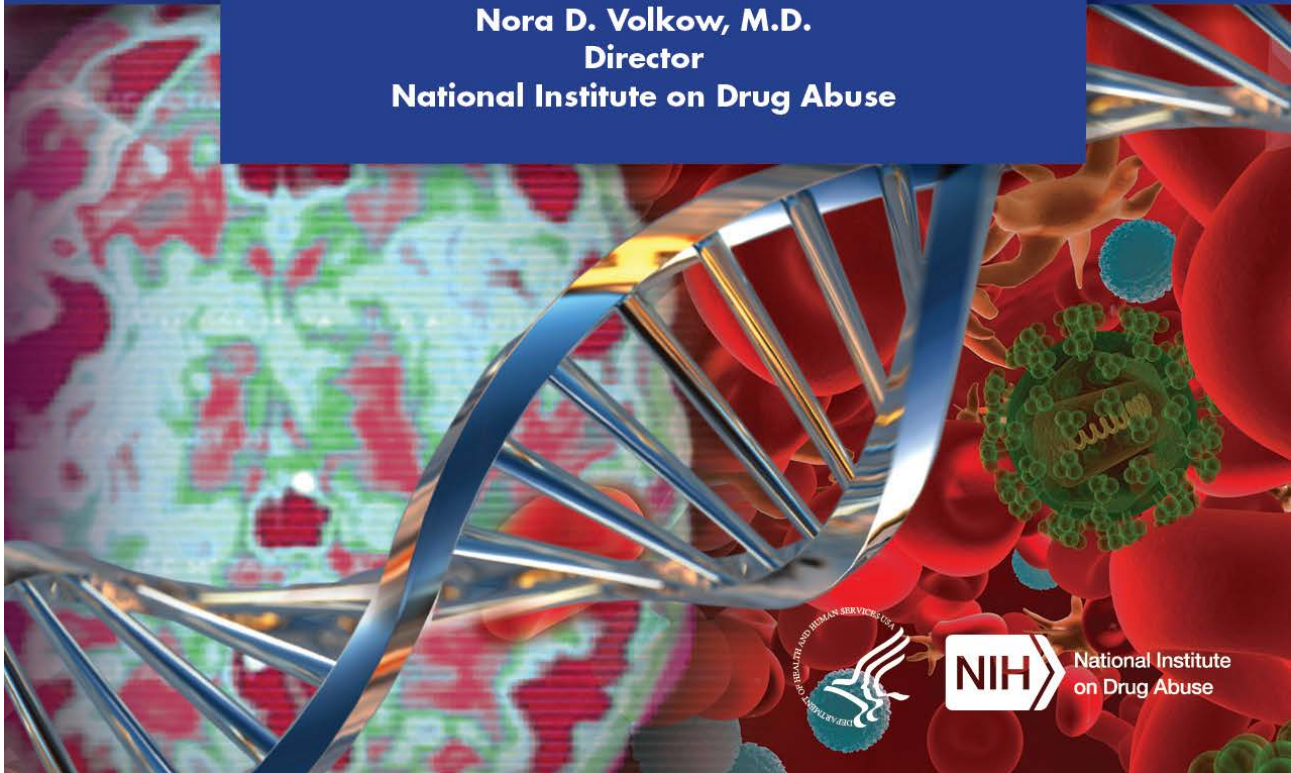




DIRECTOR'S REPORT

————— *to the* —————
National Advisory Council on Drug Abuse
————— *February 2016* —————

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



National Institute
on Drug Abuse

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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

[Nonmuscle Myosin IIB As a Therapeutic Target For the Prevention Of Relapse To](#)

[Methamphetamine Use](#) Young EJ, Blouin AM, Briggs SB, Sullivan SE, Lin L, Cameron MD, Rumbaugh G, Miller CA. Mol Psychiatry. 2015.

Memories associated with drug use increase vulnerability to relapse in substance use disorder (SUD), and there are no pharmacotherapies for the prevention of relapse. Previously, the authors reported a promising finding that storage of memories associated with methamphetamine (METH), but not memories for fear or food reward, is vulnerable to disruption by actin depolymerization in the basolateral amygdala complex (BLC). However, actin is not a viable therapeutic target because of its numerous functions throughout the body. Here the authors report the discovery of a viable therapeutic target, nonmuscle myosin IIB (NMIIB), a molecular motor that supports memory by directly driving synaptic actin polymerization. A single intra-BLC treatment with Blebbistatin (Blebb), a small-molecule inhibitor of class II myosin isoforms, including NMIIB, produced a long-lasting disruption of context-induced drug seeking (at least 30 days). Further, postconsolidation genetic knockdown of Myh10, the heavy chain of the most highly expressed NMII in the BLC, was sufficient to produce METH-associated memory loss. Blebb was found to be highly brain penetrant. A single systemic injection of the compound selectively disrupted the storage of METH-associated memory and reversed the accompanying increase in BLC spine density. This effect was specific to METH-associated memory, as it had no effect on an auditory fear memory. The effect was also independent of retrieval, as METH-associated memory was disrupted 24 h after a single systemic injection of Blebb delivered in the home cage. Together, these results argue for the further development of small-molecule inhibitors of NMII as potential therapeutics for the prevention of SUD relapse triggered by drug associations. Molecular Psychiatry advance online publication, 4 August 2015; doi:10.1038/mp.2015.103.

[Gq-DREADD Selectively Initiates Glial Glutamate Release and Inhibits Cue-induced Cocaine Seeking](#) Scofield MD, Boger HA, Smith RJ, Li H, Haydon PG, Kalivas PW. Biol Psychiatry. 2015; 78(7): 441-451.

Glial cells of the central nervous system directly influence neuronal activity by releasing neuroactive small molecules, including glutamate. Long-lasting cocaine-induced reductions in extracellular glutamate in the nucleus accumbens core (NAcore) affect synaptic plasticity responsible for relapse vulnerability. The authors transduced NAcore astrocytes with an adeno-associated virus vector expressing hM3D designer receptor exclusively activated by a designer drug (DREADD) under control of the glial fibrillary acidic protein promoter in 62 male Sprague Dawley rats, 4 dominant-negative soluble N-ethylmaleimide-sensitive factor attachment protein receptor mice, and 4 wild-type littermates. Using glutamate biosensors, they measured NAcore glutamate levels following intracranial or systemic administration of clozapine N-oxide (CNO) and tested the ability of systemic CNO to inhibit reinstated cocaine or sucrose seeking following self-administration and extinction training. Administration of CNO in glial fibrillary acidic protein-hM3D-DREADD transfected animals increased NAcore extracellular glutamate levels in vivo. The glial origin of released glutamate was validated by an absence of CNO-mediated release in mice

expressing a dominant-negative soluble N-ethylmaleimide-sensitive factor attachment protein receptor variant in glia. Also, CNO-mediated release was relatively insensitive to N-type calcium channel blockade. Systemic administration of CNO inhibited cue-induced reinstatement of cocaine seeking in rats extinguished from cocaine but not sucrose self-administration. The capacity to inhibit reinstated cocaine seeking was prevented by systemic administration of the group II metabotropic glutamate receptor antagonist LY341495. DREADD-mediated glutamate gliotransmission inhibited cue-induced reinstatement of cocaine seeking by stimulating release-regulating group II metabotropic glutamate receptor autoreceptors to inhibit cue-induced synaptic glutamate spillover.

Evidence Of CNH3 Involvement In Opioid Dependence Nelson EC, Agrawal A, Heath AC, Bogdan R, Sherva R, Zhang B, Al-Hasani R, Bruchas MR, Chou Y-L, Demers CH, Carey CE, Conley ED, Fakira AK, Farrer LA, Goate A, Gordon S, Henders AK, Hesselbrock V, Kapoor M, Lynskey MT, Madden PAF, Moron JA, Rice JP, Saccone NL, Schwab SG, Shand FL, Todorov AA, Wallace L, Wang T, Wray NR, Zhou X, Degenhardt L, Martin NG, Hariri AR, Kranzler HR, Gelernter J, Bierut LJ, Clark DJ, Montgomery GW. *Mol Psychiatry*. 2015.

Opioid dependence, a severe addictive disorder and major societal problem, has been demonstrated to be moderately heritable. The authors conducted a genome-wide association study in Comorbidity and Trauma Study data comparing opioid-dependent daily injectors (N=1167) with opioid misusers who never progressed to daily injection (N=161). The strongest associations, observed for CNH3 single-nucleotide polymorphisms (SNPs), were confirmed in two independent samples, the Yale-Penn genetic studies of opioid, cocaine and alcohol dependence and the Study of Addiction: Genetics and Environment, which both contain non-dependent opioid misusers and opioid-dependent individuals. Meta-analyses found five genome-wide significant CNH3 SNPs. The A allele of rs10799590, the most highly associated SNP, was robustly protective (P=4.30E-9; odds ratio 0.64 (95% confidence interval 0.55-0.74)). Epigenetic annotation predicts that this SNP is functional in fetal brain. Neuroimaging data from the Duke Neurogenetics Study (N=312) provide evidence of this SNP's in vivo functionality; rs10799590 A allele carriers displayed significantly greater right amygdala habituation to threat-related facial expressions, a phenotype associated with resilience to psychopathology. Computational genetic analyses of physical dependence on morphine across 23 mouse strains yielded significant correlations for haplotypes in CNH3 and functionally related genes. These convergent findings support CNH3 involvement in the pathophysiology of opioid dependence, complementing prior studies implicating the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate system. *Molecular Psychiatry* advance online publication, 4 August 2015; doi:10.1038/mp.2015.102.

Transplantation Of Human Retinal Pigment Epithelial Cells In the Nucleus Accumbens Of Cocaine Self-Administering Rats Provides Protection From Reinstatement Venkiteswaran K, Alexander DN, Puhl MD, Rao A, Piquet AL, Nyland JE, Subramanian MP, Iyer P, Boisvert MM, Handly E, Subramanian T, Grigson PS. *Brain Res Bull*. 2015 Nov 10. pii: S0361-9230(15)30060-5. doi: 10.1016/j.brainresbull.2015.11.008. [Epub ahead of print].

