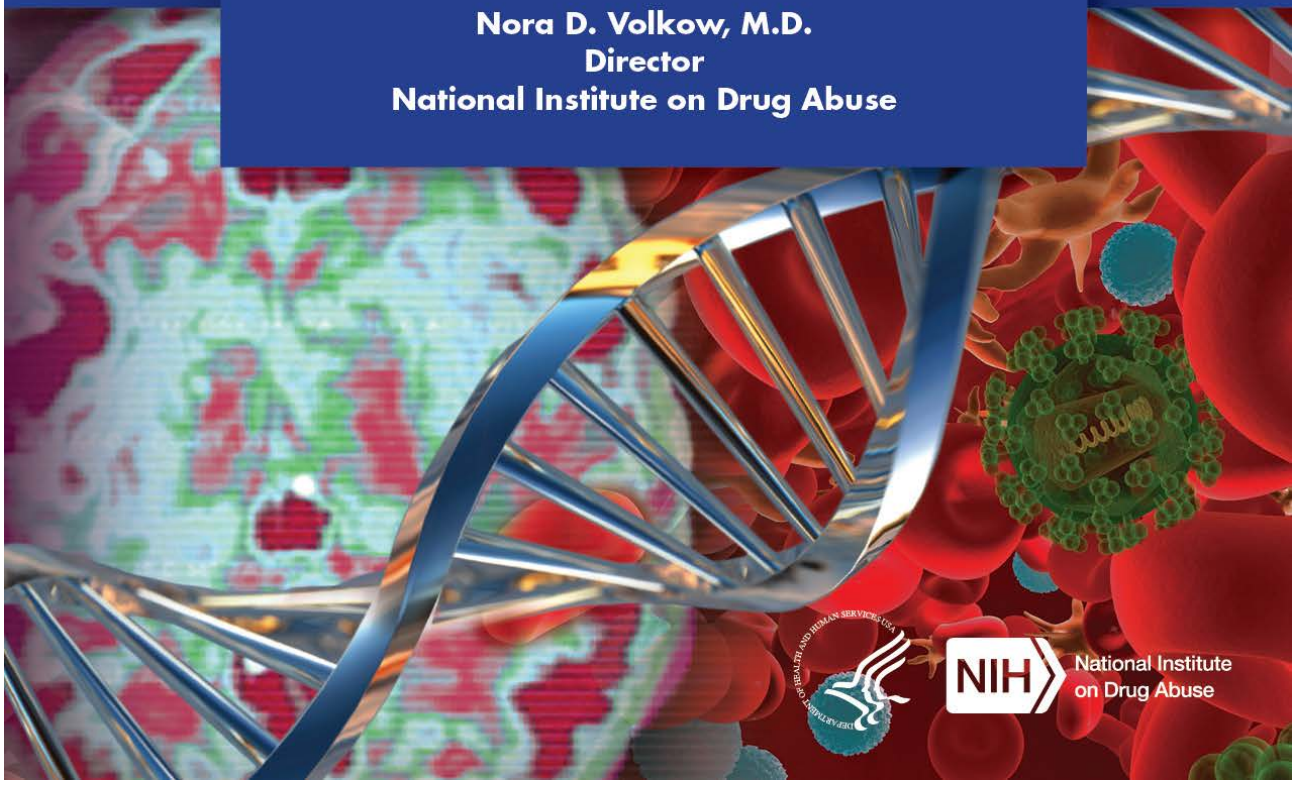
DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

February 2017

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

Cellular Taxonomy Of The Mouse Striatum As Revealed By Single-Cell RNA-Sequencing
Gokce, Ozgun; Stanley, Geoffrey M; Treutlein, Barbara; Neff, Norma F; Camp, J Gray; Malenka, Robert C; Rothwell, Patrick E; Fuccillo, Marc V; Südhof, Thomas C; Quake, Stephen R. Cell Rep. 2016; 16(4): 1126-1137.
The striatum contributes to many cognitive processes and disorders, but its cell types are incompletely characterized. The authors show that microfluidic and FACS-based single-cell RNA sequencing of mouse striatum provides a well-resolved classification of striatal cell type diversity. Transcriptome analysis revealed ten differentiated, distinct cell types, including neurons, astrocytes, oligodendrocytes, ependymal, immune, and vascular cells, and enabled the discovery of numerous marker genes. Furthermore, the authors identified two discrete subtypes of medium spiny neurons (MSNs) that have specific markers and that overexpress genes linked to cognitive disorders and addiction. They also describe continuous cellular identities, which increase heterogeneity within discrete cell types. Finally, we identified cell type-specific transcription and splicing factors that shape cellular identities by regulating splicing and expression patterns. These findings suggest that functional diversity within a complex tissue arises from a small number of discrete cell types, which can exist in a continuous spectrum of functional states.

X-ray Structure Of The Human A4β2 Nicotinic Receptor Morales-Perez, Claudio L; Noviello, Colleen M; Hibbs, Ryan E. Nature. 2016; 538(7625): 411-415.
Nicotinic acetylcholine receptors are ligand-gated ion channels that mediate fast chemical neurotransmission at the neuromuscular junction and have diverse signalling roles in the central nervous system. The nicotinic receptor has been a model system for cell-surface receptors, and specifically for ligand-gated ion channels, for well over a century. In addition to the receptors' prominent roles in the development of the fields of pharmacology and neurobiology, nicotinic receptors are important therapeutic targets for neuromuscular disease, addiction, epilepsy and for neuromuscular blocking agents used during surgery. The overall architecture of the receptor was described in landmark studies of the nicotinic receptor isolated from the electric organ of Torpedo marmorata. Structures of a soluble ligand-binding domain have provided atomic-scale insights into receptor-ligand interactions, while high-resolution structures of other members of the pentameric receptor superfamily provide touchstones for an emerging allosteric gating mechanism. All available high-resolution structures are of homopentameric receptors. However, the vast majority of pentameric receptors (called Cys-loop receptors in eukaryotes) present physiologically are heteromeric. Here the authors present the X-ray crystallographic structure of the human α4β2 nicotinic receptor, the most abundant nicotinic subtype in the brain. This structure provides insights into the architectural principles governing ligand recognition, heteromer assembly, ion permeation and desensitization in this prototypical receptor class.

Coordination Of Brain-Wide Activity Dynamics By Dopaminergic Neurons Decot, Heather K; Namboodiri, Vijay M K; Gao, Wei; McHenry, Jenna A; Jennings, Joshua H; Lee, Sung-Ho; Kantak, Pranish A; Jill Kao, Yu-Chieh; Das, Manasmita; Witten, Ilana B; Deisseroth, Karl; Shih, Yen-Yu Ian; Stuber, Garret D. Neuropsychopharmacology. 2016; [epub ahead of print].
Several neuropsychiatric conditions, such as addiction and schizophrenia, may arise in part from

dysregulated activity of ventral tegmental area dopaminergic (TH(VTA)) neurons, as well as from more global maladaptation in neurocircuit function. However, whether TH(VTA) activity affects large-scale brain-wide function remains unknown. Here the authors selectively activated TH(VTA) neurons in transgenic rats and measured resulting changes in whole-brain activity using stimulus-evoked functional magnetic resonance imaging. Applying a standard generalized linear model analysis approach, these results indicate that selective optogenetic stimulation of TH(VTA) neurons enhanced cerebral blood volume signals in striatal target regions in a dopamine receptor-dependent manner. However, brain-wide voxel-based principal component analysis of the same data set revealed that dopaminergic modulation activates several additional anatomically distinct regions throughout the brain, not typically associated with dopamine release events. Furthermore, explicit pairing of TH(VTA) neuronal activation with a forepaw stimulus of a particular frequency expanded the sensory representation of that stimulus, not exclusively within the somatosensory cortices, but brain-wide. These data suggest that modulation of TH(VTA) neurons can impact brain dynamics across many distributed anatomically distinct regions, even those that receive little to no direct TH(VTA) input. Neuropsychopharmacology advance online publication, 14 September 2016; doi:10.1038/npp.2016.151.

KAT2B Polymorphism Identified For Drug Abuse In African Americans With Regulatory Links To Drug Abuse Pathways In Human Prefrontal Cortex Johnson, Eric O; Hancock, Dana B; Levy, Joshua L; Gaddis, Nathan C; Page, Grier P; Glasheen, Cristie; Saccone, Nancy L; Bierut, Laura J; Kral, Alex H. Addict Biol. 2016; 21(6): 1217-1232.
Drug abuse is a common and heritable set of disorders, but the underlying genetic factors are largely unknown. The authors conducted genome-wide association studies of drug abuse using 7 million imputed single nucleotide polymorphisms (SNPs) and insertions/deletions in African Americans (AAs; n = 3742) and European Americans (EAs; n = 6845). Cases were drawn from the Urban Health Study of street-recruited people, who injected drugs and reported abusing opioids, cocaine, marijuana, stimulants and/or other drugs 10 or more times in the past 30 days, and were compared with population controls. Independent replication testing was conducted in 755 AAs and 1131 EAs from the Genetic Association Information Network. An intronic SNP (rs9829896) in the K(lysine) acetyltransferase 2B (KAT2B) gene was significantly associated with drug abuse in AAs ($P = 4.63 \times 10(-8)$) and independently replicated in AAs (P = 0.0019). The rs9829896-C allele (frequency = 12%) had odds ratios of 0.68 and 0.53 across the AA cohorts: meta-analysis $P = 3.93 \times 10(-10)$. Rs9829896-C was not associated with drug abuse across the EA cohorts: frequency = 36% and meta-analysis P = 0.12. Using dorsolateral prefrontal cortex data from the BrainCloud cohort, the authors found that rs9829896-C was associated with reduced KAT2B expression in AAs (n = 113, P = 0.050) but not EAs (n = 110, P = 0.39). KAT2B encodes a transcriptional regulator in the cyclic adenosine monophosphate and dopamine signaling pathways, and rs9829896-C was associated with expression of genes in these pathways: reduced CREBBP expression (P = 0.011) and increased OPRM1 expression (P = 0.016), both in AAs only. This study identified the KAT2B SNP rs9829896 as having novel and biologically plausible associations with drug abuse and gene expression in AAs but not EAs, suggesting ancestry-specific effects.

Incubation Of Cue-Induced Craving In Adults Addicted To Cocaine Measured By Electroencephalography Parvaz, Muhammad A; Moeller, Scott J; Goldstein, Rita Z. JAMA Psychiatry. 2016; 73(11): 1127-1134.
A common trigger for relapse in drug addiction is the experience of craving via exposure to cues previously associated with drug use. Preclinical studies have consistently demonstrated incubation of cue-induced drug-seeking during the initial phase of abstinence, followed by a decline over time.

In humans, the incubation effect has been shown for alcohol, nicotine, and methamphetamine addictions, but not for heroin or cocaine addiction. Understanding the trajectory of cue-induced craving during abstinence in humans is of importance for addiction medicine. The aim of this study was to assess cue-induced craving for cocaine in humans using both subjective and objective indices of cue-elicited responses. Seventy-six individuals addicted to cocaine with varying durations of abstinence (ie, 2 days, 1 week, 1 month, 6 months, and 1 year) participated in this laboratory-based cross-sectional study from June 19, 2007, to November 26, 2012. The late positive potential component of electroencephalography, a recognized marker of incentive salience, was used to track motivated attention to drug cues across these self-selected groups. Participants also completed subjective ratings of craving for cocaine before presentation of a cue, and ratings of cocaine "liking" (hedonic feelings toward cocaine) and "wanting" (craving for cocaine) after presentation of cocaine-related pictures. Data analysis was conducted from June 5, 2015, to March 30, 2016.The late positive potential amplitudes and ratings of liking and wanting cocaine in response to cocaine-related pictures were quantified and compared across groups. Among the 76 individuals addicted to cocaine, 19 (25%) were abstinent for 2 days, 20 (26%) were abstinent for 1 week, 15 (20%) were abstinent for 1 month, 12 (16%) were abstinent for 6 months, and 10 (13%) were abstinent for 1 year. In response to drug cues, the mean (SD) late positive potential amplitudes showed a parabolic trajectory that was higher at 1 (1.26 [1.36] μV) and 6 (1.17 [1.19] μV) months of abstinence and lower at 2 days (0.17 [1.09] μV), 1 week (0.36 [1.26] μV), and 1 year (-0.27 [1.74] μV) of abstinence ($P = .02$, partial $\eta 2 = 0.16$). In contrast, the subjective assessment of baseline craving (mean [SD] rating: 2 days, 26.05 [9.85]; 1 week, 18.70 [11.01]; 1 month, 10.87 [10.70]; 6 months, 6.92 [8.47]; and 1 year, 3.00 [3.77]) and cue-induced liking (mean [SD] rating: 2 days, 3.06 [2.34]; 1 week, 2.33 [2.87]; 1 month, 1.15 [2.03]; 6 months, 1.00 [2.24]; and 1 year, 1.00 [1.26]) and wanting (mean [SD] rating: 2 days, 3.44 [2.62]; 1 week, 2.72 [2.87]; 1 month, 1.46 [2.33]; 6 months, 1.00 [2.16]; and 1 year, 1.00 [1.55]) of cocaine showed a linear decline from 2 days to 1 year of abstinence ($P \leq .001$, partial $\eta 2 > 0.26$).The late positive potential responses to drug cues, indicative of motivated attention, showed a trajectory similar to that reported in animal models. In contrast, we did not detect incubation of subjective cue-induced craving. Thus, the objective electroencephalographic measure may possibly be a better indicator of vulnerability to cue-induced relapse than subjective reports of craving, although this hypothesis must be empirically tested. These results suggest the importance of deploying intervention between 1 month and 6 months of abstinence, when addicted individuals may be most vulnerable to, and perhaps least cognizant of, risk of relapse.

Less Is More: Prolonged Intermittent Access Cocaine Self-administration Produces Incentive-sensitization and Addiction-like Behavior Kawa, Alex B; Bentzley, Brandon S; Robinson, Terry E. Psychopharmacology (Berl). 2016; 233(19-20): 3587-3602.
Contemporary animal models of cocaine addiction focus on increasing the amount of drug consumption to produce addiction-like behavior. However, another critical factor is the temporal pattern of consumption, which in humans is characterized by intermittency, both within and between bouts of use. To model this, the authors combined prolonged access to cocaine (~70 days in total) with an intermittent access (IntA) self-administration procedure and used behavioral economic indicators to quantify changes in motivation for cocaine. IntA produced escalation of intake, a progressive increase in cocaine demand (incentive-sensitization), and robust drug- and cue-induced reinstatement of drug-seeking behavior. The authors also asked whether rats that vary in their propensity to attribute incentive salience to reward cues (sign-trackers [STs] vs. goal-trackers [GTs]) vary in the development of addiction-like behavior. Although STs were more motivated to take cocaine after limited drug experience, after IntA, STs and GTs no longer differed

on any measure of addiction-like behavior. Exposure to large quantities of cocaine is not necessary for escalation of intake, incentive-sensitization, or other addiction-like behaviors (IntA results in far less total cocaine consumption than 'long access' procedures). Also, the ST phenotype may increase susceptibility to addiction, not because STs are inherently susceptible to incentive-sensitization (perhaps all individuals are at risk), but because this phenotype promotes continued drug use, subjecting them to incentive-sensitization. Thus, the pharmacokinetics associated with the IntA procedure are especially effective in producing a number of addiction-like behaviors and may be valuable for studying associated neuroadaptations and for assessing individual variation in vulnerability.

