on the development of novel tools and technologies important for the advancement of basic and translational neuroscience. Michelle served as the Director for the NIH NeuroBioBank, a network of six brain and tissue repositories that provide post-mortem human brain samples for research, and has been an active member of several trans-NIH interdisciplinary teams such as the NIH BRAIN Initiative and the Blueprint for Neuroscience. As co-lead on a BRAIN Initiative team, she provided guidance and oversight for the Cells and Circuits focus area outlined in the BRAIN 2025 report. Michelle received a B.A. from the University of California, San Diego in mammalian physiology and a Ph.D. in Neuroscience from Hahnemann University in Philadelphia. Before joining NIH in 2007, she studied the role of monoamine neurotransmitters in the actions of antidepressant drugs and the interactions of stress and drug addiction.

Dr. Amy Goldstein joined the Division of Epidemiology, Services and Prevention Research as Prevention Research Branch Chief in October 2018. For 10 years she served as a Program Officer and Associate Director for Prevention at NIMH. Immediately prior to joining DESPR she was working in the private sector, as the Scientific Director for Behavioral Health Research at the MedStar Health Research Institute.

Dr. Keisher Highsmith has joined SRB as the Program Official for the HEALing communities study. Dr. Highsmith will also have a portfolio of grants in the Services Research Branch. Dr. Highsmith is a Scientist/Epidemiologist in the U.S. Public Health Service and has been a public health practitioner for over 14 years. She is coming to NIH/NIDA from the Health Resources and Services Administration (HRSA). Dr. Highsmith's tenure at HRSA includes serving as Deputy Director in the Bureau of Primary Health Care.

Dr. Jennifer Hobin joined the Office of Science Policy and Communications as the Deputy Director in October 2018. In this capacity, Dr. Hobin assumed responsibility for overseeing legislative and congressional activities as well as assisting the Director, OSPC on various other projects arising in response to the opioid crisis. Dr. Hobin joined us from NIAAA where she was the Chief of the Science Policy Branch and was responsible for policy, communications, and portfolio analysis activities aimed at advancing alcohol research and health. She previously served as Director of Science Policy at the American Association for Cancer Research (AACR). Prior to joining AACR, Dr. Hobin was Director of Science Policy at the Federation of American Societies for Experimental Biology (FASEB). Trained in psychology and neuroscience, Dr. Hobin transitioned from laboratory research into science policy via the Christine Mirzayan Science and Technology Policy Graduate Fellowship program at the National Academies. She earned her Ph.D. in biopsychology from the University of Michigan and has a BA in psychology from Stony Brook University.

Dr. Alumit Ishai joined NIDA as a Scientific Review Officer in September 2018. Alumit is an adjunct professor at Georgetown University Medical Center since 2015. Prior to joining NIDA, Alumit served as the Director of the NSF Cognitive Neuroscience Program 2014-2017, and oversaw FOA development, review and oversight. From 2004-2014, Alumit was Assistant, then Professor of Cognitive Neuroscience at the Department of Neuroradiology, University of Zurich, Switzerland. Coming to NIDA is something of an NIH homecoming as Alumit was also Research Fellow at the Laboratory of Brain and Cognition, National Institute of Mental Health earlier in her career. Alumit earned her Ph.D. with distinction from the Weizmann Institute of Science, and her bachelor's and master's degrees were from the Hebrew University of Jerusalem. Alumit has received numerous awards, and has a distinguished publication record.

Polina Klimenkova joined NIDA's Office of Management, Office of Acquisitions as a Contract Specialist on October 14, 2018. Polina comes to NIDA from a position with USU Acquisitions.

Robin Knightly joined NIDA's Office of Management, Office of Acquisitions as a Contract Specialist on September 30, 2018. Robin comes to NIDA from a position in the private sector.

Dr. Kimberly LeBlanc joined NIDA in October as a Scientific Program Manager for the Adolescent Brain Cognitive Development (ABCD) Study. She is a behavioral neuroscientist with experience in data science. For ABCD, she will be leading biospecimen activities (e.g., biorepositories, resource sharing) as well as participating in multiple ABCD workgroups (e.g., substance use, physical health, genetics). She comes to NIDA from the Scientific Review Branch of the National Institute on Aging. Previously, she completed a tour as a Visiting Bioinformatician at the National Center for Biotechnology Information as well as a detail as a Program Officer in the Division of Neuroscience and Behavior at NIDA. Dr. LeBlanc performed postdoctoral training at the National Institute of Diabetes, Digestive and Kidney Diseases, and earned her Ph.D. in Neuroscience from the University of California, Los Angeles, where her research focused on the impact of cocaine on habit formation and incentive sensitization in animal models of drug taking.