Chronic exposure to drugs and alcohol leads to damage to dopaminergic neurons and their projections in the 'reward pathway' that originate in the ventral tegmental area (VTA) and terminate in the nucleus accumbens (NAc). This damage is thought to contribute to the signature symptom of addiction: chronic relapse. In this study the authors show that bilateral transplants of human retinal pigment epithelial cells (RPECs), a cell mediated dopaminergic and trophic neuromodulator, into

the medial shell of the NAc, rescue rats with a history of high rates of cocaine self-administration from drug-seeking when returned, after 2 weeks of abstinence, to the drug-associated chamber under extinction conditions (i.e., with no drug available). Excellent survival was noted for the transplant of RPECs in the shell and/or the core of the NAc bilaterally in all rats that showed behavioral recovery from cocaine seeking. Design based unbiased stereology of tyrosine hydroxylase (TH) positive cell bodies in the VTA showed better preservation ($p < 0.035$) in transplanted animals compared to control animals. This experiment shows that RPEC grafts provide beneficial effects to prevent chronic relapse in drug addiction via its effects directly on the NAc and its neural network with the VTA.

Endocannabinoid Signaling Mediates Oxytocin-Driven Social Reward Wei D, Lee D, Cox CD, Karsten CA, Peñagarikano O, Geschwind DH, Gall CM, Piomelli D. Proc Natl Acad Sci U S A. 2015 Nov 10;112(45):14084-9. doi: 10.1073/pnas.1509795112. Epub 2015 Oct 26.

Marijuana exerts profound effects on human social behavior, but the neural substrates underlying such effects are unknown. Here the authors report that social contact increases, whereas isolation decreases, the mobilization of the endogenous marijuana-like neurotransmitter, anandamide, in the mouse nucleus accumbens (NAc), a brain structure that regulates motivated behavior. Pharmacological and genetic experiments show that anandamide mobilization and consequent activation of CB1 cannabinoid receptors are necessary and sufficient to express the rewarding properties of social interactions, assessed using a socially conditioned place preference test. The authors further show that oxytocin, a neuropeptide that reinforces parental and social bonding, drives anandamide mobilization in the NAc. Pharmacological blockade of oxytocin receptors stops this response, whereas chemogenetic, site-selective activation of oxytocin neurons in the paraventricular nucleus of the hypothalamus stimulates it. Genetic or pharmacological interruption of anandamide degradation offsets the effects of oxytocin receptor blockade on both social place preference and cFos expression in the NAc. The results indicate that anandamide-mediated signaling at CB1 receptors, driven by oxytocin, controls social reward. Deficits in this signaling mechanism may contribute to social impairment in autism spectrum disorders and might offer an avenue to treat these conditions.

Naltrexone Maintenance Decreases Cannabis Self-Administration and Subjective Effects In Daily Cannabis Smokers Haney M, Ramesh D, Glass A, Pavlicova M, Bedi G, Cooper ZD. Neuropsychopharmacology. 2015; 40(11): 2489-2498.

Given that cannabis use is increasing in the United States, pharmacological treatment options to treat cannabis use disorder are needed. Opioid antagonists modulate cannabinoid effects and may offer a potential approach to reducing cannabis use. In this double-blind, placebo-controlled human laboratory study, the authors assessed the effects of naltrexone maintenance on the reinforcing, subjective, psychomotor, and cardiovascular effects of active and inactive cannabis. Nontreatment-seeking, daily cannabis smokers were randomized to receive naltrexone (50 mg; $n=18$ M and 5 F) or placebo (0 mg; $n=26$ M and 2 F) capsules for 16 days. Before, during, and after medication maintenance, participants completed 10 laboratory sessions over 4-6 weeks, assessing cannabis' behavioral and cardiovascular effects. Medication compliance was verified by observed capsule administration, plasma naltrexone, and urinary riboflavin. Relative to placebo, maintenance on naltrexone significantly reduced both active cannabis self-administration and its positive subjective effects ('good effect'). Participants in the placebo group had 7.6 times (95% CI: 1.1-51.8) the odds of self-administering active cannabis compared with the naltrexone group. This attenuation of

reinforcing and positive subjective effects also influenced cannabis use in the natural ecology. Naltrexone had intrinsic effects: decreasing ratings of friendliness, food intake, and systolic blood pressure, and increasing spontaneous reports of stomach upset and headache, yet dropout rates were comparable between groups. In summary, the authors show for the first time that maintenance on naltrexone decreased cannabis self-administration and ratings of 'good effect' in nontreatment-seeking daily cannabis smokers. Clinical studies in patients motivated to reduce their cannabis use are warranted to evaluate naltrexone's efficacy as a treatment for cannabis use disorder.

EPIDEMIOLOGY RESEARCH

Should Pathological Gambling and Obesity Be Considered Addictive Disorders? A Factor Analytic Study In A Nationally Representative Sample Blanco C, Garc a-Anaya M, Wall M, de Los Cobos J, Carlos P, Swierad E, Wang S, Petry NM. Drug Alcohol Depend. 2015; 150: 129-134. Pathological gambling (PG) is now aligned with substance use disorders in the DSM-5 as the first officially recognized behavioral addiction. There is growing interest in examining obesity as an addictive disorder as well. The goal of this study was to investigate whether epidemiological data provide support for the consideration of PG and obesity as addictive disorders. Factor analysis of data from a large, nationally representative sample of US adults (N=43,093), using nicotine dependence, alcohol dependence, drug dependence, PG and obesity as indicators. It was hypothesized that nicotine dependence, alcohol dependence and drug use dependence would load on a single factor. It was further hypothesized that if PG and obesity were addictive disorders, they would load on the same factor as substance use disorders, whereas failure to load on the addictive factor would not support their conceptualization as addictive disorders. A model with one factor including nicotine dependence, alcohol dependence, drug dependence and PG, but not obesity, provided a very good fit to the data, as indicated by CFI=0.99, TLI=0.99 and RMSEA=0.01 and loadings of all indicators >0.4. Data from this study support the inclusion of PG in a latent factor with substance use disorders but do not lend support to the consideration of obesity, as defined by BMI, as an addictive disorder. Future research should investigate whether certain subtypes of obesity are best conceptualized as addictive disorders and the shared biological and environmental factors that account for the common and specific features of addictive disorders.

Association Of Electronic Cigarette Use With Initiation Of Combustible Tobacco Product Smoking In Early Adolescence Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR, Stone MD, Khoddam R, Samet JM, Audrain-McGovern J. JAMA. 2015; 314(7): 700-707.

Exposure to nicotine in electronic cigarettes (e-cigarettes) is becoming increasingly common among adolescents who report never having smoked combustible tobacco. The aim of the study was to evaluate whether e-cigarette use among 14-year-old adolescents who have never tried combustible tobacco is associated with risk of initiating use of 3 combustible tobacco products (ie, cigarettes, cigars, and hookah). Longitudinal repeated assessment of a school-based cohort at baseline (fall 2013, 9th grade, mean age = 14.1 years) and at a 6-month follow-up (spring 2014, 9th grade) and a 12-month follow-up (fall 2014, 10th grade). Ten public high schools in Los Angeles, California, were recruited through convenience sampling. Participants were students who reported never using combustible tobacco at baseline and completed follow-up assessments at 6 or 12 months (N = 2530). At each time point, students completed self-report surveys during in-classroom data

collections. Student self-report of whether he or she ever used e-cigarettes (yes or no) at baseline. Six- and 12-month follow-up reports on use of any of the following tobacco products within the prior 6 months: (1) any combustible tobacco product (yes or no); (2) combustible cigarettes (yes or no), (3) cigars (yes or no); (4) hookah (yes or no); and (5) number of combustible tobacco products (range: 0-3). Past 6-month use of any combustible tobacco product was more frequent in baseline e-cigarette ever users (n = 222) than never users (n = 2308) at the 6-month follow-up (30.7% vs 8.1%, respectively; difference between groups in prevalence rates, 22.7% [95% CI, 16.4%-28.9%]) and at the 12-month follow-up (25.2% vs 9.3%, respectively; difference between groups, 15.9% [95% CI, 10.0%-21.8%]). Baseline e-cigarette use was associated with greater likelihood of use of any combustible tobacco product averaged across the 2 follow-up periods in the unadjusted analyses (odds ratio [OR], 4.27 [95% CI, 3.19-5.71]) and in the analyses adjusted for sociodemographic, environmental, and intrapersonal risk factors for smoking (OR, 2.73 [95% CI, 2.00-3.73]). Product-specific analyses showed that baseline e-cigarette use was positively associated with combustible cigarette (OR, 2.65 [95% CI, 1.73-4.05]), cigar (OR, 4.85 [95% CI, 3.38-6.96]), and hookah (OR, 3.25 [95% CI, 2.29-4.62]) use and with the number of different combustible products used (OR, 4.26 [95% CI, 3.16-5.74]) averaged across the 2 follow-up periods. Among high school students in Los Angeles, those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year. Further research is needed to understand whether this association may be causal.

[Effects Of Quitting Cannabis On Respiratory Symptoms](#) Hancox RJ, Shin HH, Gray AR, Poulton R, Sears MR. *Eur Respir J.* 2015; 46(1): 80-87.

Smoking cannabis is associated with symptoms of bronchitis. Little is known about the persistence of symptoms after stopping cannabis use. The authors assessed associations between changes in cannabis use and respiratory symptoms in a population-based cohort of 1037 young adults. Participants were asked about cannabis and tobacco use at ages 18, 21, 26, 32 and 38 years. Symptoms of morning cough, sputum production, wheeze, dyspnea on exertion and asthma diagnoses were ascertained at the same ages. Frequent cannabis use was defined as ≥ 52 occasions over the previous year. Associations between frequent cannabis use and respiratory symptoms were analyzed using generalized estimating equations with adjustments for tobacco smoking, asthma, sex and age. Frequent cannabis use was associated with morning cough (OR 1.97, $p < 0.001$), sputum production (OR 2.31, $p < 0.001$) and wheeze (OR 1.55, $p < 0.001$). Reducing or quitting cannabis use was associated with reductions in the prevalence of cough, sputum and wheeze to levels similar to nonusers. Frequent cannabis use is associated with symptoms of bronchitis in young adults. Reducing cannabis use often leads to a resolution of these symptoms.