A Weighted U Statistic For Association Analyses Considering Genetic Heterogeneity Wei, Changshuai; Elston, Robert C; Lu, Qing. Stat Med. 2016; 35(16): 2802-2814.
Converging evidence suggests that common complex diseases with the same or similar clinical manifestations could have different underlying genetic etiologies. While current research interests have shifted toward uncovering rare variants and structural variations predisposing to human diseases, the impact of heterogeneity in genetic studies of complex diseases has been largely overlooked. Most of the existing statistical methods assume the disease under investigation has a homogeneous genetic effect and could, therefore, have low power if the disease undergoes heterogeneous pathophysiological and etiological processes. In this paper, the authors propose a heterogeneity-weighted U (HWU) method for association analyses considering genetic heterogeneity. HWU can be applied to various types of phenotypes (e.g., binary and continuous) and is computationally efficient for high-dimensional genetic data. Through simulations, the authors showed the advantage of HWU when the underlying genetic etiology of a disease was heterogeneous, as well as the robustness of HWU against different model assumptions (e.g., phenotype distributions). Using HWU, they conducted a genome-wide analysis of nicotine dependence from the Study of Addiction: Genetics and Environments dataset. The genome-wide analysis of nearly one million genetic markers took 7h, identifying heterogeneous effects of two new genes (i.e., CYP3A5 and IKBKB) on nicotine dependence.

Synthetic and Receptor Signaling Explorations Of The Mitragyna Alkaloids: Mitragynine As An Atypical Molecular Framework For Opioid Receptor Modulators Kruegel, Andrew C; Gassaway, Madalee M; Kapoor, Abhijeet; Váradi, András; Majumdar, Susruta; Filizola, Marta; Javitch, Jonathan A; Sames, Dalibor. J Am Chem Soc. 2016; 138(21): 6754-6764.
Mu-opioid receptor agonists represent mainstays of pain management. However, the therapeutic use of these agents is associated with serious side effects, including potentially lethal respiratory depression. Accordingly, there is a longstanding interest in the development of new opioid analgesics with improved therapeutic profiles. The alkaloids of the Southeast Asian plant Mitragyna speciosa, represented by the prototypical member mitragynine, are an unusual class of opioid receptor modulators with distinct pharmacological properties. Here the authors describe the first receptor-level functional characterization of mitragynine and related natural alkaloids at the human mu-, kappa-, and delta-opioid receptors. These results show that mitragynine and the oxidized analogue 7-hydroxymitragynine, are partial agonists of the human mu-opioid receptor and competitive antagonists at the kappa- and delta-opioid receptors. The authors also show that mitragynine and 7-hydroxymitragynine are G-protein-biased agonists of the mu-opioid receptor, which do not recruit β-arrestin following receptor activation. Therefore, the Mitragyna alkaloid scaffold represents a novel framework for the development of functionally biased opioid modulators, which may exhibit improved therapeutic profiles. Also presented is an enantioselective total synthesis of both (-)-mitragynine and its unnatural enantiomer, (+)-mitragynine, employing a

proline-catalyzed Mannich-Michael reaction sequence as the key transformation. Pharmacological evaluation of (+)-mitragynine revealed its much weaker opioid activity. Likewise, the intermediates and chemical transformations developed in the total synthesis allowed the elucidation of previously unexplored structure-activity relationships (SAR) within the Mitragyna scaffold. Molecular docking studies, in combination with the observed chemical SAR, suggest that Mitragyna alkaloids adopt a binding pose at the mu-opioid receptor that is distinct from that of classical opioids.

Prefrontal Cortex To Accumbens Projections In Sleep Regulation Of Reward Liu, Zheng; Wang, Yao; Cai, Li; Li, Yizhi; Chen, Bo; Dong, Yan; Huang, Yanhua H. J Neurosci. 2016; 36(30): 7897-7910.
Sleep profoundly affects the emotional and motivational state. In humans and animals, loss of sleep often results in enhanced motivation for reward, which has direct implications for health risks as well as potential benefits. The current study aims at understanding the mechanisms underlying sleep deprivation (SDe)-induced enhancement of reward seeking. The authors found that after acute SDe, mice had an increase in sucrose seeking and consumption but not food intake, suggesting a selective enhancement of motivation for reward. In the nucleus accumbens (NAc), a key brain region regulating emotional and motivational responses, the authors observed a decrease in the ratio of the overall excitatory over inhibitory synaptic inputs onto NAc principle neurons after SDe. The shift was partly mediated by reduced glutamatergic transmission of presynaptic origin. Further analysis revealed that there was selective reduction of the glutamate release probability at the medial prefrontal cortex (mPFC)-to-NAc synapses, but not those from the hippocampus, thalamus, or the basal lateral amygdala. To reverse this SDe-induced synaptic alteration, the authors expressed the stabilized step function opsin (SSFO) in the mPFC; optogenetic stimulation of SSFO at mPFC-to-NAc projection terminals persistently enhanced the action potential-dependent glutamate release. Intra-NAc optogenetic stimulation of SSFO selectively at mPFC-to-NAc terminals restored normal sucrose seeking in mice after SDe without affecting food intake. These results highlight the mPFC-to-NAc projection as a key circuit-based target for sleep to regulate reward-motivated behaviors. Sleep loss, a costly challenge of modern society, has profound physiological and psychological consequences, including altered reward processing of the brain. The current study aims at understanding the mechanisms underlying sleep deprivation-induced enhancement of reward seeking. The authors identify that the medial prefrontal cortex (mPFC)-to-nucleus accumbens (NAc) glutamatergic transmission is selectively weakened following acute sleep deprivation, whose restoration normalizes reward seeking in sleep-deprived mice. These results suggest a possibility of normalizing sleep deprivation-induced abnormal reward seeking by targeting specific neural projections, and they demonstrate the mPFC-to-NAc glutamatergic projection as a key circuit-based target for sleep to regulate reward-motivated behaviors.

Enhanced Anxiety In The Male Offspring Of Sires That Self-administered Cocaine White, Samantha L; Vassoler, Fair M; Schmidt, Heath D; Pierce, R Christopher; Wimmer, Mathieu E. Addict Biol. 2016; 21(4): 802-810.
The authors previously showed that paternal cocaine exposure reduced the reinforcing efficacy of cocaine in male offspring. Here, they sought to determine whether paternal cocaine experience could also influence anxiety levels in offspring. Male rats were allowed to self-administer cocaine (controls received saline passively) for 60 days and then were bred with naïve females. Measures of anxiety and cocaine-induced anxiogenic effects were assessed in the adult offspring. Cocaine-sired male offspring exhibited increased anxiety-like behaviors, as measured using the novelty-induced hypophagia and defensive burying tasks, relative to saline-sired males. In contrast, sire cocaine experience had no effect on anxiety-like behaviors in female offspring. When challenged with an

anxiogenic (but not anorectic) dose of cocaine (2.5 mg/kg, i.p.), anxiety-like behavior was enhanced in all animals to an equal degree regardless of sire drug experience. Since anxiety and depression are often co-morbid, the authors also assessed measures of depressive-like behavior. Sire cocaine experience had no effect on depression-like behaviors, as measured by the forced swim task, among male offspring. In a separate group of naïve littermates, select neuronal correlates of anxiety were measured. Male offspring of cocaine-experienced sires showed increased mRNA and protein expression of corticotropin-releasing factor receptor 2 in the hippocampus. Together, these results indicate that cocaine-experienced sires produce male progeny that have increased baseline anxiety, which is unaltered by subsequent cocaine exposure.

Genome-wide Association Studies Of Posttraumatic Stress Disorder In 2 Cohorts Of US Army Soldiers Stein, Murray B; Chen, Chia-Yen; Ursano, Robert J; Cai, Tianxi; Gelernter, Joel; Heeringa, Steven G; Jain, Sonia; Jensen, Kevin P; Maihofer, Adam X; Mitchell, Colter; Nievergelt, Caroline M; Nock, Matthew K; Neale, Benjamin M; Polimanti, Renato; Ripke, Stephan; Sun, Xiaoying; Thomas, Michael L; Wang, Qian; Ware, Erin B; Borja, Susan; Kessler, Ronald C; Smoller, Jordan W; Army Study to Assess Risk and Resilience in Servicemembers (STARRS) Collaborators. JAMA Psychiatry. 2016; 73(7): 695-704.

Posttraumatic stress disorder (PTSD) is a prevalent, serious public health concern, particularly in the military. The identification of genetic risk factors for PTSD may provide important insights into the biological foundation of vulnerability and comorbidity. To discover genetic loci associated with the lifetime risk for PTSD in 2 cohorts from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). Two coordinated genome-wide association studies of mental health in the US military contributed participants. The New Soldier Study (NSS) included 3167 unique participants with PTSD and 4607 trauma-exposed control individuals; the Pre/Post Deployment Study (PPDS) included 947 unique participants with PTSD and 4969 trauma-exposed controls. The NSS data were collected from February 1, 2011, to November 30, 2012; the PDDS data, from January 9 to April 30, 2012. The primary analysis compared lifetime DSM-IV PTSD cases with trauma-exposed controls without lifetime PTSD. Data were analyzed from March 18 to December 27, 2015.Association analyses for PTSD used logistic regression models within each of 3 ancestral groups (European, African, and Latino American) by study, followed by meta-analysis. Heritability and genetic correlation and pleiotropy with other psychiatric and immune-related disorders were estimated. The NSS population was 80.7% male (6277 of 7774 participants; mean [SD] age, 20.9 [3.3] years); the PPDS population, 94.4% male (5583 of 5916 participants; mean [SD] age, 26.5 [6.0] years). A genome-wide significant locus was found in ANKRD55 on chromosome 5 (rs159572; odds ratio [OR], 1.62; 95% CI, 1.37-1.92; $P = 2.34 \times 10\text{-}8$) and persisted after adjustment for cumulative trauma exposure (adjusted OR, 1.64; 95% CI, 1.39-1.95; $P = 1.18 \times 10\text{-}8$) in the African American samples from the NSS. A genome-wide significant locus was also found in or near ZNF626 on chromosome 19 (rs11085374; OR, 0.77; 95% CI, 0.70-0.85; $P = 4.59 \times 10\text{-}8$) in the European American samples from the NSS. Similar results were not found for either single-nucleotide polymorphism in the corresponding ancestry group from the PPDS sample, in other ancestral groups, or in transancestral meta-analyses. Single-nucleotide polymorphism-based heritability was nonsignificant, and no significant genetic correlations were observed between PTSD and 6 mental disorders or 9 immune-related disorders. Significant evidence of pleiotropy was observed between PTSD and rheumatoid arthritis and, to a lesser extent, psoriasis. In the largest genome-wide association study of PTSD to date, involving a US military sample, limited evidence of association for specific loci was found. Further efforts are needed to replicate the genome-wide significant association with ANKRD55-associated in prior research with

several autoimmune and inflammatory disorders-and to clarify the nature of the genetic overlap observed between PTSD and rheumatoid arthritis and psoriasis.

FMRI Study Of Neural Sensitization To Hedonic Stimuli In Long-term, Daily Cannabis Users
Filbey, Francesca M; Dunlop, Joseph; Ketcherside, Ariel; Baine, Jessica; Rhinehardt, Tyler; Kuhn, Brittany; DeWitt, Sam; Alvi, Talha. Hum Brain Mapp. 2016; 37(10): 3431-3443.
Although there is emergent evidence illustrating neural sensitivity to cannabis cues in cannabis users, the specificity of this effect to cannabis cues as opposed to a generalized hyper-sensitivity to hedonic stimuli has not yet been directly tested. Using fMRI, the authors presented 53 daily, long-term cannabis users and 68 non-using controls visual and tactile cues for cannabis, a natural reward, and, a sensory-perceptual control object to evaluate brain response to hedonic stimuli in cannabis users. The results showed an interaction between group and reward type such that the users had greater response during cannabis cues relative to natural reward cues (i.e., fruit) in the orbitofrontal cortex, striatum, anterior cingulate gyrus, and ventral tegmental area compared to non-users (cluster-threshold $z = 2.3$, $P < 0.05$). In the users, there were positive brain-behavior correlations between neural response to cannabis cues in fronto-striatal-temporal regions and subjective craving, marijuana-related problems, withdrawal symptoms, and levels of THC metabolites (cluster-threshold $z = 2.3$, $P < 0.05$). These findings demonstrate hyper-responsivity, and, specificity of brain response to cannabis cues in long-term cannabis users that are above that of response to natural reward cues. These observations are concordant with incentive sensitization models suggesting sensitization of mesocorticolimbic regions and disruption of natural reward processes following drug use. Although the cross-sectional nature of this study does not provide information on causality, the positive correlations between neural response and indicators of cannabis use (i.e., THC levels) suggest that alterations in the reward system are, in part, related to cannabis use.

EPIDEMIOLOGY RESEARCH

FMRI Study Of Neural Sensitization To Hedonic Stimuli In Long-term, Daily Cannabis Users
Filbey, Francesca M; Dunlop, Joseph; Ketcherside, Ariel; Baine, Jessica; Rhinehardt, Tyler; Kuhn, Brittany; DeWitt, Sam; Alvi, Talha. Hum Brain Mapp. 2016; 37(10): 3431-3443.
Although there is emergent evidence illustrating neural sensitivity to cannabis cues in cannabis users, the specificity of this effect to cannabis cues as opposed to a generalized hyper-sensitivity to hedonic stimuli has not yet been directly tested. Using fMRI, the authors presented 53 daily, long-term cannabis users and 68 non-using controls visual and tactile cues for cannabis, a natural reward, and, a sensory-perceptual control object to evaluate brain response to hedonic stimuli in cannabis users. The results showed an interaction between group and reward type such that the users had greater response during cannabis cues relative to natural reward cues (i.e., fruit) in the orbitofrontal cortex, striatum, anterior cingulate gyrus, and ventral tegmental area compared to non-users (cluster-threshold $z = 2.3$, $P < 0.05$). In the users, there were positive brain-behavior correlations between neural response to cannabis cues in fronto-striatal-temporal regions and subjective craving, marijuana-related problems, withdrawal symptoms, and levels of THC metabolites (cluster-threshold $z = 2.3$, $P < 0.05$). These findings demonstrate hyper-responsivity, and, specificity of brain response to cannabis cues in long-term cannabis users that are above that of response to natural reward cues. These observations are concordant with incentive sensitization models suggesting sensitization of mesocorticolimbic regions and disruption of natural reward processes following drug use. Although the cross-sectional nature of this study does not provide information on causality, the positive correlations between neural response and indicators of cannabis use (i.e.,

THC levels) suggest that alterations in the reward system are, in part, related to cannabis use. Hum Brain Mapp 37:3431-3443, 2016. © 2016 The Authors Human Brain Mapping Published by Wiley Periodicals, Inc.

The Genetic and Environmental Association Between Parental Monitoring and Risk Of Cannabis, Stimulants, and Cocaine Initiation In A Sample Of Male Twins: Does Parenting Matter? Olivares, Emily L; Kendler, Kenneth S; Neale, Michael C; Gillespie, Nathan A. Twin Res Hum Genet. 2016; 19(4): 297-305.

The authors' aim was to test the direction of causation between self-report parental monitoring (PM) and the liability to illicit drug initiation (DI) as indicated by cannabis, cocaine, and stimulants. They fitted a multiple indicator model to test causal and non-causal models based on a large, genetically informative cross-sectional sample of male twins. The sample comprised 1,778 males aged 24-62 years from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders. Data came from self-report measures of lifetime cannabis, stimulants, and cocaine initiation, and retrospective assessment of PM between ages 8-17 years. Multivariate modeling showed that familial aggregation in PM and DI were both explained by a combination of additive genetic and shared environmental effects. Moreover, the significant association between PM and DI was best explained by a correlated liability model versus causal models. PM has typically been assumed to be an environmental, causal risk factor for drug use and has been shown to be among the more salient environmental risk factors for illicit DI. Our data were not consistent with this causal hypothesis. Instead, a correlated liability model in which PM and risk of DI share common genetic and environmental risks provided a better fit to the data.

Racial Differences In Heritability Of Cigarette Smoking In Adolescents and Young Adults Bares, Cristina B; Kendler, Kenneth S; Maes, Hermine H M. Drug Alcohol Depend. 2016; 166: 75-84.