Dr. Yanping Liu joined the Center for the Clinical Trials Network at NIDA as a program official in November 2018. Dr. Liu will serve as a Health Scientist Administrator on CTN HEAL studies in the capacity of protocol scientific collaborator. Prior to joining NIDA, she was a Program Director in the Division for Research Capacity Building, National Institute of General Medical Sciences

(NIGMS), NIH with primary responsibilities in the Institutional Development Award (IDeA) program. She led the Center of Biomedical Research Excellence (COBRE) initiatives. She has managed clinical and translational intervention studies and clinical trials including studies of the management of opioid use disorder and pain. Before joining NIGMS, she was a medical officer in the Division of Research Infrastructure at the former National Center for Research Resources (NCRR) from 2005 to 2011. Dr. Liu received her MD degree in China and practiced in Beijing Friendship Hospital as a cardiologist for 12 years. In 1995, she received her PhD degree from the Department of Physiology, Medical College of Wisconsin. She completed her postdoctoral training in 1997 and took a faculty position as an Assistant and then Associate Professor in the Department of Medicine, Division of Cardiovascular Medicine, Medical College of Wisconsin. Her research focused on the mechanisms of vascular dysfunction in coronary microcirculation in diabetes. She led her own research prior to joining NIH.

Dr. Landhing Moran joined the Center for the Clinical Trials Network at NIDA as a program official in January 2019. Dr. Moran will serve as a Health Scientist Administrator on CTN studies providing leadership, direction and scientific oversight. Prior to joining CCTN, Dr. Moran was an IRTA Postdoctoral Fellow in the Clinical Pharmacology & Therapeutics Branch, Treatment Section and Office of the Clinical Director at the NIDA Intramural Research Program, mentored by Dr. Kenzie Preston and Dr. Karran Phillips. Dr. Moran received her PhD in Experimental Psychology from the University of South Carolina, Columbia. She has received several distinguished awards for her scientific and academic achievement, including the Fellows Award for Research Excellence (FARE), and has authored and co-authored many research papers ranging from pre-clinical to clinical science, on topics including HIV-associated neurocognitive disorders, opioid use, and ecological momentary assessment.

Dr. Carrie Mulford joined SRB as a Program Official. She has been a Social Science Analyst in the Office of Research and Evaluation at the National Institute of Justice since 2004.

Belinda Nwanguma joined NIDA's Office of Management, Office of Acquisitions as a Contract Specialist on November 11, 2018. Belinda comes to NIDA from a position with the US Air Force.

Tanea Richardson joined the Science Policy Branch, Office of Science Policy and Communications, in October 2018, as an Administrative Technician. Ms. Richardson was previously at NIDCR where she provided administrative support for the Craniofacial and Skeletal Disease Branch. Prior to joining NIDCR, Ms. Richardson worked for the Internal Revenue Service.

Alicia Torres joined NIDA's Office of Management, Office of Acquisitions as a Contract Specialist on November 11, 2018. Alicia comes to NIDA from a position with US Customs.

Dr. Jennifer Villani has joined NIDA to serve as the Associate Director for the HEALing Communities Study (Helping to End Addiction Long-term). The study will take place in areas across the country that have been highly affected by the opioid epidemic. It will test the impact of integrating evidence-based prevention and treatment interventions across multiple community-based systems (e.g., health care, behavioral health, and justice) to reduce opioid overdose fatalities and the incidence of opioid use disorder. Dr. Villani comes to us from the NIH Office of Disease Prevention (ODP) where she conducted a wide range of research activities to advance disease prevention. She developed and tested a new method for portfolio analysis that utilizes machine

learning to characterize NIH prevention re search in areas including substance use and health services. In addition, Dr. Villani is the lead NIH representative to the Healthy People Federal Interagency Workgroup, where she oversees and coordinates NIH participation in the development of the Healthy People 2030 initiative. Prior to joining the ODP, Dr. Villani worked 9 years at the National Institute of General Medical Sciences (NIGMS), where she coordinated an international consortium of investigators developing computational models to understand infectious disease dynamics. She also served as the NIGMS Planning and Evaluation Officer for a year and conducted portfolio analyses and program evaluations in infectious disease modeling, multiscale modeling, and systems biology. She earned her Ph.D. in Health Services Research from the University of Maryland, College Park, and her Master of Public Health in Epidemiology and Biostatistics from the George Washington University. Her research foci include preventive medicine, substance use prevention, patient-provider communication, health literacy, and health care disparities.