[Associations Of Adolescent Cannabis Use With Academic Performance and Mental Health: A Longitudinal Study Of Upper Middle Class Youth](#) Meier MH, Hill ML, Small PJ, Luthar SS. *Drug Alcohol Depend.* 2015; 156: 207-212.

There is a hypothesis that low socioeconomic status (SES) may explain the link between cannabis use and poorer academic performance and mental health. A key question, therefore, is whether adolescent cannabis use is associated with poorer academic performance and mental health in high SES communities where there is reduced potential for confounding. Youth (n=254) from an upper middle class community were followed prospectively through the four years of high school (from age 14/15 to age 17/18). Past-year frequency of cannabis use was assessed annually. Official school records of academic performance and self-reported mental health symptoms (externalizing and

internalizing symptoms) were assessed in grades 9 and 12. Persistent cannabis use across the four years of high school was associated with lower grade-point average ($\beta = -0.18$, $p = .006$), lower Scholastic Aptitude Test (SAT) score ($\beta = -0.13$, $p = .038$), and greater externalizing symptoms ($\beta = 0.29$, $p < .001$) in 12th grade, but not with greater internalizing symptoms ($\beta = 0.04$, $p = .53$). Moreover, persistent cannabis use was associated with lower grade-point average ($\beta = -0.13$, $p = .014$) and greater externalizing symptoms ($\beta = 0.24$, $p = .002$) in 12th grade, even after controlling for 9th grade levels of these outcomes. Similar associations were observed for persistent alcohol and tobacco use. Effects for persistent cannabis use became non-significant after controlling for persistent alcohol and tobacco use, reflecting the difficulties of disentangling effects of cannabis from effects of alcohol and tobacco. Low SES cannot fully explain associations between cannabis use and poorer academic performance and mental health.

Girls' Childhood Trajectories Of Disruptive Behavior Predict Adjustment Problems In Early Adolescence van der Molen E, Blokland AAJ, Hipwell AE, Vermeiren RRJM, Doreleijers TAH, Loeber R. *J Child Psychol Psychiatry*. 2015; 56(7): 766-773.

It is widely recognized that early onset of disruptive behavior is linked to a variety of detrimental outcomes in males, later in life. In contrast, little is known about the association between girl's childhood trajectories of disruptive behavior and adjustment problems in early adolescence. This study used nine waves of data from the ongoing Pittsburgh Girls Study. A semiparametric group-based model was used to identify trajectories of disruptive behavior in 1,513 girls from age 6 to 12 years. Adjustment problems were characterized by depression, self-harm, Post-Traumatic Stress Disorder (PTSD), substance use, interpersonal aggression, sexual behavior, affiliation with delinquent peers, and academic achievement at ages 13 and 14. Three trajectories of childhood disruptive behavior were identified: low, medium, and high. Girls in the high group were at increased risk for depression, self-harm, PTSD, illegal substance use, interpersonal aggression, early and risky sexual behavior, and lower academic achievement. The likelihood of multiple adjustment problems increased with trajectories reflecting higher levels of disruptive behavior. Girls following the high childhood trajectory of disruptive behavior require early intervention programs to prevent multiple, adverse outcomes in adolescence and further escalation in adulthood.

Childhood Maltreatment and Its Effect On Neurocognitive Functioning: Timing and Chronicity Matter Cowell RA, Cicchetti D, Rogosch FA, Toth SL. *Dev Psychopathol*. 2015; 27(2): 521-533.

Childhood maltreatment represents a complex stressor, with the developmental timing, duration, frequency, and type of maltreatment varying with each child (Barnett, Manly, & Cicchetti, 1993; Cicchetti & Manly, 2001). Multiple brain regions and neural circuits are disrupted by the experience of child maltreatment (Cicchetti & Toth, in press; DeBellis et al., 2002; McCrory & Viding, 2010; Teicher, Anderson, & Polcari, 2012). These neurobiological compromises indicate the impairment of a number of important cognitive functions, including working memory and inhibitory control. The present study extends prior research by examining the effect of childhood maltreatment on neurocognitive functioning based on developmental timing of maltreatment, including onset, chronicity, and recency, in a sample of 3- to 9-year-old nonmaltreated ($n = 136$) and maltreated children ($n = 223$). Maltreated children performed more poorly on inhibitory control and working-memory tasks than did nonmaltreated children. Group differences between maltreated children based on the timing of maltreatment and the chronicity of maltreatment also were evident. Specifically, children who were maltreated during infancy, and children with a chronic history of

maltreatment, exhibited significantly poorer inhibitory control and working-memory performance than did children without a history of maltreatment. The results suggest that maltreatment occurring during infancy, a period of major brain organization, disrupts normative structure and function, and these deficits are further instantiated by the prolonged stress of chronic maltreatment during the early years of life.

PREVENTION RESEARCH

Diffusion of Intervention Effects: The Impact Of A Family-Based Substance Use Prevention Program On Friends of Participants Rulison KL, Feinberg M, Gest SD, Osgood DW. *Journal of Adolescent Health* 2015.

The authors tested whether effects of the Strengthening Families Program for Youth 10e14 (SFP10-14) diffused from intervention participants to their friends. They also tested which program effects on participants accounted for diffusion. Data are from 5,449 students (51% female; mean initial age $\frac{1}{4}$ 12.3 years) in the PROMoting School-community-university Partnerships to Enhance Resilience community intervention trial (2001e2006) who did not participate in SFP10-14 (i.e., nonparticipants). At each of five waves, students identified up to seven friends and self-reported past month drunkenness and cigarette use, substance use attitudes, parenting practices, and unsupervised time spent with friends. The authors computed two measures of indirect exposure to SFP10-14: total number of SFP-attending friends at each wave and cumulative proportion of SFP-attending friends averaged across the current and all previous post-intervention waves. Three years post-intervention, the odds of getting drunk (odds ratio $\frac{1}{4}$ 1.4) and using cigarettes (odds ratio $\frac{1}{4}$ 2.7) were higher among nonparticipants with zero SFP-attending friends compared with nonparticipants with three or more SFP-attending friends. Multilevel analyses also provided evidence of diffusion: nonparticipants with a higher cumulative proportion of SFP attending friends at a given wave were less likely than their peers to use drugs at that wave. Effects from SFP10-14 primarily diffused through friendship networks by reducing the amount of unstructured socializing (unsupervised time that nonparticipants spent with friends), changing friends' substance use attitudes, and then changing nonparticipants' own substance use attitudes. Program developers should consider and test how interventions may facilitate diffusion to extend program reach and promote program sustainability.

Describing and Predicting Developmental Profiles Of Externalizing Problems From Childhood To Adulthood Petersen IT, Bates JE, Dodge KA, Lansford JE, Pettit GS. *Dev Psychopathol.* 2015; 27(3): 791-818.

This longitudinal study considers externalizing behavior problems from ages 5 to 27 (N = 585). Externalizing problem ratings by mothers, fathers, teachers, peers, and self-report were modeled with growth curves. Risk and protective factors across many different domains and time frames were included as predictors of the trajectories. A major contribution of the study is in demonstrating how heterotypic continuity and changing measures can be handled in modeling changes in externalizing behavior over long developmental periods. On average, externalizing problems decreased from early childhood to preadolescence, increased during adolescence, and decreased from late adolescence to adulthood. There was strong nonlinear continuity in externalizing problems over time. Family process, peer process, stress, and individual characteristics predicted externalizing problems beyond the strong continuity of externalizing problems. The model accounted for 70% of the variability in the development of externalizing problems. The model

predicted values showed moderate sensitivity and specificity in prediction of arrests, illegal drug use, and drunk driving. Overall, the study showed that by using changing, developmentally relevant measures and simultaneously taking into account numerous characteristics of children and their living situations, research can model lengthy spans of development and improve predictions of the development of later, severe externalizing problems.

Tobacco May Mask Poorer Episodic Memory Among Young Adult Cannabis Users Schuster RM, Crane NA, Mermelstein R, Gonzalez R. *Neuropsychology*. 2015; 29(5): 759-766.

Co-occurring cannabis and tobacco use has become increasingly prevalent among young adults, but it is not clear how tobacco use may alter the neurocognitive profile typically observed among cannabis users. Although there is substantial evidence citing cannabis and tobacco individual effects on episodic memory and related brain structures, few studies have examined the effects of combined cannabis and tobacco use on memory. This investigation examined relationships between amount of past year cannabis and tobacco use on 4 different indices of episodic memory among a sample of young adults who identified cannabis as their drug of choice. Results indicated that more cannabis use was linked with poorer initial acquisition, total learning, and delayed recall on the Hopkins Verbal Learning Test-Revised, but only among cannabis users who sporadically smoked cigarettes in the past year. Conversely, the amount of past year cannabis use was not associated with episodic memory performance among individuals who more consistently smoked cigarettes in the past year. These differences could not be explained by several relevant potential confounds. These findings provide important insight into a potential mechanism (i.e., attenuation of cognitive decrements) that might reinforce use of both substances and hamper cessation attempts among cannabis users who also smoke cigarettes. Ongoing and future research will help to better understand how co-use of cannabis and tobacco affects memory during acute intoxication and abstinence and the stability of these associations over time.

Early Starting, Aggressive, and/or Callous-unemotional? Examining The Overlap and Predictive Utility Of Antisocial Behavior Subtypes Hyde LW, Burt SA, Shaw DS, Donnellan MB, Forbes EE. *J Abnorm Psychol*. 2015; 124(2): 329-342.

Antisocial behavior (AB) in adolescence predicts problematic outcomes in adulthood. However, researchers have noted marked heterogeneity within the broad group of youth engaging in these destructive behaviors and have attempted to identify those with distinct etiologies and different trajectories of symptoms. In the present study, the authors evaluate 3 prominent AB subtyping approaches: age of onset, presence of callous-unemotional (CU) traits, and aggressive versus rule-breaking symptoms. They examined the overlap of these subtypes and their predictive validity in a diverse sample of 268 low-income young men followed prospectively from adolescence into emerging adulthood. They found that those with early starting AB were uniquely high on aggressive symptoms but not on CU traits. Early starting AB and both aggression and rule breaking measured during adolescence predicted most subsequent psychiatric and AB outcomes in early adulthood in univariate models, whereas CU traits were only predictive of adolescent arrests, later substance dependence diagnosis, and later CU traits. Finally, after accounting for shared variance among predictor variables, we found that aggressive symptoms explained the most unique variance in predicting several later outcomes (e.g., antisocial personality disorder) over and above other subtyping approaches. Results are discussed in relation to the use of existing subtyping approaches to AB, noting that aggression and age of onset but not CU traits appear to be the best at predicting later negative outcome.