Although epidemiologic studies suggest low levels of cigarette use among African American adolescents relative to White U.S. adolescents, it is not known whether this may be due to racial differences in the relative contribution of genes and environment to cigarette use initiation and progression to regular use. Using data from White (n=2665) and African American (n=809) twins and full siblings sampled in the National Longitudinal Study of Adolescents, the authors fitted age-, sex- and race-specific variance decomposition models to estimate the magnitude of genetic and environmental effects on cigarette use initiation and cigarette use quantity in Whites and African Americans across adolescence and adulthood. They employ a causal-contingent-common pathway model to estimate the amount of variance explained in quantity of cigarettes smoked contingent on cigarette use initiation. African Americans had lower cigarette use prevalence from adolescence through adulthood, and used cigarettes less heavily than Whites. Race-specific causal-contingent-common pathway models indicate that racial differences in genetic and environmental contributions to cigarette use initiation and cigarette use quantities are not present in adolescence but appear in young adulthood. Additive genetic factors were an important risk factor for cigarette use initiation for White but not African American young adults and adults. Genetic and environmental contributions for cigarette use are similar by race in adolescence. In adulthood, genes have a stronger influence for cigarette use among White adolescents while the influence of the environment is minimal. For African Americans, both genetic and environmental influences are important in young adulthood and adulthood.

PREVENTION RESEARCH

Protective Prevention Effects on the Association of Poverty With Brain Development Brody, Gene H., et al. JAMA Pediatrics 2016.
This study was designed to determine whether a preventive intervention focused on enhancing supportive parenting could ameliorate the association between exposure to poverty and brain development in low socioeconomic status African American individuals from the rural South. The objective of this study was to determine whether participation in an efficacious prevention program designed to enhance supportive parenting for rural African American children will ameliorate the association between living in poverty and reduced hippocampal and amygdalar volumes in adulthood. In the rural southeastern United States, African American parents and their 11-year-old children were assigned randomly to the Strong African American Families randomized prevention trial or to a control condition. Parents provided data used to calculate income-to-needs ratios when children were aged 11 to 13 years and 16 to 18 years. When the participants were aged 25 years, hippocampal and amygdalar volumes were measured using magnetic resonance imaging. Household poverty was measured by income-to-needs ratios. Young adults' whole hippocampal, dentate gyrus, and CA3 hippocampal subfields as well as amygdalar volumes were assessed using magnetic resonance imaging. Of the 667 participants in the Strong African American Families randomized prevention trial, 119 right-handed African American individuals aged 25 years living in rural areas were recruited. Years lived in poverty across ages 11 to 18 years forecasted diminished left dentate gyrus (simple slope, −14.20; standard error, 5.22; P = .008) and CA3 (simple slope, −6.42; standard error, 2.42; P = .009) hippocampal subfields and left amygdalar (simple slope, −34.62; standard error, 12.74; P = .008) volumes among young adults in the control condition (mean [SD] time, 2.04 [1.88] years) but not among those who participated in the Strong African American Families program (mean [SD] time, 2.61 [1.77] years). In this study, the authors described how participation in a randomized clinical trial designed to enhance supportive parenting ameliorated the association of years lived in poverty with left dentate gyrus and CA3 hippocampal subfields and left amygdalar volumes. These findings are consistent with a possible role for supportive parenting and suggest a strategy for narrowing social disparities.

Association Of Marijuana Use With Blunted Nucleus Accumbens Response To Reward Anticipation Martz, Meghan E; Trucco, Elisa M; Cope, Lora M; Hardee, Jillian E; Jester, Jennifer M; Zucker, Robert A; Heitzeg, Mary M. JAMA Psychiatry. 2016; 73(8): 838-844.
Marijuana use may alter ventral striatal response to reward, which might heighten susceptibility to substance use disorder. Longitudinal research is needed to determine the effects of marijuana use on neural function involved in reward response. The aim of this study was to determine whether marijuana use among young adults prospectively affects nucleus accumbens (NAcc) activation during reward anticipation. One hundred eight young adults were recruited from the Michigan Longitudinal Study, an ongoing study of youth at high risk for substance use disorder and a contrast sample of control families. Participants underwent 3 consecutive functional magnetic resonance imaging scans at approximate ages of 20 (time 1), 22 (time 2), and 24
(time 3) years. Self-report data on marijuana and other drug use occasions were collected annually since age 11 years. Cross-lagged models were used to test the association of marijuana use with neural response in the NAcc to reward anticipation during a monetary incentive delay task controlling for sex, age, other substance use, and family history of substance use disorder. Of 108 participants, 39 (36.1%) were female and mean (SD) age at baseline was 20.1 (1.4) years. Greater marijuana use was associated with later blunted activation in the NAcc during reward anticipation (time 1 to time 2: $\beta = -0.26$, P = .04; time 2 to time 3: $\beta = -0.25$, P = .01). When the cross-lagged

model was tested with the inclusion of previous and concurrent cigarette use, the effect of marijuana use from time 2 to time 3 remained significant (β = -0.29; P = .005) and the effect of cigarette use was nonsignificant. The findings of this study indicate that marijuana use is associated with decreased neural response in the NAcc during the anticipation of nondrug rewards. Over time, marijuana use may alter anticipatory reward processing in the NAcc, which may increase the risk for continued drug use and later addiction.

Predicting Substance Use In Emerging Adulthood: A Genetically Informed Study Of Developmental Transactions Between Impulsivity and Family Conflict Elam, Kit K; Wang, Frances L; Bountress, Kaitlin; Chassin, Laurie; Pandika, Danielle; Lemery-Chalfant, Kathryn. Dev Psychopathol. 2016; 28(3): 673-688.
Deviance proneness models propose a multilevel interplay in which transactions among genetic, individual, and family risk factors place children at increased risk for substance use. The authors examined bidirectional transactions between impulsivity and family conflict from middle childhood to adolescence and their contributions to substance use in adolescence and emerging adulthood (n = 380). Moreover, they examined children's, mothers, and father's polygenic risk scores for behavioral undercontrol, and mothers' and fathers' interparental conflict and substance disorder diagnoses as predictors of these transactions. The results support a developmental cascade model in which childrens' polygenic risk scores predicted greater impulsivity in middle childhood. Impulsivity in middle childhood predicted greater family conflict in late childhood, which in turn predicted greater impulsivity in late adolescence. Adolescent impulsivity subsequently predicted greater substance use in emerging adulthood. Results are discussed with respect to evocative genotype-environment correlations within developmental cascades and applications to prevention efforts.

Genetic Moderation Of Transactional Relations Between Parenting Practices And Child Self-Regulation Cho, Junhan; Kogan, Steven M; Brody, Gene H. J Fam Psychol. 2016.
The present study addressed the ways in which parent and child dopamine D4 receptor (DRD4) genotypes jointly moderate the transactional relations between parenting practices and child self-regulation. African American children (N = 309) and their parents provided longitudinal data spanning child ages 11 to 15 years and a saliva sample from which variation at DRD4 was genotyped. Based on the differential susceptibility perspective, this study examined moderation effects of DRD4 status on (a) the extent to which parenting practices affect child self-regulation and (b) the extent to which child self-regulation, as an environmental influence on the parent, affects parenting behavior. Results indicated that responsive-supportive parenting interacted with children's DRD4 status to influence increases in child self-regulation. Also, child self-regulation interacted with parent's DRD4 status to predict changes in parenting practices. Both Gene × Environment effects conformed to a differential susceptibility model in which parent's and children's DRD4 genes operated to increase environmental sensitivity "for better and for worse."

Automatic Classification Of Communication Logs Into Implementation Stages Via Text Analysis Wang, Dingding; Ogihara, Mitsunori; Gallo, Carlos; Villamar, Juan A; Smith, Justin D; Vermeer, Wouter; Cruden, Gracelyn; Benbow, Nanette; Brown, C Hendricks. Implement Sci. 2016; 11(1): 119.
To improve the quality, quantity, and speed of implementation, careful monitoring of the implementation process is required. However, some health organizations have such limited capacity to collect, organize, and synthesize information relevant to its decision to implement an evidence-based program, the preparation steps necessary for successful program adoption, the fidelity of

program delivery, and the sustainment of this program over time. When a large health system implements an evidence-based program across multiple sites, a trained intermediary or broker may provide such monitoring and feedback, but this task is labor intensive and not easily scaled up for large numbers of sites. The authors present a novel approach to producing an automated system of monitoring implementation stage entrances and exits based on a computational analysis of communication log notes generated by implementation brokers. Potentially discriminating keywords are identified using the definitions of the stages and experts coding of a portion of the log notes. A machine learning algorithm produces a decision rule to classify remaining, unclassified log notes. The authors applied this procedure to log notes in the implementation trial of multidimensional treatment foster care in the California 40-county implementation trial (CAL-40) project, using the stages of implementation completion (SIC) measure. They found that a semi-supervised non-negative matrix factorization method accurately identified most stage transitions. Another computational model was built for determining the start and the end of each stage. This automated system demonstrated feasibility in this proof of concept challenge. The authors provide suggestions on how such a system can be used to improve the speed, quality, quantity, and sustainment of implementation. The innovative methods presented here are not intended to replace the expertise and judgement of an expert rater already in place. Rather, these can be used when human monitoring and feedback is too expensive to use or maintain. These methods rely on digitized text that already exists or can be collected with minimal to no intrusiveness and can signal when additional attention or remediation is required during implementation. Thus, resources can be allocated according to need rather than universally applied, or worse, not applied at all due to their cost.

TREATMENT RESEARCH

Crystal Structure Of The Human Cannabinoid Receptor CB1 Hua, Tian; Vemuri, Kiran; Pu, Mengchen; Qu, Lu; Han, Gye Won; Wu, Yiran; Zhao, Suwen; Shui, Wenqing; Li, Shanshan; Korde, Anisha; Laprairie, Robert B; Stahl, Edward L; Ho, Jo-Hao; Zvonok, Nikolai; Zhou, Han; Kufareva, Irina; Wu, Beili; Zhao, Qiang; Hanson, Michael A; Bohn, Laura M; Makriyannis, Alexandros; Stevens, Raymond C; Liu, Zhi-Jie. Cell. 2016; 167(3): 750-762.e14.
Cannabinoid receptor 1 (CB1) is the principal target of Δ(9)-tetrahydrocannabinol (THC), a psychoactive chemical from Cannabis sativa with a wide range of therapeutic applications and a long history of recreational use. CB1 is activated by endocannabinoids and is a promising therapeutic target for pain management, inflammation, obesity, and substance abuse disorders. Here, the authors present the 2.8 Å crystal structure of human CB1 in complex with AM6538, a stabilizing antagonist, synthesized and characterized for this structural study. The structure of the CB1-AM6538 complex reveals key features of the receptor and critical interactions for antagonist binding. In combination with functional studies and molecular modeling, the structure provides insight into the binding mode of naturally occurring CB1 ligands, such as THC, and synthetic cannabinoids. This enhances our understanding of the molecular basis for the physiological functions of CB1 and provides new opportunities for the design of next-generation CB1-targeting pharmaceuticals.

Potential Anti-obesity Effects Of A Long-acting Cocaine Hydrolase Zheng, Xirong; Deng, Jing; Zhang, Ting; Yao, Jianzhuang; Zheng, Fang; Zhan, Chang-Guo. Chem Biol Interact. 2016; 259(Pt B): 99-103.
A long-acting cocaine hydrolase, known as CocH3-Fc(M3), engineered from human butyrylcholinesterase (BChE) was tested, in this study, for its potential anti-obesity effects. Mice on a high-fat diet gained significantly less body weight when treated weekly with 1 mg/kg CocH3-Fc(M3) compared to control mice, though their food intake was similar. There is no correlation between the average body weight and the average food intake, which is consistent with the previously reported observation in BChE knockout mice. In addition, molecular modeling was carried out to understand how ghrelin binds with CocH3, showing that ghrelin binds with CocH3 in a similar mode as ghrelin binding with wild-type human BChE. The similar binding structures explains why CocH3 and BChE have similar catalytic activity against ghrelin.

Effects Of A Cocaine Hydrolase Engineered From Human Butyrylcholinesterase On Metabolic Profile Of Cocaine In Rats Chen, Xiabin; Zheng, Xirong; Zhou, Ziyuan; Zhan, Chang-Guo; Zheng, Fang. Chem Biol Interact. 2016; 259(Pt B): 104-109.
Accelerating cocaine metabolism through enzymatic hydrolysis at cocaine benzoyl ester is recognized as a promising therapeutic approach for cocaine abuse treatment. The authors' more recently designed A199S/F227A/S287G/A328W/Y332G mutant of human BChE, denoted as cocaine hydrolase-3 (CocH3), has a considerably improved catalytic efficiency against cocaine and has been proven active in blocking cocaine-induced toxicity and physiological effects. In the present study, the authors have further characterized the effects of CocH3 on the detailed metabolic profile of cocaine in rats administrated intravenously (IV) with 5 mg/kg cocaine, demonstrating that IV administration of 0.15 mg/kg CocH3 dramatically changed the metabolic profile of cocaine. Without CocH3 administration, the dominant cocaine-metabolizing pathway in rats was cocaine methyl ester hydrolysis to benzoylecgonine (BZE). With the CocH3 administration, the dominant cocaine-metabolizing pathway in rats became cocaine benzoyl ester hydrolysis to ecgonine methyl ester (EME), and the other two metabolic pathways (i.e. cocaine methyl ester hydrolysis to BZE and cocaine oxidation to norcocaine) became insignificant. The CocH3-catalyzed cocaine benzoyl ester hydrolysis to EME was so efficient such that the measured maximum blood cocaine concentration (~38 ng/ml) was significantly lower than the threshold blood cocaine concentration (~72 ng/ml) required to produce any measurable physiological effects.

Pharmacokinetics and Safety Assessment Of L-Tetrahydropalmatine In Cocaine Users: A Randomized, Double-Blind, Placebo-Controlled Study Hassan, Hazem E; Kelly, Deanna; Honick, Moshe; Shukla, Sagar; Ibrahim, Ahmed; Gorelick, David A; Glassman, Matthew; McMahon, Robert P; Wehring, Heidi J; Kearns, Ann Marie; Feldman, Stephanie; Yu, Mingming; Bauer, Ken; Wang, Jia Bei. J Clin Pharmacol. 2016.
Cocaine use disorder (CUD) remains a significant public health challenge. l-Tetrahydropalmatine (l-THP), a well-tolerated and non-addictive compound, shows promise for the management of CUD. Its pharmacologic profile includes blockade at dopamine and other monoamine receptors and attenuation of cocaine self-administration, reinstatement, and rewarding properties in rats. This study evaluated the safety of l-THP in human cocaine users and its influence on the safety and pharmacokinetics (PK) of cocaine. Twenty-four cocaine-using adult men were randomized to receive l-THP (30 mg twice a day orally) or placebo double-blind for 4 days, with an intranasal cocaine (40 mg) challenge on the fourth day. Safety and tolerability were evaluated using vital signs, ECG, clinical laboratory tests, and standardized self-report instruments. Peripheral venous blood was collected periodically and later assayed for l-THP and cocaine using highly sensitive and

specific ultraperformance liquid chromatography-fluorescence detection (UPLC-FLD) methods. Twenty subjects completed the study, of whom 19 provided complete PK data. The short 3.5-day course of l-THP was safe and well tolerated and did not affect cocaine's PK or its acute cardiovascular effects. The cocaine AUC0→∞ was 211.5 and 261.4 h·ng/mL, and the Cmax was 83.3 and 104.5 ng/mL for the l-THP and placebo groups, respectively. In addition there were no significant differences in the number of side effects reported in each group (l-THP group 22 [48%], placebo group 24 [52%]) or vital signs including, heart rate, blood pressure, complete blood count, or ECG. These findings suggest that oral THP has promise for further development as a treatment for CUD.