Staff Departures

Bruce Anderson, a Contract Specialist in the Office of Management, Office of Acquisitions left NIDA on December 6, 2018.

Kenneth Janosko, a Contract Specialist in the Office of Management, Office of Acquisitions left NIDA on December 8, 2018 for a position with the US Army.

Christine Salaita, a Program Analyst in the Division of Extramural Research left NIDA on September 29, 2018 for a position with the NIH Office of the Director.

Christopher Weaver, a Contract Specialist in the Office of Management, Office of Acquisitions left NIDA on February 16, 2018 for a position with NIAID.

Leon Wong, a Contract Specialist in the Office of Management, Office of Acquisitions left NIDA on November 24, 2018 for a position with the Department of Education.

Kelley Villers, a Staff Assistant in the Office of the Director, left NIDA on January 18, 2019 for a position with the Department of the Army.

Retirements

Debra Battle Dudley, a Grants Management Specialist in NIDA's Division of Extramural Research retired on September 30, 2018.

Dr. Dionne Jones retired from her role as acting SRB branch chief in September 2019. She has been instrumental in leading the branch through a dynamic time of change and has helped to be build a solid base in which services research is now thriving at NIDA.

Elizabeth Lambert, a Statistician in DESPR's Epidemiology Research Branch, retired on January 1, 2019.

In Memoriam

Dr. Herbert D. Kleber, a guiding light for the addiction field, an early advocate for medications in the treatment of opioid addiction, and a prolific mentor and inspiration for countless clinical researchers in addiction medicine died in October 2018. As a young physician in 1964, Herb did his military service with the U.S. Public Health Service at its Prison Hospital in Lexington, Kentucky—better known as the "Narcotics Farm," and the precursor to NIDA. Although he intended to pursue a more standard psychiatric career after returning to Yale University in 1966, friends, colleagues, and strangers looking for help for their addicted patients or children sought him out as an addiction expert, and he realized that he was being called to continue the work he had begun at Lexington. In New Haven, he braved the resistance of many in his profession and in the recovery world in advocating and practicing community-based treatment and the use of methadone for people addicted to opioids. He was also one of the pioneers in the use of the opioid antagonist naltrexone for the treatment of opioid addiction. These medications are still two of the mainstays of effective opioid addiction treatment. In 1989, Herb was invited to serve as Deputy Director for Demand Reduction at the White House Office of National Drug Control Policy (ONDCP) under the first Bush Administration. Two and a half years later he moved to Columbia University, where along with Dr. Marian Fischman, he founded the Substance Abuse Division in the Department of Psychiatry. His research at Columbia in the 1990s included important studies establishing the reality of marijuana dependence as well as some of the pioneering research on buprenorphine that led ultimately to its approval for treating opioid addiction in 2002. At Columbia, Herb also co-founded the National Center on Addiction and Substance Abuse (CASA) with Joseph Califano.

Dr. Conan Kornetsky, a renowned pioneer in drug addiction research died in December 2018. Born in Portland, Maine, he spent his early childhood in Roxbury and Chelsea and then returned to Portland at age 9. He was a flight mechanic in the Army Air Corps during World War II. After graduating from the University of Maine, he received his doctorate at the University of Kentucky, where he undertook seminal research on addiction at the Federal Narcotics Hospital (Narcotic Farm) in Lexington, KY. After completing his graduate studies, he worked for the Public Health Service in New York and the National Institute of Mental Health (NIMH) in Bethesda. In 1959 he and his family moved to Boston, where he was a professor in the Departments of Psychiatry and Pharmacology at Boston University School of Medicine for almost 60 years. His contributions to the field of drug abuse include studies on the causes of juvenile heroin abuse, the effects of LSD on cognitive function, and the effects of drugs of abuse on brain reward systems. He received multiple awards and accolades including distinguished alumnus awards from both the University of Maine and the University of Kentucky. In addition he received the prestigious Nathan B. Eddy Memorial Award for research in the field of drug dependence.

Nancy Soulen, J.D., Program Analyst in the Office of the Director, Office of Science Policy and Communications, NIDA, passed away in December 2018. Nancy joined NIDA in 1990. She had been in government service for nearly 50 years and served as attorney advisor with the HHS Office of General Council and a staff attorney with NIDA when it was part of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) before it became part of NIH.

National Institute
on Drug Abuse