Divergent Responses Of the Amygdala and Ventral Striatum Predict Stress-related Problem Drinking In Young Adults: Possible Differential Markers Of Affective and Impulsive Pathways Of Risk For Alcohol Use Disorder Nikolova YS, Knodt AR, Radtke SR, Hariri AR.

Mol Psychiatry. 2015.

Prior work suggests that there may be two distinct pathways of alcohol use disorder (AUD) risk: one associated with positive emotion enhancement and behavioral impulsivity, and another associated with negative emotion relief and coping. The authors sought to map these two pathways onto individual differences in neural reward and threat processing assessed using blood-oxygen-level-dependent functional magnetic resonance imaging in a sample of 759 undergraduate students (426 women, mean age 19.65 ± 1.24 years) participating in the Duke Neurogenetics Study. The authors demonstrate that problem drinking is highest in the context of stress and in those with one of two distinct neural phenotypes: (1) a combination of relatively low reward-related activity of the ventral striatum (VS) and high threat-related reactivity of the amygdala; or (2) a combination of relatively high VS activity and low amygdala reactivity. In addition, the authors demonstrate that the relationship between stress and problem alcohol use is mediated by impulsivity, as reflected in monetary delay discounting rates, for those with high VS-low amygdala reactivity, and by anxious/depressive symptomatology for those with the opposite neural risk phenotype. Across both neural phenotypes, we found that greater divergence between VS and amygdala reactivity predicted greater risk for problem drinking. Finally, for those individuals with the low VS-high amygdala risk phenotype we found that stress not only predicted the presence of AUD diagnosis at the time of neuroimaging but also subsequent problem drinking reported 3 months following study completion. These results offer new insight into the neural basis of AUD risk and suggest novel biological targets for early individualized treatment or prevention. Molecular Psychiatry advance online publication, 30 June 2015; doi:10.1038/mp.2015.85.

Variations In Parental Monitoring and Predictions Of Adolescent Prescription Opioid and Stimulant Misuse Donaldson CD, Nakawaki B, Crano WD. Addict Behav. 2015; 45: 14-21.

This study examined relations between adolescents' family structures, social ties, and drug-related attitudes, and their misuse of prescription opioids and stimulants. Different relationships were anticipated for the substances based on prior research highlighting varying motivations for their use. Based on an earlier model of adolescent substance misuse, two path analytic models were tested using data from 12 to 17 year olds in the 2012 U.S. National Survey on Drug Use and Health (NSDUH: N=17,399). Female respondents reported higher levels of parental warmth, as did youth from wealthier families. Greater parental monitoring was reported by adolescents from wealthier and intact families. Parental monitoring and warmth predicted adolescents' social ties and individual differences associated with drug use, and both variables predicted prescription opioid and stimulant misuse. Contrary to previous research, for adolescents aged 12 to 14, high levels of parental monitoring, while positively associated with attitudes and social ties, also predicted higher rates of prescription stimulant misuse when combined with low levels of parental warmth. Results were cross-validated with data from the 2011 NSDUH. Analyses highlighted the importance of understanding and differentiating the underlying factors associated with adolescent prescription stimulant and opioid misuse, and the role of parental behaviors in prevention.

Detecting Initiation Or Risk For Initiation Of Substance Use Before High School During Pediatric Well-child Check-ups

Ridenour TA, Willis D, Bogen DL, Novak S, Scherer J, Reynolds MD, Zhai ZW, Tarter RE. *Drug Alcohol Depend.* 2015; 150: 54-62.

Youth substance use (SU) is prevalent and costly, affecting mental and physical health. American Academy of Pediatrics and Affordable Care Act call for SU screening and prevention. The Youth Risk Index (©) (YRI) was tested as a screening tool for having initiated and propensity to initiate SU before high school (which forecasts SU disorder). YRI was hypothesized to have good to excellent psychometrics, feasibility and stakeholder acceptability for use during well-child check-ups. A high-risk longitudinal design with two cross-sectional replication samples, ages 9-13 was used. Analyses included receiver operating characteristics and regression analyses. A one-year longitudinal sample (N=640) was used for YRI derivation. Replication samples were a cross-sectional sample (N=345) and well-child check-up patients (N=105) for testing feasibility, validity and acceptability as a screening tool. YRI has excellent test-retest reliability and good sensitivity and specificity for concurrent and one-year-later SU (odds ratios=7.44, CI=4.3-13.0) and conduct problems (odds ratios=7.33, CI=3.9-13.7). Results were replicated in both cross-sectional samples. Well-child patients, parents and pediatric staff rated YRI screening as important, acceptable, and a needed service. Identifying at-risk youth prior to age 13 could reap years of opportunity to intervene before onset of SU disorder. Most results pertained to YRI association with concurrent or recent past risky behaviors; further replication ought to specify its predictive validity, especially adolescent-onset risky behaviors. YRI well identifies youth at risk for SU and conduct problems prior to high school, is feasible and valid for screening during well-child check-ups, and is acceptable to stakeholders.

Benefit-Cost Analysis Of A Randomized Evaluation Of Communities That Care: Monetizing Intervention Effects On the Initiation Of Delinquency and Substance Use Through Grade 12

Kuklinski MR, Fagan AA, Hawkins JD, Briney JS, Catalano RF. *J Exp Criminol.* 2015; 11(2): 165-192.

The aim of this study was to determine whether the Communities That Care (CTC) prevention system is a cost-beneficial intervention. Data were from a longitudinal panel of 4,407 youth participating in a randomized controlled trial including 24 towns in 7 states, matched in pairs within state and randomly assigned to condition. Significant differences favoring intervention youth in sustained abstinence from delinquency, alcohol use, and tobacco use through Grade 12 were monetized and compared to economic investment in CTC. CTC was estimated to produce \$4,477 in benefits per youth (discounted 2011 dollars). It cost \$556 per youth to implement CTC for 5 years. The net present benefit was \$3,920. The benefit-cost ratio was \$8.22 per dollar invested. The internal rate of return was 21%. Risk that investment would exceed benefits was minimal. Investment was expected to be recouped within 9 years. Sensitivity analyses in which effects were halved yielded positive cost-beneficial results. CTC is a cost-beneficial, community-based approach to preventing initiation of delinquency, alcohol use, and tobacco use. CTC is estimated to generate economic benefits that exceed implementation costs when disseminated with fidelity in communities.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Long-Acting Cocaine Hydrolase For Addiction Therapy Chen X, Xue L, Hou S, Jin Z, Zhang T, Zheng F, Zhan CG. Proc Natl Acad Sci U S A. 2015 Dec 28. pii: 201517713. [Epub ahead of print].

Cocaine abuse is a world-wide public health and social problem without a US Food and Drug Administration-approved medication. An ideal anticocaine medication would accelerate cocaine metabolism, producing biologically inactive metabolites by administration of an efficient cocaine-specific exogenous enzyme. The authors' recent studies have led to the discovery of the desirable, highly efficient cocaine hydrolases (CocHs) that can efficiently detoxify and inactivate cocaine without affecting normal functions of the CNS. Preclinical and clinical data have demonstrated that these CocHs are safe for use in humans and are effective for accelerating cocaine metabolism. However, the actual therapeutic use of a CocH in cocaine addiction treatment is limited by its short biological half-life (e.g., 8 h or shorter in rats). Here the authors demonstrate a novel CocH form, a catalytic antibody analog, which is a fragment crystallizable (Fc)-fused CocH dimer (CocH-Fc) constructed by using CocH to replace the Fab region of human IgG1. The CocH-Fc not only has a high catalytic efficiency against cocaine but also, like an antibody, has a considerably longer biological half-life (e.g., ~107 h in rats). A single dose of CocH-Fc was able to accelerate cocaine metabolism in rats even after 20 d and thus block cocaine-induced hyperactivity and toxicity for a long period. Given the general observation that the biological half-life of a protein drug is significantly longer in humans than in rodents, the CocH-Fc reported in this study could allow dosing once every 2-4 wk, or longer, for treatment of cocaine addiction in humans.

Medication Nonadherence, "Professional Subjects," and Apparent Placebo Responders

McCann DJ, Petry NM, Bresell A, Isacson E, Wilson E, Alexander R.

Nonadherence is a major problem in clinical trials of new medications. To evaluate the extent of nonadherence, this study evaluated pharmacokinetic sampling from 1765 subjects receiving active therapy across 8 psychiatric trials conducted between 2001 and 2011. With nonadherence defined as greater than 50% of plasma samples below the limit of quantification for study drug, the percentage of nonadherent subjects ranged from 12.8% to 39.2%. There was a trend towards increased nonadherence in studies with greater numbers of subjects, but an association with nonadherence was not apparent for other study design parameters or subject characteristics. For 2 trials with multiple recruitment sites in geographical proximity, several subjects attempted to simultaneously enroll at separate site locations. The construct of "professional subjects" those who enroll in trials only for financial gain, is gaining attention and we therefore modeled the impact of professional subjects on medication efficacy trials. The results indicate that enrollment of professional subjects who are destined to success (those who will appear to achieve treatment success regardless of study drug assignment) can substantially increase both the apparent placebo response rate and the sample size requirement for statistical power, while decreasing the observed effect size. The overlapping nature of nonadherence, professional subjects, and placebo response suggests that these issues should be considered and addressed together. Following this approach, we describe a novel clinical trial design to minimize the adverse effects of professional subjects on trial outcomes and discuss methods to monitor adherence.