The Next-generation Nicotine Vaccine: A Novel and Potent Hybrid Nanoparticle-based Nicotine Vaccine Hu, Yun; Smith, Daniel; Frazier, Evan; Hoerle, Reece; Ehrich, Marion; Zhang, Chenming. Biomaterials. 2016; 106: 228-239.
Owing to the urgent need for more effective treatment against nicotine addiction, a hybrid nanoparticle-based nicotine vaccine (NanoNiccine) was developed in this study. NanoNiccine was composed of a poly(lactide-co-glycolide) acid (PLGA) core, keyhole limpet hemocyanin (KLH) as an adjuvant protein enclosed within the PLGA core, a lipid layer, and nicotine haptens conjugated to the outer surface of the lipid layer. In contrast to the traditional nicotine vaccine, NanoNiccine is not a nicotine-protein conjugate vaccine. Instead, the nicotine hapten and protein are separately located in the nanostructure to minimize antibody production towards KLH. The cellular uptake study demonstrated that NanoNiccine was ideal for internalization and processing by dendritic cells (DCs). Mice immunized with NanoNiccine produced much lower IgG level against KLH as compared to that immunized with the traditional nicotine-KLH (Nic-KLH) vaccine. In addition, NanoNiccine achieved up to a 400% higher titer of anti-nicotine IgG than the positive control, Nic-KLH. Additionally, the Th1/Th2 index of NanoNiccine suggested that the immune response induced by NanoNiccine was antibody response dominant. Furthermore, NanoNiccine was found to be safe in mice.

Efficacy Of An Adenovirus-based Anti-cocaine Vaccine To Reduce Cocaine Self-administration and Reacqusition Using A Choice Procedure In Rhesus Macaques Evans, Suzette M; Foltin, Richard W; Hicks, Martin J; Rosenberg, Jonathan B; De, Bishnu P; Janda, Kim D; Kaminsky, Stephen M; Crystal, Ronald G. Pharmacol Biochem Behav. 2016; 150-151: 76-86.
Immunopharmacotherapy offers an approach for treating cocaine abuse by specifically targeting the cocaine molecule and preventing its access to the CNS. dAd5GNE is a novel cocaine vaccine that attenuates the stimulant and the reinforcing effects of cocaine in rats. The goal of this study was to extend and validate dAd5GNE vaccine efficacy in non-human primates. Six experimentally naïve adult female rhesus monkeys (Macaca mulatta) were trained to self-administer 0.1mg/kg/injection intravenous (i.v.) cocaine or receive candy; then 4 monkeys were administered the vaccine and 2 monkeys were administered vehicle intramuscularly, with additional vaccine boosts throughout the study. The reinforcing effects of cocaine were measured during self-administration, extinction, and reacquisition (relapse) phases. Serum antibody titers in the vaccinated monkeys remained high throughout the study. There was no change in the preference for cocaine over candy over a 20-week period in 5 of the 6 monkeys; only one of the 4 (25%) vaccinated monkeys showed a decrease in cocaine choice. All 6 monkeys extinguished responding for cocaine during saline extinction testing; vaccinated monkeys tended to take longer to extinguish responding than control monkeys (17.5 vs. 7.0 sessions). Vaccination substantially retarded reacquisition of cocaine self-administration; control monkeys resumed cocaine self-administration within 6-41 sessions and 1 vaccinated monkey resumed cocaine self-administration in 19 sessions. The other 3 vaccinated monkeys

required between 57 and 94 sessions to resume cocaine self-administration even in the context of employing several manipulations to encourage cocaine reacquisition. These data suggest that the dAdGNE vaccine may have therapeutic potential for humans who achieve cocaine abstinence as part of a relapse prevention strategy.

L-tetrahydropalmatine Reduces Nicotine Self-administration and Reinstatement In Rats
Faison, Shamia L; Schindler, Charles W; Goldberg, Steven R; Wang, Jia Bei. BMC Pharmacol Toxicol. 2016; 17(1): 49. The negative consequences of nicotine use are well known and documented, however, abstaining from nicotine use and achieving abstinence poses a major challenge for the majority of nicotine users trying to quit. l-Tetrahydropalmatine (l-THP), a compound extracted from the Chinese herb Corydalis, displayed utility in the treatment of cocaine and heroin addiction via reduction of drug-intake and relapse. The present study examined the effects of l-THP on abuse-related effects of nicotine. Self-administration and reinstatement testing was conducted. Rats trained to self-administer nicotine (0.03 mg/kg/injection) under a fixed-ratio 5 schedule (FR5) of reinforcement were pretreated with l-THP (3 or 5 mg/kg), varenicline (1 mg/kg), bupropion (40 mg/kg), or saline before daily 2-h sessions. Locomotor, food, and microdialysis assays were also conducted in separate rats.l-THP significantly reduced nicotine self-administration (SA). l-THP's effect was more pronounced than the effect of varenicline and similar to the effect of bupropion. In reinstatement testing, animals were pretreated with the same compounds, challenged with nicotine (0.3 mg/kg, s.c.), and reintroduced to pre-extinction conditions. l-THP blocked reinstatement of nicotine seeking more effectively than either varenicline or bupropion. Locomotor data revealed that therapeutic doses of l-THP had no inhibitory effects on ambulatory ability and that l-THP (3 and 5 mg/kg) significantly blocked nicotine induced hyperactivity when administered before nicotine. In in-vivo microdialysis experiments, l-THP, varenicline, and bupropion alone elevated extracellular dopamine (DA) levels in the nucleus accumbens shell (nAcb).Since l-THP reduces nicotine taking and blocks relapse it could be a useful alternative to varenicline and bupropion as a treatment for nicotine addiction.

A Randomized Controlled Trial Of Buprenorphine Taper Duration Among Opioid-dependent Adolescents and Young Adults Marsch, Lisa A; Moore, Sarah K; Borodovsky, Jacob T; Solhkhah, Ramon; Badger, Gary J; Semino, Shelby; Jarrett, Kate; Condon, Kathleen DiGangi; Rossettie, Kate; Vincent, Phillip; Hajizadeh, Neda; Ducat, Elizabeth. Addiction. 2016; 111(8): 1406-1415.
Few randomized controlled trials have evaluated buprenorphine treatment interventions for opioid-dependent youth. Consequently, optimal administration strategies for this cohort are unclear. The authors' aim was to evaluate the relative efficacy of two different buprenorphine taper lengths in promoting abstinence from illicit opioids and treatment retention among opioid-dependent youth. A double-blind, placebo controlled, multicenter randomized controlled trial. Two hospital-based research clinics (Manhattan and Brooklyn) in New York City, USA from 2005 to 2010.Volunteer sample of 53 primarily Caucasian participants between the ages of 16 and 24 (n = 11 under age 18) who met DSM-IV opioid dependence criteria. Participants were assigned randomly to either a 28-day buprenorphine taper (n = 28) or 56-day buprenorphine taper (n = 25) via a parallel-groups design during a 63-day period. Both groups received behavioral counseling and opioid abstinence incentives. Both taper conditions had a minimum of 1 week of placebo dosing at the end of the taper. The primary outcome was opioid abstinence measured as a percentage of scheduled urine toxicology tests documented to be negative for opioids. The secondary outcome was treatment retention, measured as number of days attended scheduled visits. Intent-to-treat analyses revealed that participants who received a 56-day buprenorphine taper had a significantly higher percentage of

opioid-negative scheduled urine tests compared with participants who received a 28-day buprenorphine taper [35 versus 17%, P = 0.039; Cohen'sd = 0.57, 95% confidence interval (CI) = 0.02, 1.13]. Participants who received a 56-day buprenorphine taper were retained in treatment significantly longer than participants who received a 28-day buprenorphine taper (37.5 versus 26.4 days, P = 0.027; Cohen'sd = 0.63, 95% CI = 0.06, 1.19). Daily attendance requirement was associated with decreased abstinence and shorter retention compared with a two to three times weekly attendance requirement, independent of taper duration. Follow-up data were insufficient to report. Longer (56-day) buprenorphine taper produces better opioid abstinence and retention outcomes than shorter (28-day) buprenorphine taper for opioid-dependent youth.

Sex-dependent Effects Of Cannabis-induced Analgesia Cooper, Ziva D; Haney, Margaret. Drug Alcohol Depend. 2016; 167: 112-120.
Preclinical studies demonstrate that cannabinoid-mediated antinociceptive effects vary according to sex; it is unknown if these findings extend to humans. This retrospective analysis compared the analgesic, subjective and physiological effects of active cannabis (3.56-5.60% THC) and inactive cannabis (0.00% THC) in male (N=21) and female (N=21) cannabis smokers under double-blind, placebo-controlled conditions. Pain response was measured using the Cold-Pressor Test (CPT). Participants immersed their hand in cold water (4°C); times to report pain (pain sensitivity) and withdraw the hand (pain tolerance) were recorded. Subjective drug ratings were also measured. Among men, active cannabis significantly decreased pain sensitivity relative to inactive cannabis ($p<0.01$). In women, active cannabis failed to decrease pain sensitivity relative to inactive. Active cannabis increased pain tolerance in both men women immediately after smoking ($p<0.001$); a trend was observed for differences between men and women ($p<0.10$). Active cannabis also increased subjective ratings of cannabis associated with abuse liability ('Take again'; 'Liking' and 'Good drug'), drug strength, and 'High'; relative to inactive in both men and women ($p<0.01$). These results indicate that in cannabis smokers, men exhibit greater cannabis-induced analgesia relative to women. These sex-dependent differences are independent of cannabis-elicited subjective effects associated with abuse-liability, which were consistent between men and women. As such, sex-dependent differences in cannabis's analgesic effects are an important consideration that warrants further investigation when considering the potential therapeutic effects of cannabinoids for pain relief.

Bupropion and Naltrexone For Smoking Cessation: A Double-blind Randomized Placebo-controlled Clinical Trial Mooney, M E; Schmitz, J M; Allen, S; Grabowski, J; Pentel, P; Oliver, A; Hatsukami, D K. Clin Pharmacol Ther. 2016; 100(4): 344-352.
Combination of non-nicotine pharmacotherapies has been underexamined for cigarette smoking cessation. A randomized, double-blind, parallel-group double-dummy study evaluated two medications, bupropion (BUP) and naltrexone (NTX), in treatment-seeking cigarette smokers (N = 121) over a 7-week treatment intervention with 6-month follow-up. Smokers were randomized to either BUP (300 mg/day) + placebo (PBO) or BUP (300 mg/day) + NTX (50 mg/day). The primary outcome was biochemically verified (saliva cotinine, carbon monoxide) 7-day, point-prevalence abstinence. BUP + NTX was associated with significantly higher point-prevalence abstinence rates after 7-weeks of treatment (BUP + NTX, 54.1%; BUP + PBO, 33.3%), P = 0.0210, but not at 6-month follow-up (BUP + NTX, 27.9%; BUP + PBO, 15.0%), P = 0.09. Continuous abstinence rates did not differ, P = 0.0740 (BUP + NTX, 26.2%; BUP + PBO, 13.3%). Those receiving BUP + NTX reported reduced nicotine withdrawal, P = 0.0364. The BUP + NTX combination was associated with elevated rates of some side effects, but with no significant difference in retention between the groups.

Bupropion Sustained Release For Pregnant Smokers: A randomized, Placebo-controlled Trial
Nanovskaya, Tatiana N; Oncken, Cheryl; Fokina, Valentina M; Feinn, Richard S; Clark, Shannon M; West, Holly; Jain, Sunil K; Ahmed, Mahmoud S; Hankins, Gary D V. Am J Obstet Gynecol. 2016.
Bupropion is used to treat depression during pregnancy. However, its usefulness as a smoking cessation aid for pregnant women is not fully known. The objective of the study was to evaluate the preliminary efficacy of bupropion sustained release for smoking cessation during pregnancy. The authors conducted a randomized, prospective, double-blind, placebo-controlled, pilot trial. Pregnant women who smoked daily received individualized behavior counseling and were randomly assigned to a 12 week, twice-a-day treatment with 150 mg bupropion sustained release or placebo. The primary study objectives were to determine whether bupropion sustained release reduces nicotine withdrawal symptoms on the quit date and during the treatment period compared with placebo and whether it increases 7day point prevalence abstinence at the end of the treatment period and at the end of pregnancy. Subjects in the bupropion (n = 30) and placebo (n = 35) groups were comparable in age, smoking history, number of daily smoked cigarettes, and nicotine dependence. After controlling for maternal age and race, bupropion sustained release reduced cigarette cravings (1.5 ± 1.1 vs 2.1 ± 1.2, P = .02) and total nicotine withdrawal symptoms (3.8 ± 4.3 vs 5.4 ± 5.1, P = .028) during the treatment period. Administration of bupropion sustained release reduced tobacco exposure, as determined by levels of carbon monoxide in exhaled air (7.4 ± 6.4 vs 9.1 ± 5.8, P = .053) and concentrations of cotinine in urine (348 ± 384 ng/mL vs 831 ± 727 ng/mL, P = .007) and increased overall abstinence rates during treatment (19% vs 2%, P = .003). However, there was no significant difference in 7day point prevalence abstinence rates between the 2 groups at the end of medication treatment (17% vs 3%, P = .087) and at the end of pregnancy (10% vs 3%, P = .328). Individual smoking cessation counseling along with the twice-daily use of 150 mg bupropion sustained release increased smoking cessation rates and reduced cravings and total nicotine withdrawal symptoms during the treatment period. However, there was no significant difference in abstinence rates between groups at the end of medication treatment and at the end of pregnancy, likely because of the small sample size. A larger study is needed to confirm these findings and to examine the potential benefit/ risk ratio of bupropion sustained release for smoking cessation during pregnancy.

Maintenance Pharmacotherapy Normalizes The Relapse Curve In Recently Abstinent Tobacco Smokers With Schizophrenia and Bipolar Disorder Evins, A Eden; Hoeppner, Susanne S; Schoenfeld, David A; Hoeppner, Bettina B; Cather, Corinne; Pachas, Gladys N; Cieslak, Kristina M; Maravic, Melissa Culhane. Schizophr Res. 2016.
The aim of this study was to compare the effect of maintenance pharmacotherapy on sustained abstinence rates between recently abstinent smokers with schizophrenia and bipolar disorder (SBD) and general population smokers without psychiatric illness. The authors performed a person-level, pooled analysis of two randomized controlled trials of maintenance varenicline, conducted in adult smokers with SBD and general population smokers, controlling for severity of dependence. Smokers abstinent after 12-weeks of open varenicline treatment were randomly assigned to ≥12-weeks maintenance varenicline or identical placebo. In those assigned to maintenance placebo, the abstinence rate at week-24 was lower in those with SBD than for those without psychiatric illness (29.4±1.1% vs. 61.8±0.4%, OR:0.26, 95% CI: 0.13, 0.52, p<0.001). In smokers assigned to maintenance pharmacotherapy, however, there was no effect of diagnosis on abstinence rates at week-24 (87.2±0.8% vs. 81.9±0.2%, OR: 1.68, 95% CI: 0.53, 5.32, p=0.38). Time to first lapse was shortest in those with SBD assigned to maintenance placebo (Q1=12days, 95%CI: 4, 16), longer in those without psychiatric illness assigned to maintenance placebo (Q1=17days, 95%CI: 17, 29), still

longer in general-population smokers assigned to maintenance varenicline (Q1=88, 95% CI:58,91, and longest in those with SBD who received maintenance varenicline (Q1>95days, 95%CI:non-est), ($X(2)3df=96.99$, $p<0.0001$; all pairwise comparisons $p<0.001$). Following a standard 12-week course of pharmacotherapy, people with schizophrenia and bipolar disorder were more likely to relapse to smoking without maintenance varenicline treatment. Maintenance pharmacotherapy could improve longer-term tobacco abstinence rates and reduce known smoking-related health disparities in those with SMI.

MEDICAL CONSEQUENCES OF DRUG ABUSE RESEARCH

Acute HIV Infection Transmission Among People Who Inject Drugs In A Mature Epidemic Setting Escudero, DJ; Lurie, MN; Mayer, KH; Weinreb, C; King, M; Galea, S; Friedman, SR; Marshall, BDL. AIDS 2016; 30:2537–2544.
Estimates for the contribution of transmission arising from acute HIV infections (AHIs) to overall HIV incidence vary significantly. Furthermore, little is known about AHI-attributable transmission among people who inject drugs (PWID), including the extent to which interventions targeting chronic infections (e.g. HAART as prevention) are limited by AHI transmission. Thus, the authors estimated the proportion of transmission events attributable to AHI within the mature HIV epidemic among PWID in New York City (NYC). This was a modeling study in which the authors constructed an interactive sexual and injecting transmission network using an agent-based model simulating the HIV epidemic in NYC between 1996 and 2012. Using stochastic microsimulations, the authors cataloged transmission from PWID based on the disease stage of index agents to determine the proportion of infections transmitted during AHI (in primary analyses, assumed to last 3 months). The authors'calibrated model approximated the epidemiological features of the mature HIV epidemic in NYC between 1996 and 2012. Annual HIV incidence among PWID dropped from approximately 1.8% in 1996 to 0.7% in 2012. Over the 16-year period, AHI accounted for 4.9% (10th/90th percentile: 0.1–12.3%) of incident HIV cases among PWID. The annualized contribution of AHI increased over this period from 3.6% in 1996 to 5.9% in 2012. These results suggest that, in mature epidemics such as NYC, between 3% and 6% of transmission events are attributable to AHI among PWID. Current HIV treatment as prevention strategies are unlikely to be substantially affected by AHI-attributable transmission among PWID populations in mature epidemic settings.