Measures Of Outcome For Stimulant Trials: ACTION Recommendations and Research

Agenda Kiluk BD, Carroll KM, Duhig A, Falk DE, Kampman K, Lai S, Litten RZ, McCann DJ, Montoya ID, Preston KL, Skolnick P, Weisner C, Woody G, Chandler R, Detke MJ, Dunn K, Dworkin RH, Fertig J, Gewandter J, Moeller FG, Ramey T, Ryan M, Silverman K, Strain EC. The development and approval of an efficacious pharmacotherapy for stimulant use disorders has been limited by the lack of a meaningful indicator of treatment success, other than sustained abstinence. In March, 2015, a meeting sponsored by Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTION) was convened to discuss the current state of the evidence regarding meaningful outcome measures in clinical trials for stimulant use disorders. Attendees included members of academia, funding and regulatory agencies, pharmaceutical companies, and healthcare organizations. The goal was to establish a research agenda for the development of a meaningful outcome measure that may be used as an endpoint in clinical trials for stimulant use disorders. Based on guidelines for the selection of clinical trial endpoints, the lessons learned from prior addiction clinical trials, and the process that led to identification of a meaningful indicator of treatment success for alcohol use disorders, several recommendations for future research were generated. These include a focus on the validation of patient reported outcome measures of functioning, the exploration of patterns of stimulant abstinence that may be associated with physical and/or psychosocial benefits, the role of urine testing for validating self-reported measures of stimulant abstinence, and the operational definitions for reduction-based measures in terms of frequency rather than quantity of stimulant use. These recommendations may be useful for secondary analyses of clinical trial data, and in the design of future clinical trials that may help establish a meaningful indicator of treatment success.

Quinine As A Potential Tracer For Medication Adherence: A Pharmacokinetic and Pharmacodynamic Assessment Of Quinine Alone and In Combination With Oxycodone In Humans

Babalonis S, Hampson AJ, Lofwall MR, Nuzzo PA, Walsh SL. *J Clin Pharmacol*. 2015 Jun 1. doi: 10.1002/jcph.557. [Epub ahead of print].

Effective strategies to monitor pharmacotherapy adherence are necessary, and sensitive biological markers are lacking. This study examined a subtherapeutic dose of quinine as a potential adherence tracer. Primary aims included examination of the plasma and urinary pharmacokinetic profile of once-daily quinine; secondary aims assessed pharmacokinetic/pharmacodynamic interactions with oxycodone (a CYP3A and CYP2D substrate). Healthy, nondependent opioid users (n = 9) were enrolled in this within-subject, double-blind, placebo-controlled inpatient study. Participants received the following oral doses: day 1, oxycodone (30 mg); days 2-4, quinine (80 mg); day 5, quinine and oxycodone (2 hours postquinine). Blood and 24-hour urine samples were collected throughout the study, and pharmacodynamic outcomes were assessed during experimental sessions (days 1, 4, 5). Quinine displayed a plasma T_{max} ~2 hours and $t_{1/2}$ ~10 hours. Oxycodone and noroxycodone parameters (T_{max} , C_{max} , $t_{1/2}$) were similar with or without quinine present, although drug exposure (AUC) was slightly greater when combined with quinine. No pharmacodynamic interactions were detected, and doses were safely tolerated. During washout, quinine urinary concentrations steadily declined (elimination $t_{1/2}$ ~16 hours), with a 94% decrease observed 72 hours postdose. Overall, low-dose quinine appears to be a good candidate for a medication additive to monitor adherence for detection of missed medication.

[Randomized Trial Of Reduced-Nicotine Standards For Cigarettes](#) Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobos DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. N Engl J Med. 2015; 373(14): 1340-1349.

The Food and Drug Administration can set standards that reduce the nicotine content of cigarettes. The authors conducted a double-blind, parallel, randomized clinical trial between June 2013 and July 2014 at 10 sites. Eligibility criteria included an age of 18 years or older, smoking of five or more cigarettes per day, and no current interest in quitting smoking. Participants were randomly assigned to smoke for 6 weeks either their usual brand of cigarettes or one of six types of investigational cigarettes, provided free. The investigational cigarettes had nicotine content ranging from 15.8 mg per gram of tobacco (typical of commercial brands) to 0.4 mg per gram. The primary outcome was the number of cigarettes smoked per day during week 6. A total of 840 participants underwent randomization, and 780 completed the 6-week study. During week 6, the average number of cigarettes smoked per day was lower for participants randomly assigned to cigarettes containing 2.4, 1.3, or 0.4 mg of nicotine per gram of tobacco (16.5, 16.3, and 14.9 cigarettes, respectively) than for participants randomly assigned to their usual brand or to cigarettes containing 15.8 mg per gram (22.2 and 21.3 cigarettes, respectively; $P < 0.001$). Participants assigned to cigarettes with 5.2 mg per gram smoked an average of 20.8 cigarettes per day, which did not differ significantly from the average number among those who smoked control cigarettes. Cigarettes with lower nicotine content, as compared with control cigarettes, reduced exposure to and dependence on nicotine, as well as craving during abstinence from smoking, without significantly increasing the expired carbon monoxide level or total puff volume, suggesting minimal compensation. Adverse events were generally mild and similar among groups. In this 6-week study, reduced-nicotine cigarettes versus standard-nicotine cigarettes reduced nicotine exposure and dependence and the number of cigarettes smoked. (Funded by the National Institute on Drug Abuse and the Food and Drug Administration Center for Tobacco Products; ClinicalTrials.gov number, NCT01681875.)

RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS

[Cell-to-Cell Transmission of HIV-1 Is Required to Trigger Pyroptotic Death of Lymphoid-Tissue-Derived CD4 T Cells](#) Galloway NL, Doitsh G, Monroe KM, Yang Z, Muñoz-Arias I, Levy DN, Greene WC. Cell Rep. 2015 Sep 8; 12(10): 1555-1563. doi: 10.1016/j.celrep.2015.08.011. Epub 2015 Aug 28.

The progressive depletion of CD4 T cells underlies clinical progression to AIDS in untreated HIV-infected subjects. Most dying CD4 T cells correspond to resting nonpermissive cells residing in lymphoid tissues. Death is due to an innate immune response against the incomplete cytosolic viral DNA intermediates accumulating in these cells. The viral DNA is detected by the IFI16 sensor, leading to inflammasome assembly, caspase-1 activation, and the induction of pyroptosis, a highly inflammatory form of programmed cell death. The authors now show that cell-to-cell transmission of HIV is obligatorily required for activation of this death pathway. Cell-free HIV-1 virions, even when added in large quantities, fail to activate pyroptosis. These findings underscore the infected

CD4 T cells as the major killing units promoting progression to AIDS and highlight a previously unappreciated role for the virological synapse in HIV pathogenesis.

SERINC3 and SERINC5 Restrict HIV-1 Infectivity and are Counteracted By Nef

Usami Y, Wu Y, Göttlinger HG. *Nature*. 2015 Oct 8;526(7572):218-23. doi: 10.1038/nature15400. Epub 2015 Sep 30.

HIV-1 Nef and the unrelated mouse leukaemia virus glycosylated Gag (glycoGag) strongly enhance the infectivity of HIV-1 virions produced in certain cell types in a clathrin-dependent manner. Here the authors show that Nef and glycoGag prevent the incorporation of the multipass transmembrane proteins serine incorporator 3 (SERINC3) and SERINC5 into HIV-1 virions to an extent that correlates with infectivity enhancement. Silencing of both SERINC3 and SERINC5 precisely phenocopied the effects of Nef and glycoGag on HIV-1 infectivity. The infectivity of nef-deficient virions increased more than 100-fold when produced in double-knockout human CD4(+) T cells that lack both SERINC3 and SERINC5, and re-expression experiments confirmed that the absence of SERINC3 and SERINC5 accounted for the infectivity enhancement. Furthermore, SERINC3 and SERINC5 together restricted HIV-1 replication, and this restriction was evaded by Nef. SERINC3 and SERINC5 are highly expressed in primary human HIV-1 target cells, and inhibiting their down regulation by Nef is a potential strategy to combat HIV/AIDS.

HIV Transmission Networks in the San Diego-Tijuana Border Region

Mehta SR, Wertheim JO, Brouwer KC, Wagner KD, Chaillon A, Strathdee S, Patterson TL, Rangel MG, Vargas M, Murrell B, Garfein R, Little SJ, Smith DM. *EBioMedicine*. 2015 Jul 18; 2(10): 1456-1463. doi: 10.1016/j.ebiom.2015.07.024. eCollection 2015.

HIV sequence data can be used to reconstruct local transmission networks. Along international borders, like the San Diego-Tijuana region, understanding the dynamics of HIV transmission across reported risks, racial/ethnic groups, and geography can help direct effective prevention efforts on both sides of the border. The authors gathered sociodemographic, geographic, clinical, and viral sequence data from HIV infected individuals participating in ten studies in the San Diego-Tijuana border region. Phylogenetic and network analysis was performed to infer putative relationships between HIV sequences. Correlates of identified clusters were evaluated and spatiotemporal relationships were explored using Bayesian phylogeographic analysis. After quality filtering, 843 HIV sequences with associated demographic data and 263 background sequences from the region were analyzed, and 138 clusters were inferred (2-23 individuals). Overall, the rate of clustering did not differ by ethnicity, residence, or sex, but bisexuals were less likely to cluster than heterosexuals or men who have sex with men ($p = 0.043$), and individuals identifying as white ($p \leq 0.01$) were more likely to cluster than other races. Clustering individuals were also 3.5 years younger than non-clustering individuals ($p < 0.001$). Although the sampled San Diego and Tijuana epidemics were phylogenetically compartmentalized, five clusters contained individuals residing on both sides of the border. This study sampled ~ 7% of HIV infected individuals in the border region, and although the sampled networks on each side of the border were largely separate, there was evidence of persistent bidirectional cross-border transmissions that linked risk groups, thus highlighting the importance of the border region as a "melting pot" of risk groups.

Marijuana Use as a Sex-Drug is Associated with HIV Risk Among Black MSM and Their Network

Morgan E, Skaathun B, Michaels S, Young L, Khanna A, Friedman SR, Davis B, Pitrak D, Schneider J, UConnect Study Team. *AIDS Behav.* 2015 Sep 23. [Epub ahead of print]. Black men who have sex with men (BMSM) are at highest risk for HIV seroconversion in the United States. Little attention has been paid to marijuana use among BMSM and potential for HIV risk. A sample of 202 BMSM was generated through respondent driven sampling. The relationship between differential marijuana use and both HIV risk behavior and social network factors were examined using weighted logistic regression. Of the BMSM in this sample 60.4 % use marijuana in general and 20.8 % use marijuana as a sex-drug. General marijuana use was significantly associated with participation in group sex (AOR 3.50; 95 % CI 1.10-11.10) while marijuana use as a sex drug was significantly associated with both participation in condomless sex (AOR 2.86; 95% CI 1.07-7.67) and group sex (AOR 3.39; 95% CI 1.03-11.22). Respondents with a moderate or high perception of network members who use marijuana were more likely to use marijuana both in general and as a sex-drug. Network member marijuana use, while not associated with risk behaviors, is associated with individual marijuana use and individual marijuana use in the context of sex is associated with risk practices. Targeting interventions towards individuals and their respective networks that use marijuana as a sex drug may reduce HIV risk.

SERVICES RESEARCH

States' Implementation of the Affordable Care Act and the Supply of Physicians Waivered to Prescribe Buprenorphine for Opioid Dependence

Knudsen HK, Lofwall MR, Havens JR, Walsh SL. *Drug and Alcohol Dependence.* Accepted Manuscript, downloaded October 22, 2015. Although the Affordable Care Act (ACA) is anticipated to affect substance use disorder (SUD) treatment, its impact on the supply of physicians waivered to treat opioid dependence with buprenorphine has not been considered. This study examined whether states more supportive of ACA, meaning those that had opted to expand Medicaid and establish a state based health insurance exchange, experienced greater growth in physician supply than less supportive states. Buprenorphine physician supply, including total physician supply, supply of 30-patient physicians, and supply of 100-patient physicians per 100,000 state residents, was measured from June 2013 to May 2015. State characteristics were drawn from multiple secondary sources, with states categorized as ACA-supportive, ACA-hybrid (where states either expanded Medicaid or established a state-based exchange), or ACA-resistant (where states took neither action). Mixed effects regression was used to estimate state-level growth curves to test whether rates of growth varied by states' approaches to implementing ACA. The supply of waivered physicians grew significantly over the two-year period. Rates of growth were significantly lower in ACA-hybrid and ACA-resistant states relative to growth in ACA supportive states. Average buprenorphine physician supply at baseline varied by region, the percentage of residents covered by Medicaid, and the supply of specialty SUD treatment programs. This study found a positive impact of the ACA on growth in the supply of buprenorphine-waivered physicians in US states. Future research should address whether the ACA affects the number of patients receiving buprenorphine, Medicaid spending, and the quality of treatment services delivered.

Messaging to Increase Public Support for Naloxone Distribution Policies in the United States: Results from a Randomized Survey Experiment Bachhuber MA, McGinty EE,; Kennedy-

Hendricks A, Niederdeppe J, Barry CL. PLOS One. 2015; July 1.

Barriers to public support for naloxone distribution include lack of knowledge, concerns about potential unintended consequences, and lack of sympathy for people at risk of overdose. A randomized survey experiment was conducted with a nationally-representative web-based survey research panel (GfK KnowledgePanel). Participants were randomly assigned to read different messages alone or in combination: 1) factual information about naloxone; 2) pre-emptive refutation of potential concerns about naloxone distribution; and 3) a sympathetic narrative about a mother whose daughter died of an opioid overdose. Participants were then asked if they support or oppose policies related to naloxone distribution. For each policy item, logistic regression models were used to test the effect of each message exposure compared with the no-exposure control group. The final sample consisted of 1,598 participants (completion rate: 72.6%). Factual information and the sympathetic narrative alone each led to higher support for training first responders to use naloxone, providing naloxone to friends and family members of people using opioids, and passing laws to protect people who administer naloxone. Participants receiving the combination of the sympathetic narrative and factual information, compared to factual information alone, were more likely to support all policies: providing naloxone to friends and family members (OR: 2.0 [95% CI: 1.4 to 2.9]), training first responders to use naloxone (OR: 2.0 [95% CI: 1.2 to 3.4]), passing laws to protect people if they administer naloxone (OR: 1.5 [95% CI: 1.04 to 2.2]), and passing laws to protect people if they call for medical help for an overdose (OR: 1.7 [95% CI: 1.2 to 2.5]). All messages increased public support, but combining factual information and the sympathetic narrative was most effective. Public support for naloxone distribution can be improved through education and sympathetic portrayals of the population who stands to benefit from these policies.

Racialized Risk Environments In A Large Sample Of People Who Inject Drugs In The United States Cooper HLF, Linton S, Kelley ME, Ross Z, Wolfe ME, Chen Y-T, Zlotorzynsk M, Hunter-

Jones J, Friedman SR, Des Jarlais D, Semaan S, Tempalski B, DiNenno E, Broz D, Wejnert C, Paz-Bailey G, National HIV Behavioral Surveillance Study Group. Int J Drug Policy. 2015.

Substantial racial/ethnic disparities exist in HIV infection among people who inject drugs (PWID) in many countries. To strengthen efforts to understand the causes of disparities in HIV-related outcomes and eliminate them, the authors expand the "Risk Environment Model" to encompass the construct "racialized risk environments," and investigate whether PWID risk environments in the United States are racialized. Specifically, we investigate whether black and Latino PWID are more likely than white PWID to live in places that create vulnerability to adverse HIV-related outcomes. As part of the Centers for Disease Control and Prevention's National HIV Behavioral Surveillance, 9170 PWID were sampled from 19 metropolitan statistical areas (MSAs) in 2009. Self-reported data were used to ascertain PWID race/ethnicity. Using Census data and other administrative sources, the authors characterized features of PWID risk environments at four geographic scales (i.e., ZIP codes, counties, MSAs, and states). Means for each feature of the risk environment were computed for each racial/ethnic group of PWID, and were compared across racial/ethnic groups.

Almost universally across measures, black PWID were more likely than white PWID to live in environments associated with vulnerability to adverse HIV-related outcomes. Compared to white PWID, black PWID lived in ZIP codes with higher poverty rates and worse spatial access to substance abuse treatment and in counties with higher violent crime rates. Black PWID were less likely to live in states with laws facilitating sterile syringe access (e.g., laws permitting over-the-

counter syringe sales). Latino/white differences in risk environments emerged at the MSA level (e.g., Latino PWID lived in MSAs with higher drug-related arrest rates).PWID risk environments in the US are racialized. Future research should explore the implications of this racialization for racial/ethnic disparities in HIV-related outcomes, using appropriate methods.

CTN-RELATED RESEARCH

Hispanic Subgroups, Acculturation, and Substance Abuse Treatment Outcomes Chartier KG, Carmody T, Akhtar M, Stebbins MB, Walters ST, Warden D. *J Subst Abuse Treat.* 2015 Dec;59:74-82. Epub 2015 Jul 26.

This study explored Hispanic subgroup differences in substance use treatment outcomes, and the relationship of acculturation characteristics to these outcomes. Data were from a multisite randomized clinical trial of motivational enhancement therapy versus treatment as usual in a sample of Spanish-speaking substance abusers. Participants were Cuban American (n=34), Mexican American (n=209), Puerto Rican (n=78), and other Hispanic American (n=54). Results suggested that Cuban Americans and individuals with more connection to Hispanic culture had lower treatment retention. Hispanics born in the U.S and those who spoke English at home had a lower percentage of days abstinent during weeks 5-16, although Puerto Ricans born in the U.S. and Cuban Americans living more years in the U.S. had a higher percentage of days abstinent in weeks 1-4 and 5-16, respectively. Results may inform future hypothesis-driven studies in larger Hispanic treatment seeking samples of the relationship between acculturation and treatment outcome.

Long-Term Outcomes After Randomization To Buprenorphine/Naloxone Versus Methadone In A Multi-Site Trial Hser YI, Evans E, Huang D, Weiss R, Saxon A, Carroll KM, Woody G, Liu D, Wakim P, Matthews AG, Hatch-Maillette M, Jelstrom E, Wiest K, McLaughlin P, Ling W. *Addiction.* 2015 Nov 24. [Epub ahead of print].

The aims of the present study were to compare long-term outcomes among participants randomized to buprenorphine or methadone. Follow-up was conducted in 2011-2014 of 1,080 opioid-dependent participants entering 7 opioid treatment programs in the USA between 2006 and 2009 and randomized (within each program) to receive open-label buprenorphine/naloxone or methadone for up to 24 weeks; 795 participants completed in-person interviews (~74% follow-up interview rate) covering on average 4.5 years. Outcomes were indicated by mortality and opioid use. Covariates included demographics, site, cocaine use, and treatment experiences. Mortality was not different between the two randomized conditions with 23 (3.6%) of 630 participants randomized to buprenorphine having died, versus 26 (5.8%) of 450 participants randomized to methadone. Opioid use at follow-up was higher among participants randomized to buprenorphine relative to methadone (42.8% vs. 31.7% positive opioid urine specimens, $p < .01$, effect size (h) = 0.23 [0.09, 0.38]; 5.8 days vs. 4.4 days of past 30-day heroin use, $p < .05$, effect size (d) = 0.14 [0.00, 0.28]). Opioid use over the follow-up period by randomization condition was also significant ($F(7,39600) = 3.16$; $p < .001$) mostly due to less treatment participation among participants randomized to buprenorphine than methadone. Less opioid use was associated with both buprenorphine and methadone treatment (relative to no treatment); no difference was found between the two treatments. Individuals who are white or used cocaine at baseline responded better to methadone than to buprenorphine. The authors conclude that there are few differences in long-term outcomes between buprenorphine and methadone treatment for opioid dependence, and treatment with each medication is associated with a strong reduction in opioid use.

Depressive Symptoms and Associated Clinical Characteristics in Outpatients Seeking Community-Based Treatment for Alcohol and Drug Problems Sanchez K, Walker R, Campbell AN, Greer TL, Hu MC, Grannemann BD, Nunes EV, Trivedi MH. *Subst Abus.* 2015;36(3):297-303. Epub 2014 Aug 1.