A Cas9 Ribonucleoprotein Platform for Functional Genetic Studies of HIV-Host Interactions in Primary Human T Cells Hultquist, JF; Schumann, K; Woo, JM; Manganaro, L; McGregor, MJ; Doudna, J; Simon, V; Krogan, NJ; Marson, A. Cell Rep. 2016 October 25; 17(5): 1438–1452.
New genetic tools are needed to understand the functional interactions between HIV and human host factors in primary cells. The authors recently developed a method to edit the genome of primary CD4+ T cells by electroporation of CRISPR/Cas9 ribonucleoproteins (RNPs). Here, they adapted this methodology to a high-throughput platform for the efficient, arrayed editing of candidate host factors. CXCR4 or CCR5 knock-out cells generated with this method are resistant to HIV infection in a tropism-dependent manner, whereas knock-out of LEDGF or TNPO3 results in a tropism-independent reduction in infection. CRISPR/Cas9 RNPs can furthermore edit multiple genes simultaneously, enabling studies of interactions among multiple host and viral factors. Finally, in an arrayed screen of 45 genes associated with HIV integrase, the authors identified several candidate dependency/restriction factors, demonstrating the power of this approach as a

discovery platform. This technology should accelerate target validation for pharmaceutical and cell-based therapies to cure HIV infection.

The mTOR Complex Controls HIV Latency Besnard, E; Hakre, S; Kampmann, M; Lim, HW; Hosmane, NN; Martin, A; Bassik, MC; Verschueren, E; Battivelli, E; Chan, J; Svensson, JP; Gramatica, A; Conrad, RJ; Ott, M; Greene, WC; Krogan, NJ; Siliciano,,RF; Weissman, JS; Verdin, E. Cell Host and Microbe 2016; 20:285-297.
A population of CD4 T lymphocytes harboring latent HIV genomes can persist in patients on antiretroviral therapy, posing a barrier to HIV eradication. To examine cellular complexes controlling HIV latency, the authors conducted a genome-wide screen with a pooled ultracomplex shRNA library and in vitro system modeling HIV latency and identified the mTOR complex as a modulator of HIV latency. Knockdown of mTOR complex subunits or pharmacological inhibition of mTOR activity suppresses reversal of latency in various HIV-1 latency models and HIV-infected patient cells. mTOR inhibitors suppress HIV transcription both through the viral transactivator Tat and via Tat-independent mechanisms. This inhibition occurs at least in part via blocking the phosphorylation of CDK9, a p-TEFb complex member that serves as a cofactor for Tat-mediated transcription. The control of HIV latency by mTOR signaling identifies a pathway that may have significant therapeutic opportunities.

Epigenome-Wide Differential DNA Methylation Between HIV-Infected and Uninfected Individuals Zhanga, X; Justice, AC; Hud, Y; Wange, Z; Zhaof, H; Wangg, G; Johnson, EO, Emue, B; Suttone, RE; Krystal, JA; Xua, K. Epigenetics 2016; 11(10): 750-760.
Epigenetic control of human immunodeficiency virus-1 (HIV-1) genes is critical for viral integration and latency. However, epigenetic changes in the HIV-1-infected host genome have not been well characterized. Here, the authors report the first large-scale epigenome-wide association study of DNA methylation for HIV-1 infection. They recruited HIV-infected (n D 261) and uninfected (n D 117) patients from the Veteran Aging Cohort Study (VACS) and all samples were profiled for 485,521 CpG sites in DNA extracted from the blood. After adjusting for cell type and clinical confounders, we identified 20 epigenome-wide significant CpGs for HIV-1 infection. Importantly, 2 CpGs in the promoter of the NLR family, CARD domain containing gene 5 (NLRC5), a key regulator of major histocompatibility complex class I gene expression, showed significantly lower methylation in HIV-infected subjects than in uninfected subjects (cg07839457: t D ¡6.03, Pnominal D 4.96 £ 10¡9; cg16411857: t D ¡7.63, Pnominal D 3.07 £ 10¡13). Hypomethylation of these 2 CpGs was replicated in an independent sample (GSE67705: cg07839457: t D¡4.44, Pnominal D 1.61 £ 10¡5; cg16411857: t D ¡5.90; P D 1.99 £ 10¡8). Methylation of these 2 CpGs in NLRC5 was negatively correlated with viral load in the 2 HIV-infected samples (cg07839457: P D 1.8 £ 10¡4; cg16411857: P D 0.03 in the VACS; and cg07839457: P D 0.04; cg164111857: P D 0.01 in GSE53840). These findings demonstrate that differential DNA methylation is associated with HIV infection and suggest the involvement of a novel host gene, NLRC5, in HIV pathogenesis.

Association Of Injection Drug Use With Incidence Of HIV-Associated Non-AIDS-Related Morbidity By Age, 1995–2014 Leskoa, KR; Moorea, RD; Tonga, W; Laua, B. AIDS 2016; 30:1447-1455.
Incidence of HIV-associated non-AIDS (HANA) related comorbidities is increasing in HIV-infected individuals. The authors'objective was to estimate the risk of HANA comorbidity associated with history of injection drug use (IDU) correctly accounting for higher death rates

among people who inject drugs (PWID). The authors followed HIV-infected persons aged 25–59 years who enrolled in the Johns Hopkins HIV Clinical Cohort between 1995 and May 2014, from enrollment until HANA comorbidity diagnosis, death, age 60, or administrative censoring. They compared cumulative incidence ('risk'), by age, of validated diagnoses of HANA comorbidities among HIV-infected PWID and non-IDU; specifically, they considered end-stage renal disease (ESRD), end-stage liver disease (ESLD), myocardial infarction, stroke, and non-AIDS-defining cancer. The authors used competing risk methods appropriate to account for death, standardized to the marginal distribution of baseline covariates, and adjusted for potential differential loss-to-clinic. Of 5490 patients included in this analysis, 37% reported IDU as an HIV transmission risk. By age 55 years, PWID had higher risk of ESLD [risk difference¼6.8, 95% confidence interval (CI): _1.9, 15.5] and ESRD (risk difference¼11.1, 95% CI: 1.2, 21.0) than did non-IDU. Risk of myocardial infarction and stroke were similar among PWID and non-IDU. Risk of non-AIDS-defining cancer was lower among PWID than among non-IDU (risk difference at 55 years: _4.9, 95% CI: _11.2, 1.3). The authors concluded that not all HANA comorbidities occur with higher incidence in PWID compared with non-IDU. However, higher incidence of ESRD and ESLD among PWIDs highlights the importance of recognition and management of markers of these comorbidities in early stages among PWID.

Coronary Plaque Progression and Regression in Asymptomatic African American Chronic Cocaine Users With Obstructive Coronary Stenoses: **A Preliminary Study** Sandfort V; Bluemke, DA; Vargas, J; Brinker, JA; Gerstenblith, G; Kickler, T; Zheng, G; Li, J, Chen, S; Lai, H; Fishman, EK; Lai, S. J Addict Med. 2017 Jan 6. doi: 0.1097/ADM.0000000000000282. [Epub ahead of print].

Although rapid progression of coronary atherosclerosis was observed in chronic cocaine users, it is unknown whether reduced cocaine use retards the progression of atherosclerosis. The authors investigated whether reduced cocaine use over a 12-month period was associated with coronary plaque regression in cocaine users. Fifteen African American chronic cocaine users with previously coronary computed tomography angiography (CCTA)-confirmed >50% coronary stenosis in Baltimore, Maryland, were enrolled in a study to investigate whether reduced cocaine use is associated with changes in coronary plaque burden over a 12-month period of cash-based incentive intervention, which was implemented to systematically reinforce cocaine abstinence. In addition to previous CCTA (pre-intervention), CCTA was performed at the intervention baseline and at post-intervention. Plaque analyses were performed to determine the trajectory of plaque changes in the absence of intervention by comparing the pre-intervention with the intervention baseline studies; the trajectory of plaque changes associated with the intervention by comparing the intervention baseline with the post-intervention studies; and (3) whether reduced cocaine use was independently associated with changes in coronary plaque burden. During the 12-month cash-based incentive intervention period, cocaine use in participants was lower. The medians of noncalcified plaque indices were 37.8 (interquartile range [IQR] 29.3-44.0), 43.1 (IQR 38.3-49.0), and 38.7 (IQR 31.2-46.8) mm at pre-intervention, intervention baseline, and post-intervention, respectively. Multivariable generalized estimating equation analysis showed that both total plaque and noncalcified plaque indices at pre-intervention were significantly lowered as compared with intervention baseline levels; both total plaque and noncalcified plaque indices after intervention were significantly lowered as compared with intervention baseline levels; and reduced cocaine use was independently associated with lower total plaque volume index ($P<0.0001$) and noncalcified plaque volume index ($P=0.010$). These findings suggest that continued cocaine use may be associated with noncalcified plaque progression, whereas reduced cocaine use may be associated with noncalcified plaque regression. Larger studies are needed to confirm these findings.

Hepatitis C Virus Testing and Treatment Among Persons Receiving Buprenorphine In An Office-Based Program For Opioid Use Disorders Carey, Katelyn J; Huang, Wei; Linas, Benjamin P; Tsui, Judith I. J Subst Abuse Treat. 2016; 66: 54-59.
In the United States, hepatitis C virus (HCV) infection is primarily spread through injection drug use. There is an urgent need to improve access to care for HCV among persons with opioid use disorders who inject drugs. The purpose of this study was to determine the prevalence of HCV, patient characteristics, and receipt of appropriate care in a sample of patients treated with buprenorphine for their opioid use disorders in a primary care setting. This study used retrospective clinical data from the electronic medical record. The study population included patients receiving buprenorphine in the Office Based Opioid Treatment (OBOT) clinic within the adult primary medicine clinic at Boston Medical Center between October 2003 and August 2013 who received a conclusive HCV antibody (Ab) test within a year of clinic entry. The authors compared characteristics by HCV serostatus using Pearson's chi-square and provided numbers/percentages receiving appropriate care. The sample comprised 700 patients. Slightly less than half of all patients (n=334, 47.7%) were HCV Ab positive, and were significantly more likely to be older, Hispanic or African American, have diagnoses of post-traumatic stress disorder (PTSD) or bipolar disorder, have prior heroin or cocaine use, and be HIV-infected. Among the 334 HCV Ab positive patients, 226 (67.7%) had detectable HCV ribonucleic acid (RNA) indicating chronic HCV infection; only 5 patients (2.21%) with chronic HCV infection ever initiated treatment. Nearly half of patients (47.7%) receiving office-based treatment with buprenorphine for their opioid use disorder had a positive hepatitis C virus antibody screening test although initiation of HCV treatment was nearly non-existent (2.21%).

Frailty and Constellations Of Factors In Aging HIV-infected and Uninfected Women--The Women's Interagency HIV Study Gustafson, D R; Shi, Q; Thurn, M; Holman, S; Minkoff, H; Cohen, M; Plankey, M W; Havlik, R; Sharma, A; Gange, S; Gandhi, M; Milam, J; Hoover, D. J Frailty Aging. 2016; 5(1): 43-48.
Biological similarities are noted between aging and HIV infection. Middle-aged adults with HIV infection may present as elderly due to accelerated aging or having more severe aging phenotypes occurring at younger ages. The authors explored age-adjusted prevalence of frailty, a geriatric condition, among HIV+ and at risk HIV- women. Cross-sectional. The Women's Interagency HIV Study (WIHS).2028 middle-aged (average age 39 years) female participants (1449 HIV+; 579 HIV-). The Fried Frailty Index (FFI), HIV status variables, and constellations of variables representing Demographic/health behaviors and Aging-related chronic diseases. Associations between the FFI and other variables were estimated, followed by stepwise regression models. Overall frailty prevalence was 15.2% (HIV+, 17%; HIV-, 10%). A multivariable model suggested that HIV infection with CD4 count<200; age>40 years; current or former smoking; income ≤$12,000; moderate vs low fibrinogen-4 (FIB-4) levels; and moderate vs high estimated glomerular filtration rate (eGFR) were positively associated with frailty. Low or moderate drinking was protective. Frailty is a multidimensional aging phenotype observed in mid-life among women with HIV infection. Prevalence of frailty in this sample of HIV-infected women exceeds that for usual elderly populations. This highlights the need for geriatricians and gerontologists to interact with younger 'at risk' populations, and assists in the formulation of best recommendations for frailty interventions to prevent early aging, excess morbidities and early death.

Chronic Pain, Craving, and Illicit Opioid Use Among Patients Receiving Opioid Agonist Therapy Tsui, Judith I; Lira, Marlene C; Cheng, Debbie M; Winter, Michael R; Alford, Daniel P; Liebschutz, Jane M; Edwards, Robert R; Samet, Jeffrey H. Drug Alcohol Depend. 2016; 166:26-31.
In a sample of patients receiving opioid agonist therapy, the authors evaluated whether having chronic pain was associated with (a) craving for opioids and (b) illicit opioid use. In a cross-sectional study of adults on buprenorphine or methadone maintenance recruited from an urban medical center, the authors examined any craving for opioids (primary dependent variable) in the past week and recent illicit opioid use (secondary dependent variable). Illicit opioid use was defined as a positive urine drug test (UDT) for opiates and chronic pain was defined as bodily pain that had been present for at least 3 months. Multivariable logistic regression models were fit for each outcome, adjusting for age, sex, and non-white race. Additional models adjusted for depression (PHQ-9) and anxiety (STAI). The sample included 105 adults on methadone or buprenorphine maintenance. Mean age was 43.8 (SD ±9.4) years; 48% were female and 32% non-white; 19% were on methadone. Chronic pain was present in 68% of the sample, 51% reported craving opioids in the past week, and 16% had a positive UDT. Chronic pain was associated with 3-fold higher odds of reporting craving in the past week (aOR=3.10; 95% CI: 1.28-7.50, p-value=0.01). The relative odds for having a positive UDT were not statistically significant (aOR=2.52; 95% CI: 0.64-9.90, p=0.18). In this sample of patients treated with opioid agonist therapy, those with chronic pain had higher odds of reporting craving for opioids. Chronic pain with associated opioid craving potentially places this population at risk for relapse.

Electrochemical Monitoring-on-chip (E-MoC) Of HIV-infection In Presence Of Cocaine and Therapeutics Kaushik, Ajeet; Vabbina, Phani Kiran; Atluri, Venkata; Shah, Pratikkumar; Vashist, Arti; Jayant, Rahul Dev; Yandart, Adriana; Nair, Madhavan. Biosens Bioelectron. 2016; 86:426-31.
Electrochemical monitoring-on-chip (E-MoC)-based approach for rapid assessment of human immunodeficiency virus (HIV)-infection in the presence of cocaine (Coc) and specific drugs namely i.e., tenofovir (Tef), rimcazole (RA) is demonstrated here, for the first time, using electrochemical impedance spectroscopy (EIS). An in-vitro primary human astrocytes (HA) model was developed using a cultureware chip (CC, used for E-MoC) for HIV-infection, Coc exposure and treatment with anti-HIV drug i.e., Tef, and Coc antagonist i.e., RA. The charge transfer resistance (Rct) value of each CC well varies with respect to infection and treatment demonstrated highly responsive sensitivity of developed chip. The results of E-MoC, a proof-of-the concept, suggested that HIV-infection progression due to Coc ingestion and therapeutic effects of highly specific drugs are measurable on the basis of cell electrophysiology. Though, this work needs various molecular biology-based optimizations to promote this technology as an analytical tool for the rapid assessment of HIV-infection in a patient to manage HIV diseases for timely diagnosis. The presented study is based on using CNS cells and efforts are being made to perform this method using peripheral cells such as monocytes derived dendritic cells.