Comorbid psychiatric and substance use disorders are common and associated with poorer treatment engagement, retention, and outcomes. This study examines the presence of depressive symptoms and the demographic and clinical correlates in a diverse sample of substance abuse treatment seekers to better characterize patients with co-occurring depressive symptoms and substance use disorders and understand potential treatment needs. Baseline data from a randomized clinical effectiveness trial of a computer-assisted, Web-delivered psychosocial intervention were analyzed. Participants (N = 507) were recruited from 10 geographically diverse outpatient drug treatment programs. Assessments included the self-report Patient Health Questionnaire, and measures of coping strategies, social functioning, physical health status, and substance use. One fifth (21%; n = 106) of the sample screened positive for depression; those screening positive for depression were significantly more likely to screen positive for anxiety (66.9%) and posttraumatic stress disorder (PTSD; 42.9%). After controlling for anxiety and PTSD symptoms, presence of depressive symptoms remained significantly associated with fewer coping strategies (P = .001), greater impairment in social adjustment (P < .001), and poorer health status (P < .001), but not to days of drug use in the last 90 days (P = .14). Depression is a clinically significant problem among substance abusers, and, in this study, patients who screened positive for depression were more likely to have co-occurring symptoms of anxiety and PTSD. Additionally, the presence of depressive symptoms was associated with fewer coping strategies and poorer social adjustment. Coping skills are a significant predictor of addiction outcomes, and it may be especially important to screen for and enhance coping among depressed patients. Evidence-based interventions that target coping skills and global functioning among substance abusers with depressive symptoms may be important adjuncts to usual treatment.

Substance Use, Depression and Sociodemographic Determinants of HIV Sexual Risk Behavior in Outpatient Substance Abuse Treatment Patients Tross S, Feaster DJ, Thorens G, Duan R, Gomez Z, Pavlicova M, Hu MC, Kyle T, Erickson S, Spector A, Haynes L, Metsch LR. *J Addict Med.* 2015 Dec;9(6):457-463.

The NIDA Clinical Trials Network trial of rapid HIV testing/counseling in 1281 patients was a unique opportunity to examine relationships among substance use, depressive symptoms, and sex risk behavior. Past 6-month substance use; substance use severity (Drug Abuse Screening Test - 10); depressive symptoms (Quick Inventory of Depressive Symptomatology); and three types of sex risk behavior (unprotected sex occasions [USOs] with primary partners; USOs with nonprimary partners; and USOs while high/drunk) were assessed. Zero-inflated negative binomial analyses provided: probability and rate of sex risk behavior (in risk behavior subsample). Levels of sexual risk behavior were high, while variable across the three types of sex risk behaviors. Among the patients, 50.4% had engaged in USOs with primary partners, 42% in sex while drunk or high, and 23.8% in USOs with nonprimary partners. Similar factors were significantly associated with all three types of sex risk behaviors. For all types, problem drinking, cocaine use, and substance use severity had an exacerbating effect. Older age was associated with lower risk behavior; other relationship categories (e.g., married, separated/divorced, cohabitating) were associated with greater risk behavior than was single status. Depressive symptoms were associated with decreased

likelihood of USOs with a primary partner. Sexual risk behavior is common among individuals in outpatient substance abuse treatment. Results highlight problem drinking (eg, up to three-fold) and cocaine (eg, up to twice) in increasing sex risk behavior. They demonstrate the utility of distinguishing between partner types and presence/absence of alcohol/drugs during sex. Findings argue for the need to integrate sex risk reduction into drug treatment.

Substance Use and Mental Diagnoses Among Adults With and Without Type 2 Diabetes: Results From Electronic Health Records Data Wu LT, Ghitza UE, Batch BC, Pencina MJ, Rojas LF, Goldstein BA, Schibler T, Dunham AA, Rusincovitch S, Brady KT. Drug Alcohol Depend. 2015 Nov 1;156:162-9. Epub 2015 Sep 12.

Comorbid diabetes and substance use diagnoses (SUD) represent a hazardous combination, both in terms of healthcare cost and morbidity. To date, there is limited information about the association of SUD and related mental disorders with type 2 diabetes mellitus (T2DM). The authors examined the associations between T2DM and multiple psychiatric diagnosis categories, with a focus on SUD and related psychiatric comorbidities among adults with T2DM. They analyzed electronic health record (EHR) data on 170,853 unique adults aged ≥ 18 years from the EHR warehouse of a large academic healthcare system. Logistic regression analyses were conducted to estimate the strength of an association for comorbidities. Overall, 9% of adults (n=16,243) had T2DM. Blacks, Hispanics, Asians, and Native Americans had greater odds of having T2DM than whites. All 10 psychiatric diagnosis categories were more prevalent among adults with T2DM than among those without T2DM. Prevalent diagnoses among adults with T2DM were mood (21.22%), SUD (17.02%: tobacco 13.25%, alcohol 4.00%, drugs 4.22%), and anxiety diagnoses (13.98%). Among adults with T2DM, SUD was positively associated with mood, anxiety, personality, somatic, and schizophrenia diagnoses. The authors examined a large diverse sample of individuals and found clinical evidence of SUD and psychiatric comorbidities among adults with T2DM. These results highlight the need to identify feasible collaborative care models for adults with T2DM and SUD related psychiatric comorbidities, particularly in primary care settings, that will improve behavioral health and reduce health risk.

INTRAMURAL RESEARCH

Molecular Targets and Medications Discovery Branch Medicinal Chemistry Section

High Affinity Dopamine D3 Receptor (D3R)-Selective Antagonists Attenuate Heroin Self-Administration In Wildtype But Not D3R Knockout Mice Boateng CA, Bakare OM, Zhan J, Banala AK, Burzynski C, Pommier E, Keck TM, Donthamsetti P, Javitch JA, Rais R, Slusher BS, Xi Z-X, Newman AH J Med Chem 2015; 58(15): 6195-6213.

The dopamine D3 receptor (D3R) is a promising target for the development of pharmacotherapeutics to treat substance use disorders. Several D3R-selective antagonists are effective in animal models of drug abuse, especially in models of relapse. Nevertheless, poor bioavailability, metabolic instability, and/or predicted toxicity have impeded success in translating these drug candidates to clinical use. Herein, the authors report a series of D3R-selective 4-phenylpiperazines with improved

metabolic stability. A subset of these compounds was evaluated for D3R functional efficacy and off target binding at selected 5-HT receptor subtypes, where significant overlap in SAR with D3R has been observed. Several high affinity D3R antagonists, including compounds 16 ($K_i = 0.12$ nM) and 32 ($K_i = 0.35$ nM), showed improved metabolic stability compared to the parent compound, PG648 (6). Notably, 16 and the classic D3R antagonist SB277011A (2) were effective in reducing self-administration of heroin in wildtype but not D3R knockout mice.

Integrative Neuroscience Branch Cellular Pathobiology Section

[Sigma-1 Receptor Mediates Cocaine-Induced Transcriptional Regulation By Recruiting Chromatin-Remodeling Factors At the Nuclear Envelope](#) Tsai SY, Chuang JY, Tsai MS, Wang XF, Xi ZX, Hong JJ, Chang WC, Bonci A, Su TP. Proceedings of the National Academy of Sciences, U.S.A. 2015; 112: E6562-E6570.

The sigma-1 receptor (Sig-1R) chaperone at the endoplasmic reticulum (ER) plays important roles in cellular regulation. Here the authors found a new function of Sig-1R in that it translocates from the ER to the nuclear envelope to recruit chromatin-remodeling molecules and regulate the gene transcription thereof. Sig-1Rs mainly reside at the ER-mitochondrion interface. However, upon stimulation by agonists like cocaine, Sig-1Rs translocate from ER to the nuclear envelope (NE) where Sig-1Rs bind NE protein emerin and recruit chromatin-remodeling molecules including lamin A/C, BAF, and HDAC to form a complex with the gene repressor Sp3. Knockdown of Sig-1Rs attenuates the complex formation. Cocaine was found to suppress the gene expression of monoamine oxidase B (MAOB) in the brain of wild type but not Sig-1R knockout mouse. A single dose of cocaine (20 mg/kg) in rats suppresses the level of MAOB at nuclear accumbens without affecting the level of dopamine transporter. Daily injections of cocaine in rats caused behavioral sensitization. Withdrawal from cocaine in cocaine-sensitized rats induced an apparent time-dependent rebound of the MAOB protein level to about at a 200% over control on day 14 after withdrawal. Treatment of cocaine-withdrawn rats with the MAOB inhibitor deprenyl completely alleviated the behavioral sensitization to cocaine. The authors' results demonstrate a role of Sig-1R in transcriptional regulation and suggest that cocaine may work through this newly discovered genomic action to achieve its addictive action. Results also suggest the MAOB inhibitor deprenyl as a therapeutic agent to block certain action of cocaine during withdrawal.

Behavioral Neuroscience Branch Preclinical Pharmacology Section

[The Novel Metabotropic Glutamate Receptor 2 Positive Allosteric Modulator, AZD8529, Decreases Nicotine Self-Administration and Relapse In Squirrel Monkeys](#) Justinova Z, Panlilio LV, Secci ME, Redhi GH, Schindler CW, Cross AJ, Mrzljak L, Medd A, Shaham Y, Goldberg SR Biological Psychiatry 2015;78: 452-462.

Based on rodent studies, group II metabotropic glutamate receptors (mGluR2 and mGluR3) were suggested as targets for addiction treatment. However, LY379268 and other group II agonists do not discriminate between the mainly presynaptic inhibitory mGluR2 (the proposed treatment target) and mGluR3. These agonists also produce tolerance over repeated administration and are no longer

considered for addiction treatment. Here, the authors determined the effects of AZD8529, a selective positive allosteric modulator of mGluR2, on abuse-related effects of nicotine in squirrel monkeys and rats. The authors first assessed modulation of mGluR2 function by AZD8529 using functional in vitro assays in membranes prepared from a cell line expressing human mGluR2 and in primate brain slices. They then determined AZD8529 (.03-10 mg/kg, intramuscular injection) effects on intravenous nicotine self-administration and reinstatement of nicotine seeking induced by nicotine priming or nicotine-associated cues. They also determined AZD8529 effects on food self-administration in monkeys and nicotine-induced dopamine release in accumbens shell in rats. AZD8529 potentiated agonist-induced activation of mGluR2 in the membrane-binding assay and in primate cortex, hippocampus, and striatum. In monkeys, AZD8529 decreased nicotine self-administration at doses (.3-3 mg/kg) that did not affect food self-administration. AZD8529 also reduced nicotine priming- and cue-induced reinstatement of nicotine seeking after extinction of the drug-reinforced responding. In rats, AZD8529 decreased nicotine-induced accumbens dopamine release. These results provide evidence for efficacy of positive allosteric modulators of mGluR2 in nonhuman primate models of nicotine reinforcement and relapse. This drug class should be considered for nicotine addiction treatment.