HIV, Cocaine Use, and Hepatitis C Virus: A Triad Of Nontraditional Risk Factors For Subclinical Cardiovascular Disease Lucas, Gregory M; Atta, Mohamed G; Fine, Derek M; McFall, Allison M; Estrella, Michelle M; Zook, Katie; Stein, James H. Arterioscler Thromb Vasc Biol. 2016; 36(10): 2100-2107.
The authors assessed cross-sectional and longitudinal associations of 3 nontraditional cardiovascular disease risk factors-HIV, cocaine use, and chronic hepatitis C virus infection-with 3 validated markers of subclinical cardiovascular disease: carotid artery plaque, albuminuria, and aortic pulse wave velocity in a well-characterized cohort. They measured carotid plaque at baseline and after 24 months, urine albumin/creatinine ratio every 6 months, and pulse wave velocity

annually for up to 36 months in a predominantly black cohort of 292 participants (100 HIV negative and 192 HIV positive). Thirty-nine percent had chronic hepatitis C virus infection and 20%, 28%, and 52% were never, past, and current cocaine users, respectively. Sixteen percent, 47%, and 64% of those with none, 1 or 2, or all 3 nontraditional risk factors had ≥2 abnormal cardiovascular disease risk markers (P=0.001). In fully adjusted models that included all 3 nontraditional risk factors, HIV infection was independently associated with carotid plaque progression (increase in the number of anatomic segments with plaque), albuminuria (albumin-creatinine ratio >30 mg/g), albuminuria progression (doubling of albumin-creatinine ratio from baseline to a value >30 mg/g), and pulse wave velocity. Cocaine use was associated with an ≈3-fold higher odds of carotid plaque at baseline, and hepatitis C virus infection was significantly associated with a higher risk of carotid plaque progression. These results suggest that HIV infection, cocaine use, and hepatitis C virus infection are important nontraditional risk factors for cardiovascular disease and highlight the need to understand the distinct and overlapping mechanisms of the associations.

SERVICES RESEARCH

Past Year Non-medical Opioid Use and Abuse and PTSD Diagnosis: Interactions With Sex and Associations With Symptom Clusters Smith, Kathryn Z; Smith, Philip H; Cercone, Sarah A; McKee, Sherry A; Homish, Gregory G. Addict Behav. 2016; 58: 167-174.
Few studies have examined the associations between posttraumatic stress disorder (PTSD) and non-medical opioid use (NMOU), particularly in general U.S. The authors analyzed data from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationally representative sample of non-institutionalized adults, to examine (1) the relationship between PTSD diagnosis with NMOU, Opioid Use Disorder diagnosis, and average monthly frequency of NMOU; and (2) the relationship between PTSD symptom clusters with NMOU, Opioid Use Disorder diagnosis, and average monthly frequency of NMOU. The authors also explored sex differences among these associations. In the adjusted model, a past year PTSD diagnosis was associated with higher odds of past year NMOU for women and men, but the association was stronger for women. In addition, PTSD was associated with higher odds of an Opioid Use Disorder diagnosis for women, but not for men. With regard to the relationship between specific symptom clusters among those with a past year PTSD diagnosis, important sex differences emerged. For women, the avoidance symptom cluster was associated with higher odds of NMOU, an Opioid Use Disorder diagnosis, and higher rate of average monthly frequency of NMOU, while for men the arousal/reactivity cluster was associated with higher odds of NMOU, an Opioid Use Disorder diagnosis, and a higher rate of average monthly frequency of NMOU. In addition, for men, the avoidance symptom cluster was associated with higher odds of an Opioid Use Disorder diagnosis, but a lower rate of average monthly frequency of NMOU. Results add to the literature showing an association between PTSD and NMOU and suggest that PTSD is more strongly associated with substance use for women than men. Further, results based on individual symptom clusters suggest that men and women with PTSD may be motivated to use substances for different reasons.

Prevalence and Predictors Of Substance Use Disorders Among HIV Care Enrollees In The United States Hartzler, Bryan; Dombrowski, Julia C; Crane, Heidi M; Eron, Joseph J; Geng, Elvin H; Christopher Mathews, W; Mayer, Kenneth H; Moore, Richard D; Mugavero, Michael J; Napravnik, Sonia; Rodriguez, Benigno; Donovan, Dennis M. AIDS Behav. 2016.
Prior efforts to estimate U.S. prevalence of substance use disorders (SUDs) in HIV care have been undermined by caveats common to single-site trials. The current work reports on a cohort of 10,652

HIV-positive adults linked to care at seven sites, with available patient data including geography, demography, and risk factor indices, and with substance-specific SUDs identified via self-report instruments with validated diagnostic thresholds. Generalized estimating equations also tested patient indices as SUD predictors. Findings were: (1) a 48 % SUD prevalence rate (between-site range of 21-71 %), with 20 % of the sample evidencing polysubstance use disorder; (2) substance-specific SUD rates of 31 % for marijuana, 19 % alcohol, 13 % methamphetamine, 11 % cocaine, and 4 % opiate; and (3) emergence of younger age and male gender as robust SUD predictors. Findings suggest high rates at which SUDs occur among patients at these urban HIV care sites, detail substance-specific SUD rates, and identify at-risk patient subgroups.

A Facebook Follow-Up Strategy For Rural Drug-Using Women Dickson, Megan F; Staton-Tindall, Michele; Smith, Kirsten E; Leukefeld, Carl; Webster, J Matthew; Oser, Carrie B. J Rural Health. 2016.
Facebook (FB) use has grown exponentially over the past decade, including in rural areas. Despite its popularity, FB has been underutilized as a research follow-up approach to maintain contact with research participants and may have advantages in less densely populated areas and among more hard-to-reach, at-risk groups. The overall goal of this study was to examine FB as a supplemental follow-up approach to other follow-up strategies with rural drug-using women. Face-to-face interviews were conducted with randomly selected women who completed baseline interviews in 3 rural jails in 1 state. Analyses focus on participants who were released from jail and were eligible for 3-month follow-up (n = 284). Bivariate analyses were used to examine differences between FB users and nonusers, and multivariate logistic regression models examined predictors of 3-month follow-up participation and being located for follow-up using FB. About two-thirds (64.4%) of participants were regular FB users. Bivariate analyses indicated that FB users were younger, more educated, and more likely to have used alcohol in the 30 days before incarceration but less likely to have a chronic health problem. Regression analyses indicated that rural FB users had more than 5 times the odds of being located for the 3-month follow-up interview, even after controlling for other variables. There were no significant predictors of being followed up using FB. Findings suggest that FB is widely used and well accepted among rural drug-using women. Among hard-to-reach populations, including those in rural, geographically isolated regions, FB serves as a method to improve participant follow-up.

Association Between Quality Measures and Mortality In Individuals With Co-Occurring Mental Health and Substance Use Disorders Watkins, Katherine E; Paddock, Susan M; Hudson, Teresa J; Ounpraseuth, Songthip; Schrader, Amy M; Hepner, Kimberly A; Sullivan, Greer. J Subst Abuse Treat. 2016; 69: 1-8.
Individuals with co-occurring mental and substance use disorders have increased rates of mortality relative to the general population. The relationship between measures of treatment quality and mortality for these individuals is unknown. The aim of this study was to examine the association between 5 quality measures and 12- and 24-month mortality. This was a retrospective cohort study of patients with co-occurring mental illness (schizophrenia, bipolar disorder, post-traumatic stress disorder and major depression) and substance use disorders who received care for these disorders paid for by the Veterans Administration between October 2006 and September 2007. Logistic regression models were used to examine the association between 12 and 24-month mortality and 5 patient-level quality measures, while risk-adjusting for patient characteristics. Quality measures included receipt of psychosocial treatment, receipt of psychotherapy, treatment initiation and engagement, and a measure of continuity of care. The authors also examined the relationship between number of diagnosis-related outpatient visits and mortality, and conducted sensitivity

analyses to examine the robustness of their findings to an unobserved confounder. Mortality 12 and 24 months after the end of the observation period. All measures except for treatment engagement at 24 months were significantly associated with lower mortality at both 12 and 24 months. At 12 months, receiving any psychosocial treatment was associated with a 21% decrease in mortality; psychotherapy, a 22% decrease; treatment initiation, a 15% decrease, treatment engagement, a 31% decrease; and quarterly, diagnosis-related visits a 28% decrease. Increasing numbers of visits were associated with decreasing mortality. Sensitivity analyses indicated that the difference in the prevalence of an unobserved confounder would have to be unrealistically large given the observed data, or there would need to be a large effect of an unobserved confounder, to render these findings non-significant. This is the first study to show an association between process-based quality measures and mortality in patients with co-occurring mental and substance use disorders, and provides initial support for the predictive validity of the measures. By devising strategies to improve performance on these measures, health care systems may be able to decrease the mortality of this vulnerable population.

CTN-RELATED RESEARCH

Performance of the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool for Substance Use Screening in Primary Care Patients McNeely, J; Wu, LT; Subramaniam, G; Sharma, G; Cathers, LA; Svikis, D; Sleiter, L; Russell, L; Nordeck, C; Sharma, A; O'Grady, KE; Bouk, LB; Cushing, C; King, J; Wahle, A; Schwartz, RP. Ann Intern Med. 2016 Nov 15;165(10):690-699. doi: 10.7326/M16-0317. Epub 2016 Sep 6.
Substance use, a leading cause of illness and death, is underidentified in medical practice. The Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) tool was developed to address the need for a brief screening and assessment instrument that includes all commonly used substances and fits into clinical workflows. The goal of this study was to assess the performance of the TAPS tool in primary care patients. This was a multisite study, conducted within the National Drug Abuse Treatment Clinical Trials Network, comparing the TAPS tool with a reference standard measure. (ClinicalTrials.gov: NCT02110693). This study was conducted in 5 adult primary care clinics. Participants comprised 2000 adult patients consecutively recruited from clinic waiting areas. Interviewer- and self-administered versions of the TAPS tool were compared with a reference standard, the modified World Mental Health Composite International Diagnostic Interview (CIDI), which measures problem use and substance use disorder (SUD). Interviewer- and self-administered versions of the TAPS tool had similar diagnostic characteristics. For identifying problem use (at a cutoff of 1+), the TAPS tool had a sensitivity of 0.93 (95% CI, 0.90 to 0.95) and specificity of 0.87 (CI, 0.85 to 0.89) for tobacco and a sensitivity of 0.74 (CI, 0.70 to 0.78) and specificity of 0.79 (CI, 0.76 to 0.81) for alcohol. For problem use of illicit and prescription drugs, sensitivity ranged from 0.82 (CI, 0.76 to 0.87) for marijuana to 0.63 (CI, 0.47 to 0.78) for sedatives; specificity was 0.93 or higher. For identifying any SUD (at a cutoff of 2+), sensitivity was lower. The low prevalence of some drug classes led to poor precision in some estimates. Research assistants were not blinded to participants' TAPS tool responses when they administered the CIDI. The authors conclude that in a diverse population of adult primary care patients, the TAPS tool detected clinically relevant problem substance use. Although it also may detect tobacco, alcohol, and marijuana use disorders, further refinement is needed before it can be recommended broadly for SUD screening.

Mortality Rates Among Substance Use Disorder Participants in Clinical Trials: Pooled Analysis of Twenty-Two Clinical Trials Within the National Drug Abuse Treatment Clinical Trials Network Lindblad, R; Hu, L; Oden, N; Wakim, P; Rosa, C; VanVeldhuisen, P. J Subst Abuse Treat. 2016 Nov; 70:73-80. doi: 10.1016/j.jsat.2016.08.010. Epub 2016 Aug 15.
Most substance use disorders (SUD) treatment clinical trials are too short and small to reliably estimate the incidence of rare events like death. The aim of this study is to estimate the overall mortality rates among a SUD treatment-seeking population by pooling participants from multiple clinical trials conducted through the National Institute on Drug Abuse (NIDA)-sponsored National Drug Abuse Treatment Clinical Trials Network (CTN). Study participants were drug and or alcohol users (N=9866) who sought treatment and participated in one of the twenty-two CTN trials. Data were collected through randomized clinical trials in national community treatment programs for SUD. Pooled analysis was performed to assess age- and gender-standardized mortality rate(s) (SM rate(s)), and mortality ratio(s) (SM ratio(s)) of CTN trial participants compared to the U.S. general population. The age- and gender-SM rate among CTN trials participants was 1403 (95% CI: 862-2074) per 100,000 person years (PY) compared to 542 (95% CI: 541-543) per 100,000 PY among the U.S. general population in 2005. By gender, age-adjusted SM ratio for female CTN trial participants was over five times (SM ratio=5.35, 95% CI: 3.31-8.19)), and for male CTN trial participants, it was over three times (SM ratio=3.39, 95% CI: 2.25-4.90) higher than their gender comparable peers in the U.S. general population. Age and gender-standardized mortality rates and ratios among NIDA CTN SUD treatment-seeking clinical trial participants are higher than the age and gender comparable U.S. general population. The overall mortality rates of CTN trial participants are similar to in-treatment mortality reported in large U.S. and non-U.S. cohorts of opioid users. Future analysis with additional CTN trial participants and risk times will improve the stability of estimates, especially within subgroups based on primary substance of abuse. These SUD mortality rates can be used to facilitate safety monitoring within SUD clinical trials.

A Polymorphism In The OPRM1 3'-Untranslated Region Is Associated With Methadone Efficacy In Treating Opioid Dependence Crist, RC; Doyle, GA; Nelson, EC; Degenhardt, L; Martin, NG; Montgomery, GW; Saxon, AJ; Ling, W; Berrettini, WH. Pharmacogenomics J. 2016 Dec 13. doi: 10.1038/tpj.2016.89. [Epub ahead of print].
The μ-opioid receptor (MOR) is the primary target of methadone and buprenorphine. The primary neuronal transcript of the OPRM1 gene, MOR-1, contains a ~13 kb 3' untranslated region with five common haplotypes in European-Americans. The authors analyzed the effects of these haplotypes on the percentage of opioid positive urine tests in European-Americans (n=582) during a 24-week, randomized, open-label trial of methadone or buprenorphine/naloxone (Suboxone) for the treatment of opioid dependence. A single haplotype, tagged by rs10485058, was significantly associated with patient urinalysis data in the methadone treatment group. Methadone patients with the A/A genotype at rs10485058 were less likely to have opioid-positive urine drug screens than those in the combined A/G and G/G genotypes group (relative risk=0.76, 95% confidence intervals=0.73-0.80, P=0.0064). Genotype at rs10485058 also predicted self-reported relapse rates in an independent population of Australian patients of European descent (n=1215) who were receiving opioid substitution therapy (P=0.003). In silico analysis predicted that miR-95-3p would interact with the G, but not the A allele of rs10485058. Luciferase assays indicated miR-95-3p decreased reporter activity of constructs containing the G, but not the A allele of rs10485058, suggesting a potential mechanism for the observed pharmacogenetic effect. These findings suggest that selection of a medication for opioid dependence based on rs10485058 genotype might improve outcomes in this ethnic group. The Pharmacogenomics Journal advance online publication, 13 December 2016; doi:10.1038/tpj.2016.89.

Examining the Efficacy of HIV Risk-Reduction Counseling on the Sexual Risk Behaviors of a National Sample of Drug Abuse Treatment Clients: Analysis of Subgroups Gooden, L; Metsch, LR; Pereyra, MR; Malotte, CK; Haynes, LF; Douaihy, A; Chally, J; Mandler, RN; Feaster, DJ. AIDS Behav. 2016 Sep;20(9):1893-906. doi: 10.1007/s10461-016-1300-6.
HIV counseling with testing has been part of HIV prevention in the U.S. since the 1980s. Despite the long-standing history of HIV testing with prevention counseling, the CDC released HIV testing recommendations for health care settings contesting benefits of prevention counseling with testing in reducing sexual risk behaviors among HIV-negatives in 2006. Efficacy of brief HIV risk-reduction counseling (RRC) in decreasing sexual risk among subgroups of substance use treatment clients was examined using multi-site RCT data. Interaction tests between RRC and subgroups were performed; multivariable regression evaluated the relationship between RRC (with rapid testing) and sex risk. Subgroups were defined by demographics, risk type and level, attitudes/perceptions, and behavioral history. There was an effect ($p < .0028$) of counseling on number of sex partners among some subgroups. Certain subgroups may benefit from HIV RRC; this should be examined in studies with larger sample sizes, designed to assess the specific subgroup(s).

An Item Bank for Abuse of Prescription Pain Medication from the Patient-Reported Outcomes Measurement Information System (PROMIS®) Pilkonis, PA; Yu, L; Dodds, NE; Johnston, KL; Lawrence, SM; Hilton, TF; Daley, DC; Patkar, AA; McCarty, D. Pain Med 2016;1-12.
There is a need to monitor patients receiving prescription opioids to detect possible signs of abuse. To address this need, the authors developed and calibrated an item bank for severity of abuse of prescription pain medication as part of the Patient-Reported Outcomes Measurement Information System (PROMIS®). Comprehensive literature searches yielded an initial bank of 5,310 items relevant to substance use and abuse, including abuse of prescription pain medication, from over 80 unique instruments. After qualitative item analysis (i.e., focus groups, cognitive interviewing, expert review, and item revision), 25 items for abuse of prescribed pain medication were included in field testing. Items were written in a first-person, past-tense format, with a three-month time frame and five response options reflecting frequency or severity. The calibration sample included 448 respondents, 367 from the general population (ascertained through an internet panel) and 81 from community treatment programs participating in the National Drug Abuse Treatment Clinical Trials Network. A final bank of 22 items was calibrated using the two-parameter graded response model from item response theory. A seven-item static short form was also developed. The test information curve showed that the PROMIS® item bank for abuse of prescription pain medication provided substantial information in a broad range of severity. The initial psychometric characteristics of the item bank support its use as a computerized adaptive test or short form, with either version providing a brief, precise, and efficient measure relevant to both clinical and community samples.

INTRAMURAL RESEARCH

Highly Selective D3R Antagonists and Partial Agonists Based On Eticlopride and the D3R Crystal Structure: New Leads For Opioid Dependence Treatment Kumar, V; Bonifazi, A; Ellenberger, MP; Keck, TM; Pommier, E; Rais, R; Slusher, BS; Gardner, E; You, Z-B; Xi, Z-X; Newman, AH. J Med. Chem 2016; 59: 7634-7650.
The recent and precipitous increase in opioid analgesic abuse and overdose has inspired investigation of the dopamine D3 receptor (D3R) as a target for therapeutic intervention. Metabolic instability or predicted toxicity has precluded successful translation of previously reported D3R-

selective antagonists to clinical use for cocaine abuse. Herein, the authors report a series of novel and D3R crystal structure-guided 4-phenylpiperazines with exceptionally high D3R affinities and/or selectivities with varying efficacies. Lead compound 19 was selected based on its in vitro profile: D3R Ki = 6.84 nM, 1700 fold D3R versus D2R binding selectivity, and its metabolic stability in mouse microsomes. Compound 19 inhibited oxycodone-induced hyperlocomotion in mice and reduced oxycodone-induced locomotor sensitization. In addition, pretreatment with 19 also dose-dependently inhibited the acquisition of oxycodone-induced conditioned place preference (CPP) in rats. These findings support the D3R as a target for opioid dependence treatment and compound 19 as a new lead molecule for development.

CYP2A6 Genetic Variation Alters Striatal-Cingulate Circuits, Network Hubs, and Executive Processing In Smokers Li, S; Yang, Y; Hoffmann, E; Tyndale, RF; Stein, EA. Biological Psychiatry 2016 Sep 28. pii: S0006-3223(16)32824-4. doi: 10.1016/j.biopsych.2016.09.013.
Variation in the CYP2A6 gene alters the rate of nicotine metabolic inactivation and is associated with smoking behaviors and cessation success rates. The underlying neurobiological mechanisms of this genetic influence are unknown. Intrinsic functional connectivity strength, a whole-brain, data-driven, graph theory-based method, was applied to resting-state functional magnetic resonance imaging data in 66 smokers and 92 nonsmokers. A subset of subjects (n = 23/20; smokers/ nonsmokers) performed the monetary incentive delay task, probing reward anticipation, and a go/no-go task, probing response inhibition, on two occasions, in the presence and absence of a nicotine patch. A significant CYP2A6 genotype × smoking effect was found in the dorsal anterior cingulate cortex and ventral striatum, such that the normal (vs. slow) genotype individuals showed greater functional connectivity strength among smokers but not nonsmokers. Functional connectivity strength was negatively associated with severity of nicotine dependence in slow metabolizers. Both hubs were biased by inputs from the insula identified from seed-based connectivity. Similar gene × environment interactions were seen in ventral striatum during smoking abstinence when subjects performed the monetary incentive delay task and in dorsal anterior cingulate cortex when they performed the go/no-go task; both reductions were "normalized" in smokers (and increased in nonsmokers) after acute nicotine administration. Because the CYP2A6 effect was seen only in smokers, these data suggest that the rate of nicotine metabolism-and thus the concentration of nicotine presented to the brain over the course of nicotine addiction-shapes brain circuits that, among other functions, compute reward and impulsivity processes.

Pathway- and Cell-Cpecific Kappa-Opioid Receptor Modulation Of Excitation-Inhibition Balance Differentially Gates D1 and D2 Accumbens Neuron Activity Tejeda, HA; Wu, J; Kornspun, AR; Pignatelli, M; Kashtelyan, V; Krashes, MJ; Lowell, BB; Carlezon, WA; Bonci, A. Neuron 2017;93:147–163.
Endogenous dynorphin signaling via the kappa opioid receptor (KOR) in the nucleus accumbens(NAcc) powerfully mediates negative affective states and stress reactivity. Excitatory inputs from the hippocampus and amygdala play a fundamental role in shaping the activity of both NAcc D1 and D2 MSNs, which encode positive and negative motivational valences, respectively. However, a circuitbased mechanismby which KOR modulation of excitation- inhibition balance modifies D1 and D2 MSN activity is lacking. Here, the authors provide a comprehensive synaptic framework wherein presynaptic KOR inhibition decreases the excitatory drive of D1 MSN activity by the amygdala, but not the hippocampus. Conversely, presynaptic inhibition by KORs of inhibitory synapses on D2 MSNs enhances integration of excitatory drive by the amygdala and hippocampus. In conclusion, the authors describe a circuit-based mechanism showing differential gating of afferent control of D1 and D2 MSN activity by KORs in a pathwayspecific manner.

Pontomesencephalic Tegmental Afferents To VTA Non-Dopamine Neurons Are Necessary For Appetitive Pavlovian Learning Yau, HJ; Wang, DV; Tsou, JH; Chuang, YF; Chen, BT; Deisseroth, K; Ikemoto, S; Bonci, A. Cell Rep. 2016 Sep 6;16(10):2699-2710.
The ventral tegmental area (VTA) receives phenotypically distinct innervations from the pedunculopontine tegmental nucleus (PPTg). While PPTg-to-VTA inputs are thought to play a critical role in stimulus-reward learning, direct evidence linking PPTg-to-VTA phenotypically distinct inputs in the learning process remains lacking. Here, the authors used optogenetic approaches to investigate the functional contribution of PPTg excitatory and inhibitory inputs to the VTA in appetitive Pavlovian conditioning. They show that photoinhibition of PPTg-to-VTA cholinergic or glutamatergic inputs during cue presentation dampens the development of anticipatory approach responding to the food receptacle during the cue. Furthermore, The authors employed in vivo optetrode recordings to show that photoinhibition of PPTg cholinergic or glutamatergic inputs significantly decreases VTA non-dopamine (non-DA) neural activity. Consistently, photoinhibition of VTA non-DA neurons disrupts the development of cue-elicited anticipatory approach responding. Taken together, this study reveals a crucial regulatory mechanism by PPTg excitatory inputs onto VTA non-DA neurons during appetitive Pavlovian conditioning.

Spatially Compact Neural Clusters In The Dorsal Striatum Encode Locomotion Relevant Information Barbera, G; Liang, B; Zhang, LF; Gerfen, CR; Culurciello, E; Chen, R; Li, Y; Lin, DT. 2016. Neuron 92, pp. 202-213 doi: 10.1016/j.neuron.2016.08.037.
An influential striatal model postulates that neural activities in the striatal direct and indirect pathways promote and inhibit movement, respectively. Normal behavior requires coordinated activity in the direct pathway to facilitate intended locomotion and indirect pathway to inhibit unwanted locomotion. In this striatal model, neuronal population activity is assumed to encode locomotion relevant information. Here, the authors propose a novel encoding mechanism for the dorsal striatum. They identified spatially compact neural clusters in both the direct and indirect pathways. Detailed characterization revealed similar cluster organization between the direct and indirect pathways, and cluster activities from both pathways were correlated with mouse locomotion velocities. Using machine-learning algorithms, cluster activities could be used to decode locomotion relevant behavioral states and locomotion velocity. The authors propose that neural clusters in the dorsal striatum encode locomotion relevant information and that coordinated activities of direct and indirect pathway neural clusters are required for normal striatal controlled behavior.

GRANTEE HONORS AND AWARDS

CTN Pacific Northwest Node

Kari Stephens, Ph.D., was featured as one of nine "**rising stars**" in the American Psychological Association's *Monitor on Psychology* journal (v. 47(9), p. 46). The piece features a "group of early career psychologists who confronted problems and found unique ways to solve them." Dr. Stephens, an assistant professor in the University of Washington's Psychiatry and Behavioral Science department, is recognized for her work on "**extracting elusive health data**" by leading a groundbreaking project that aims to help community health clinics gather research data using electronic health records. That project, **Data QUEST**, is capable of **harmonizing EHR data from multiple clinics** using different platforms across the 5-state WWAMI (Washington, Wyoming, Alaska, Montana, and Idaho) region. Both the CDC and NIDA are already using the system in their research, and the data have also been used by UW researchers studying wellness counseling for Native American women.

CTN New England Consortium Node

Shelly F. Greenfield, MD, MPH, was recently honored to serve as the first Kristine M. Trustey Endowed Professor of Psychiatry chair at McLean Hospital in recognition of the hospital's Division of Women's Mental Health. At McLean Hospital, Dr. Greenfield serves as the Chief of the Division of Women's Health and the hospital's Chief Academic Officer (CAO). Dr. Greenfield is a national expert for her research work on substance use disorders, particularly in the areas of women's treatment and health services.

CTN Gender Special Interest Group

R. Kathryn McHugh, Ph.D., a psychologist in the Division of Alcohol and Drug Abuse at McLean Hospital, and a member of the CTN Gender Special Interest Group from the New England Consortium Node, joined ABC's Elizabeth Vargas on *NPR's On Point* as a subject matter expert on Thursday September 16, 2016. The interview was hosted by Jane Clayson of WBUR (Boston). They discussed stigma and gender differences in substance abuse disorders.

Professor Ben Cravatt is the distinguished recipient of the 2017 ACS Chemical Biology Lectureship. The award is in recognition of Prof. Cravatt's ground-breaking development of activity-based protein profiling technology, which enables the functional annotation of enzymes using active site-directed chemical probes. Through post-genomic profiling of the functional state of enzymes in complex proteomes, Prof. Cravatt has identified key mammalian enzymes involved in regulation of lipid signaling pathways in cancer. Utilizing his activity-based profiling technology in conjunction with advanced mass spectrometry methods, Prof. Cravatt has generated global-scale maps of lipid-binding proteins, amino acid reactivities, and novel functional residues within the proteome. Prof. Cravatt's technologies have been adopted by academic and industrial labs worldwide for broad-scale functional characterization of enzymes within biological systems, thus having far-reaching implications for our understanding of mammalian physiology and disease.

STAFF HONORS AND AWARDS

2016 NIDA DIRECTOR'S AWARDS

Center for the Clinical Trials Network

Kristen Huntley - In recognition of your extraordinary efforts and accomplishments in leading the CTN Taskforce to integrate Opioid Use Disorder Treatment into general medical settings.

CTN Clinical Trials Stewardship Group

Carol Cushing, Ronald Dobbins, Carmen Rosa - In recognition of your superior scientific administrative skills in managing network multisite clinical trials that bridge the gap between research and practice.

Division of Epidemiology, Services and Prevention Research

Richard Jenkins - In recognition of your dedication to stimulating HIV-related substance use prevention research in support of NIDA's mission.

Principles of Substance Abuse Prevention for Early Childhood Release Team

Mark Fleming, Eve Reider, Elizabeth Robertson, Belinda Sims, Jennifer Sizemore, Eric Wargo - In recognition of the 4th released online guide in a series of evidence based principles produced by collaborating divisions of NIDA recognizing how roots of substance abuse begin even before birth.

Division of Extramural Research

NIDA ABCD Study Team

Will Aklin

Carol Alderson

Kevin Conway

Bethany Deeds

Gaya Dowling

Kathleen Etz

Meyer Glantz

Steve Grant

Elizabeth Hoffman

Katia Howlett

Donna Jones

Heather Kimmel

Carol Krause

Geoffrey Laredo

Roger Little

Marsha Lopez

Ivan Montoya

Vani Pariyadath

Jonathan Pollock

Shirley Simson

Mark Swieter

Carolyn Tucker

Eric Wargo

Naimah Weinberg

Susan Weiss

In recognition of your exemplary contributions to the successful scientific and programmatic stewardship of the ABCD Study activities.

Division of Neuroscience and Behavior

Rao Rapaka - In recognition of your dedication, commitment, leadership, and creativity in enhancing medicinal chemistry and pharmacology research and encouraging early stage investigators in research careers in support of the mission of NIDA.

Division of Therapeutics and Medical Consequences

Aidan Hampson - In recognition of your successful design and management of the FDA approvable lofexidine clinical program.

Intramural Research Program

Michael Baumann - In recognition of your work to communicate the science behind designer drugs and their danger to public health.

IRP Biomedical Informatics Section

Pe-Li Chao, Kandi Culbertson, William Elgie, Mark Forster, Wayne Johnson, Jia-Ling Lin, Corey McKenzie, Mustapha Mezghanni, Massoud Vahabzadeh - In recognition of your dedication to providing secure, innovative IT support to NIDA IRP.

Office of the Director

Office of Translational Initiatives and Program Innovations

Elena Koustova, Victor Prikhodko, Irina Sazonova, Tamara Slipchenko - In recognition of your extraordinary business development skills and accomplishments in your innovations in promoting, developing, and advancing NIDA's special program.

Office of Management

Information Resource Management Branch

Stacey Berry, Gregg Friedman, Sandip Ghosh, Marguerite Lewis, Robert Myers, Zoe Shieh, Anatoli Stetsioura, Berhane Yitbarek - In recognition of your seamless support in converting NIDA hosting desktop support from NCI. The transition and deployment was done by the end of the calendar year and improved the IT infrastructure of NIDA.

Office of Science Policy and Communications

Carol Krause - In recognition of your leadership and creativity in communicating NIDA's research achievements to the public.

College and Young Adult Web Resource Team

Carol Krause, Janet Linton, Brian Marquis, Stephanie Older, Juli Rose, Jennifer Sizemore - In recognition of your contribution in the creation of a college and young adult resource on the web promoting schools specializing in addictions as a career field.

Director's Award For Technical/Administrative Support

Josie Anderson, Sara Smith -In recognition of your Social Media Support for Marijuana and Cannabinoids: A Neuroscience Research Summit.

NIDA Director's Award For Collaboration

Marsha Lopez, Shelley Su - In recognition of your efforts in advancing the Institute's mission through active and successful cross-divisional collaborations with partners across NIDA.

Travel Expert Group

Denise Cottingham, Amy Doster, Jessica Hemmati, Keisha Miller, Chanvadey Nhim, Mary Jane Robinson, Kelli Russell, Adrienne Snyder, Nadine Storey, Anna Wheeler - In recognition of your collaborative efforts to improving the travel processes throughout NIDA.

NIDA Diversity and Quality of Worklife Award

Jack Stein - In recognition of your outstanding commitment to maintaining strong morale, a positive work environment, and high quality of life for OSPC and NIDA as a whole.

NIDA Director's Award Rising Star

Gloria Dabbondanza, Emily Einstein, David Epstein, Vani Pariyadath - In recognition of individual staff who enrich and impact NIDA through creativity, competence, and energy, and inspire colleagues and staff.

NIDA Director's Innovator Award

Da Ting Lin - In recognition of your original and inventive accomplishments.

- Developing an in vivo calcium imaging miniScope system in freely-moving mice to visualize neural activity with single neuron resolution in deep brain areas.
- Using artificial intelligence algorithms to decode striatal neural activity to predict mice behavior under normal conditions and after cocaine exposure.
- The innovative miniScope system and the novel computational algorithms will pave the way for better brain-machine interface in the future.

30 Years of Government Service Awards

Mary Beth Babecki, Christopher Belt, Mark Coggiano, Joseph Frascella, Lyle Furr, Kenneth Goodling, Steven Gust, Donna Inman, Minda Lynch

40 Years of Government Service Award

Suezette Epps, Kirkland Davis

Other Awards

Dr. Antonello Bonci, IRP, was elected to the National Academy of Medicine.

Dr. Amy Newman, IRP, was the first woman recipient of the 2016 Philip S. Portoghese Journal of Medicinal Chemistry and Division of Medicinal Chemistry Lectureship Award.

Dr. Brandon Harvey, IRP, received the Staff Scientist Mentor of the Year Award.

Dr. Brandon Harvey was appointed as a tenure track investigator of the newly formed Molecular Mechanisms of Cellular Stress and Inflammation Unit.

Khaled Moussawi, Clinical Fellow, IRP, received a travel award to the American College of Neuropsychopharmacology.

Dr. Kenner Rice, IRP, received the 2016 Mentorship Award of the College on Problems of Drug Dependence.

Dr. Lorenzo Leggio, IRP, was selected by Healio Gastroenterology as one of the 200 “leading innovators in the field of gastroenterology and hepatology.”

Dr. Geoffrey Schoenbaum, IRP, won the Pavlovian Research Award from the Pavlovian Society in October for “contributions made by applying learning theory to an understanding of reward processes, decision making, and neuropsychiatric disorders.”

Dr. Geetha Subramaniam, CCTN, was made a Distinguished Fellow of the American Academy of Child and Adolescent Psychiatry (AACAP) in October 2016.

STAFF CHANGES

New Appointments/Employees

Dr. Katia Delrahim Howlett has been appointed as Deputy Director of the Division of Extramural Research (DER). Katia joined DER after several years of contract service with the Center for the Clinical Trials Network and brought with her energy and enthusiasm that she has continued to use in her various roles within DER. Katia Delrahim-Howlett received her Ph.D. in Public Health from the University of California, San Diego, her Master's in Public Policy from Pepperdine University, and her Master of Business Administration from the Johns Hopkins University. At the University of California, San Diego she focused on Health Behavior and prevention of risky behaviors including primary prevention of Fetal Alcohol Spectrum Disorders and other consequences of alcohol misuse. She has expertise in the fields of psychiatric disorders, public health and safety, health policy, health communication, and substance abuse and addiction. She is widely published in the field of mental illness and substance use disorders, on topics as varied as adolescent substance abuse, technology based health interventions, schizophrenia, antidepressant treatment, panic disorder, mood and anxiety disorders, the burden of phobias on the health-related quality of life, and minor depression. Before coming to NIDA, she served as Project Director of the NIDA Blending Initiative and the SAMHSA National Campaigns contracts. Prior to that, she served as Deputy Director of the Underage Drinking Prevention Education Initiatives contract with SAMHSA. Dr. Delrahim-Howlett became interested in substance abuse prevention and co-morbid mental health issues early in her education when she interned at the NIDA CCTN during her undergraduate studies at the University of California, San Diego. That interest grew as she took part in research projects in drug treatment, psychiatry, and drug trafficking. As Research Associate at the Cedars-Sinai Department of Psychiatry, she contributed to the design of new research protocols and served as lead clinical coordinator for industry sponsored clinical trials. Previously, she served as research assistant for several different psychiatric clinical trials and federal grants.

Dr. Michele Rankin has been appointed as the Research Training Director for NIDA. Dr. Rankin comes to DER from the Office of Science Policy and Communications, where she served as the Deputy Chief of the Science Policy Branch. Michele Rankin earned a B.S. in Chemistry with a minor in English, an M.S. in Biochemistry studying rRNA processing, and a Ph.D. in Neurobiology from the Dept. of Biological Sciences at Louisiana State University in Baton Rouge where her dissertation research focused on olfactory signal transduction and receptor regulation. Michele completed her postdoctoral training in the NINDS Intramural program in David Sibley's laboratory (Molecular Neuropharmacology Section) studying molecular mechanisms that govern dopamine D1 receptor signaling. In 2010, Michele joined the NINDS Division of Extramural Research as a Health Program Specialist in the Neurodegeneration Cluster where she helped manage the research portfolio for Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and others. In December 2011, Michele joined the Office of Science Policy and Communications in the Science Policy Branch, where she currently serves as Deputy Branch Chief. Michele has been the office lead for Congressional BRAIN brief preparation; the Blending Initiative; and official Research, Condition, and Disease Categorization (RCDC) reporting. Michele's recent efforts in these areas include the establishment of three new RCDC categories (Cannabinoid Research, Therapeutic Cannabinoid Research, and Cannabidiol Research) in 2015. She also served as the office contact for HIV and HCV materials, aided in the analysis of the NIDA research

portfolio, annual Government Performance and Results Act reporting, and created various reports and materials for a variety of stakeholders about the science of substance use disorders.

Dr. Jose Ruiz has joined the NIDA Office of Diversity and Health Disparities. The combination of experience and expertise gained from 9 years in the SRO role and his in-depth knowledge of scientific program analysis will come in handy as he oversees the Diversity Supplement Program. In addition, his database design and computer programming skills will be valuable in upgrading our program evaluation capabilities as well as in transforming the supplement review process into an electronic format. Dr. Ruiz earned a B.A. in Biochemistry and Molecular Biology from Boston University and a Ph.D. in Genetics from George Washington University. During his studies, he made significant scientific contributions to the understanding of ligand-receptor interactions pertinent to atherosclerosis, Alzheimer's disease, coagulation, angiogenesis, tumor growth, and neuronal cell development. Dr. Ruiz has also contributed to studies of chromium-DNA adducts and processing of plasma reelin in humans. While at NIDA Dr. Jose Ruiz has served NIDA as a Scientific Review Officer (SRO) since 2007. In addition to serving in the SRO role, Dr. Ruiz has participated in numerous activities attentive to training, workforce development, and diversity across the spectrum of training/career development stages. Dr. Ruiz is also experienced in developing tools for research program analyses/evaluations and the identification of subject matter experts. Prior to joining NIDA, at the National Institute of Nursing Research (NINR), Dr. Ruiz served as a Health Science Policy Analyst with responsibility for analyzing and reporting on research program activities and related budgets, all aspects of Government Performance and Results Act (GPRA) goals, communication products, and various science policy issues.

Christina Page has been appointed as the Lead Extramural Support Administrator for OEPR. Her strengths include prioritizing, multi-tasking, improving processes and procedures, and following through to achieve project goals.

Dr. Julia Berzhanskaya comes to OEPR/DER/NIDA from the NCCIH Division of Extramural Research where she served as a program analyst since 2015. In addition to providing analytical support to NCCIH's basic and clinical research branches Julia was responsible for outreach and planning for the Center's SBIR/STTR programs and BD2K program. Julia received her undergraduate diploma in applied physics and mathematics from the Moscow Institute of Physics and Technology, her M.S. in neuroscience from the University of Pittsburgh, and her Ph.D. in cognitive and neural systems from Boston University. Her research experience includes conducting experimental and computational research on modulation of neuronal ensembles by electric fields and on EEG markers in the fragile X animal model.

Zenab Chowdhry joined NIDA's OM OA Station Suport Branch as a Contract Specialist on 9/4/16. Zenab comes to NIDA from the private sector.

Jermaine Duncan joined NIDA's OM OA Station Suport Branch as a Contract Specialist on 10/30/16. Jermaine comes to NIDA from the Department of Commerce.

Kathleen Elliot joined NIDA's OSPC PILB as an NIH Student Trainee on 1/8/17.

Kelley Henry joined NIDA's Office of the Director as a Staff Assistant to the NIDA Deputy Director on 2/6/17. Kelley comes to NIDA from the NIAID Office of the Director.

Dr. Christine Herdman joined the IRP Drug Design and Synthesis section as an IRTA Postdoctoral Fellow.

Sally Ibrahim joined NIDA's OM OA Station Support Branch as a Contract Specialist on 1/8/17. Sally comes to NDA from a position with the DC government.

Jagdeep Kathuria joined NIDA's IRMB as an IT Specialist on 10/2/16.

Charlotte McCormack joined NIDA's OM OA Station Support Branch (STOPS) Section--Supervisory as a Contract Specialist on 8/21/16. Charlotte comes to NIDA from NCI.

Michelle Morelli joined NIDA's OM OA Station Suport Branch as a Contract Specialist on 11/27/16. Michelle comes to NIDA from the private sector.

Megan Nathan joined NIDA's OM OA NIDA R&D Branch as a Contract Specialist on 12/11/16. Megan come to NIDA from the private sector.

Dr. Ivan K. Navarro comes to OEPR/DER/NIDA from NHLBI where he served as a Program Analyst since 2013. In addition to the many hats Ivan has worn at NHLBI, including serving as a referral liaison and SBIR/STTR liaison for his Division, he has extensive expertise in neuroscience and clinical research. He is well versed in INDs, IDEs and clinical trials as well as NIH policy and procedures. Prior to his tenure with NHLBI, Ivan spent time as a Health Program Specialist and research contractor at NINDS and prior to that providing management and oversight of clinical research programs at Children's National Medical Center. He received undergraduate and master's degrees from Moscow State University and his Ph.D. in Biomedical Sciences at the National Autonomous University of Mexico. His research interests in neuroscience include Neurogenesis, Gene Therapy, Cell Biology, as well as Neurodegenerative and Neurological Disorders.

Kumar Sajith joined NIDA's IRMB as an IT Specialist on 8/21/16. Kumar comes to NIDA from the private sector.

Hilda Schulke joined NIDA's Office of the Director as a Staff Assistant to the NIDA Director on 1/8/17. Hilda comes to NIDA from the NIH Office of the Director.

Christopher Squiers joined NIDA's IRMB as an IT Specialist on 8/21/16. Christopher comes to NIDA from NIAMS.

Dr. Shang-Yi Anne Tsai comes to OEPR/DER/NIDA from the NIDA IRP where she served as a Staff Scientist since 2010 within the Cellular Pathology Section, Integrative Neuroscience Research Branch, led by Tsung-Ping Su. Anne's research interests include understanding the neurobiological actions and biochemical characterizations of sigma receptors as ligand-regulated molecular chaperone proteins. In addition to her many years of service to NIDA IRP, Anne also completed a 6-month detail at NIDA HQ (2016) within DNB where she led the development of several FOAs and managed an extramural grant portfolio encompassing basic research on the neurobiological actions of drugs of abuse. Anne received her MSPH in Public Health and Environmental Health Science from Tulane School of Public Health and Tropical Medicine and her PhD in Cell/Cellular and Molecular Biology, Toxicology from Tulane University.

Andrew Varley joined NIDA's OM OA NIDA R&D Branch as a Contract Specialist on 12/11/16.

Ms. Aytaj Vily has joined the Division of Epidemiology, Services, and Prevention Research as a Public Health Analyst. Aytaj previously worked at the National Institute of Allergies and Infectious Diseases as a grants management specialist, where she oversaw a large and complex grants portfolio. Prior to NIAID, Aytaj served as a program specialist in the Office of Chief Financial Officer, Division of GAO-OIG Liaison at the Department of Homeland Security, and as an analyst in the Office of Management Policy and Analysis Branch at the National Eye Institute. Before joining the federal government, Aytaj worked in the private sector as a marketing project manager and training/conference planner for events held across the U.S. and abroad. She received a Master of Science degree in Health Care Administration from the University of Maryland.

Separations

Stephanie Older, Deputy Chief of NIDA's OSPC PILB left NIDA on 1/7/17 for a position with NIGMS.

Sara Smith, Technical Writer Editor with OSPC's Digital Communications Branch, left NIDA on 10/15/16 for a position with NIH OD.

Farrin Stanton, Contract Specialist in NIDA's Office of Management, Office of Acquisitions' **Station Support Branch, left NIDA on 11/26/16 for a position with DOE.**

Elizabeth Davis, Public Health Analyst with NIDA's OSPC Digital Communications Branch left NIDA on 12/24/16 for a position with FDA.

Dr. Mimi Ghim left her **Health Scientist Administrator position in DER on 1/7/17** to pursue an opportunity with the Office of Research on Women's Health, NIH. We are grateful for her 10 years of service to NIDA as the Research Training Director and to the research community. During that time she provided expert leadership in research training activities for young scientists and new grantees; led outreach activities at scientific meetings and NIDA-sponsored training conferences; conducted evaluation of NIDA's training programs (NRSA and mentored K); and vetted issues of concern to the training community and Institute Director. Her efforts in training have helped create a new generation of young scientists in the field of substance abuse.

Retirements

Carol Cushing, CCTN, retired from government service on 12/31/16. Carol has been with the CTN since its inception and has played as central a role as anyone in bringing together a diverse group of providers, researchers, funders and policy-makers to make CTN the collegial and productive network that it has become. Carol supported the CTP caucus, almost single-handedly published the CTN Bulletin for over a decade, and took on a range of responsibilities in CCTN that none of us fully appreciated until they needed to be reassigned. By training, Carol is a nurse who has brought her clinical background to serving the public health and the Federal government with unyielding commitment. She's known for her generosity and kindness in spirit and in action, particularly to junior investigators and supporting staff both within the CTN and across NIDA, and

she's unselfish in helping others achieve their successes while she stays backstage. We all know and recognize that her competency, in everything she takes on, is un-matched.

Dr. Moo Park, Program Director of Pharmaceutics in the Division of Therapeutics and Medical Consequences (DTMC), retired on January 30, 2017 after 28 years of federal service. Prior to joining DTMC in 1998, Dr. Park had 10 years of FDA experience in bioequivalence/ pharmaco-kinetics and 18 years of industrial experience in pharmaceutical product research and development. He brought to DTMC a broad knowledge of pharmaceutical science, pharmaco-kinetics and FDA regulations. He assumed the responsibility for directing and evaluating research, development and manufacture of new and improved drug products for treating substance use disorders. He also provided valuable assistance to the pharmacokinetic research program related to medications development. He oversaw and coordinated the manufacturing, procurement and distribution of clinical supplies to support clinical trials. He made significant contributions to the medications development program at DTMC.

Pamela Goodlow retired from government service after 29 years with NIDA. During her time at NIDA, she worked on nearly every aspect of diversity-related initiatives and served on various NIH-wide committees. We will sincerely miss her knowledge and presence in the office.

Dr. Minda Lynch, Chief of DNB's Cognitive and Behavioral Neuriosciences Branch, retired from Federal service on 12/31/16.

Brenda Monarque, Staff Assistant to the NIDA Director, retired from Federal service on 12/31/16.

Jim Quinn, Chief of OM's Office of Acquisitions Branch, retired from Federal service on 1/2/17.

Suzette Epps, Grants Management Specialist in DER, retired from Federal service on 1/3/17.

Doug Janes, Grants Clerk in OM's Administrative Management and Analysis Branch, retired from Federal service on 10/28/16.

National Institute
on Drug Abuse