Cellular Neurobiology Research Branch Behavioral Neurophysiology Research Section

[Brief Optogenetic Inhibition Of Dopamine Neurons Mimics Endogenous Negative Reward Prediction Errors](#) Chang CY, Esber GR, Marrero-Garci Y, Yau HJ, Bonci A, Schoenbaum G. 2015. Nature Neuroscience. Epub ahead of print.

Correlative studies have strongly linked phasic changes in dopamine activity with reward prediction error signaling. But causal evidence that these brief changes in firing actually serve as error signals to drive associative learning is more tenuous. Although there is direct evidence that brief increases can substitute for positive prediction errors, there is no comparable evidence that similarly brief pauses can substitute for negative prediction errors. In the absence of such evidence, the effect of increases in firing could reflect novelty or salience, variables also correlated with dopamine activity. Here the authors provide evidence in support of the proposed linkage, showing in a modified Pavlovian over-expectation task that brief pauses in the firing of dopamine neurons in rat ventral tegmental area at the time of reward are sufficient to mimic the effects of endogenous negative prediction errors. These results support the proposal that brief changes in the firing of dopamine neurons serve as full-fledged bidirectional prediction error signals.

Behavioral Neuroscience Branch Neurobiology of Relapse Section

[Effect Of the Novel Positive Allosteric Modulator Of mGluR2 AZD8529 On Incubation Of Methamphetamine Craving After Prolonged Voluntary Abstinence In A Rat Model](#) Caprioli D, Venniro M, Zeric T, Li, X, Adhikary S, Madangopal R, Marchant NJ, Lucantonio F, Schoenbaum G, Bossert JM, Shaham Y Biological Psychiatry 2015; 78: 463-473.

Cue-induced methamphetamine craving increases after prolonged forced (experimenter-imposed) abstinence from the drug (incubation of methamphetamine craving). Here, the authors determined

whether this incubation phenomenon would occur under conditions that promote voluntary (self-imposed) abstinence. They also determined the effect of the novel mGluR2 positive allosteric modulator, AZD8529, on incubation of methamphetamine craving after forced or voluntary abstinence. The authors trained rats to self-administer palatable food (6 sessions) and then to self-administer methamphetamine under two conditions: 12 sessions (9-hr/day) or 50 sessions (3-hr/day). They then assessed cue-induced methamphetamine seeking in extinction tests after 1 or 21 abstinence days. Between tests, the rats underwent either forced abstinence (no access to the food- or drug-paired levers) or voluntary abstinence for 19 days (achieved via a discrete choice procedure between methamphetamine and palatable food; 20 trials per day). The authors also determined the effect of subcutaneous injections of AZD8529 (20 and 40 mg/kg) on cue-induced methamphetamine seeking 1 or 21 days after forced or voluntary abstinence. Under both training and abstinence conditions, cue-induced methamphetamine seeking in the extinction tests was higher after 21 abstinence days than after 1 day (incubation of methamphetamine craving). AZD8529 decreased cue-induced methamphetamine seeking on day 21 but not day 1 of forced or voluntary abstinence. The authors introduce a novel animal model to study incubation of drug craving and cue-induced drug seeking after prolonged voluntary abstinence, mimicking the human condition of relapse after successful contingency management treatment. Their data suggest that PAMs of mGluR2 should be considered for relapse prevention.

Cellular Neurobiology Branch Electrophysiology Research Section

[Cocaine-Induced Endocannabinoid Mobilization In The Ventral Tegmental Area](#) Wang H, Treadway T, Covey DP, Cheer JF, Lupica CR. *Cell Reports*, 2015; 12: 1997-2008. doi: 10.1016/j.celrep.2015.08.041. Epub 2015 Sep 10.

Cocaine is a highly addictive drug that acts upon the brain's reward circuitry via the inhibition of monoamine uptake. Endogenous cannabinoids (eCB) are lipid molecules released from midbrain dopamine (DA) neurons that modulate cocaine's effects through poorly understood mechanisms. The authors find that cocaine stimulates release of the eCB, 2-arachidonoylglycerol (2-AG), in the rat ventral midbrain to suppress GABAergic inhibition of DA neurons, through activation of presynaptic cannabinoid CB1 receptors. Cocaine mobilizes 2-AG via inhibition of Norepinephrine uptake and promotion of a cooperative interaction between Gq/11-coupled type-1 metabotropic glutamate and α 1-adrenergic receptors to stimulate internal calcium stores and activate phospholipase C. The disinhibition of DA neurons by cocaine-mobilized 2-AG is also functionally relevant because it augments DA release in the nucleus accumbens in vivo. The authors' results identify a mechanism through which the eCB system can regulate the rewarding and addictive properties of cocaine.

GRANTEE HONORS AND AWARDS

Kenneth A. Dodge, Ph.D., a William McDougall Professor at the Sanford School of Public Policy, Duke University, Durham, N.C., was recently inducted into the National Academy of Medicine, formerly the Institute of Medicine.

Frank Porreca, Ph.D., was selected for the Ronald Melzack Lecture Award at the 16th World Congress on Pain in Yokohama, Japan, September 2015.

Steffanie Strathdee, Ph.D., a NIDA T32 training program principal investigator at the University of California San Diego Department of Medicine's research was recently highlighted in "Means to an end: Cities, states and provinces are gearing up to halt their AIDS epidemics- though the definition of success varies." Joh Cohen. *Science*. 2015 July 15; 349 (6245): 226-231. The article featured several NIDA-funded research programs, including her former protégé and NIDA T32 fellow and recent NIDA K01 awardee, Dr. Laramie Smith's research on the HIV care cascade in Tijuana. In addition, it featured the work of Dr. Jose Luis Burgos, a former NIDA diversity supplement awardee. Dr. Strathdee directs a NIDA-funded T32 training program and Fogarty-funded HIV prevention training program grant focused on the Mexico-US border region. In 2010, she received a MERIT award from NIDA for her research on HIV prevention among drug users in Tijuana.

STAFF HONORS AND AWARDS

STAFF AWARDS

Wilson Compton, M.D., NIDA Deputy Director, **Jack Stein, Ph.D.**, OSPC Director, and **Maureen Boyle, Ph.D.**, Science Policy Branch Chief, received the HHS award for Distinguished Service for their work on the Secretary's Opioid Initiative.

Peter Hartsock, Ph.D., DESPR, was inducted as a Fellow in to The College of Physicians of Philadelphia, November 20th, Philadelphia, PA. The College is one of the oldest such institutions in the U.S. and is the birthplace of American public health. Other Fellows have included Dr. Benjamin Rush, signer of the Declaration of Independence, and the late Surgeon General C. Everett Koop with whom Dr. Hartsock served as co-author of the "Surgeon General's Report on AIDS."

David Thomas, Ph.D., DESPR, was awarded the NIH Director's Award for his part in developing the DHHS National Pain Strategy.

2015 NIDA Director's Awards

The CCTN Scientific Collaborator Group

Udi Ghitza, Ph.D., CCTN
David Liu, M.D., CCTN
Carmen Rosa, M.S., CCTN
Steven Sparenborg, Ph.D., CCTN

The ABCD Planning Group

Ishmael Amarreh, Ph.D., NIMH
Carol Alderson, DER
Cheryl Boyce, Ph.D., DESPR
Kevin Conway, Ph.D., DESPR
Bethany Deeds, Ph.D., DESPR
Matthew Finger, DESPR
Pamela Fleming, DESPR
Joe Frascella, Ph.D., OD
Steven Grant, Ph.D., DNB
Steve Gust, Ph.D., OD
Katia Howlett, Ph.D., DER
Donna Jones, OM
Marya Levintova, Ph.D., FIC
Roger Little, Ph.D., DNB
Vani Pariyadath, Ph.D., DNB
Thomas Radman, Ph.D., DNB
Mark Swieter, Ph.D., DER
Susan Weiss, Ph.D., DER

Christine Salaita, DER

Roger Sorensen, Ph.D., DNB

Kevin Conway, Ph.D., DESPR

Brain Imaging Drug Use Prevention Message Team

Usha Charya, OSPC

Bethany Deeds, Ph.D., DESPR

Steven Grant, Ph.D., DNB

Mary Kautz, Ph.D., DNB

Jacqueline Lloyd, Ph.D., DESPR

Harold Perl, Ph.D., DESPR

The Naloxone Team

Nora Chiang, Ph.D., DTMC

Shwe Gyaw, M.D., DTMC

Phillip Krieter, Ph.D., DTMC

David McCann, Ph.D., DTMC

Moo Park, Ph.D., DTMC

Robert Walsh, DTMC

Will Aklin, Ph.D., DTMC

Marisela Morales, Ph.D., IRP

The NIDA Strategic Planning Workgroup

Ishmael Amarreh, Ph.D., NIMH

Albert Avila, Ph.D., OD

Ruben Baler, Ph.D., OSPC

Jamie Biswas, Ph.D., DTMC

Maureen Boyle, Ph.D., OSPC

Katherine Davenny, M.P.H., OD

Meyer Glantz, Ph.D., DESPR

Elena Koustova, Ph.D., OD

Michelle Leff, M.D., IRP

Roger Little, Ph.D., DNB

Geetha Subramaniam, M.D., CCTN

David Thomas, Ph.D., DESPR

Eric Wargo, Ph.D., OSPC

Susan Weiss, Ph.D., DER

2015 NIDA Director's Innovator Award

Amy Newman, Ph.D., IRP

2015 NIDA Director's Award for Plain Language Writing
Eric Wargo, Ph.D., OSPC

2015 NIDA Director's Award for EEO, Diversity and Quality of Worklife
Susan Harrelson, IRP

30 Years of Government Service Awards

Montré Crawford, OM
Hirsch Davis, DTMC
Lynda Erinoff, Ph.D. OD
Douglas Janes, OM
Brenda Monarque, OD
Vishnudutt Purohit, D.V.M., Ph.D., DNB

40 Years of Government Service Awards

Marguerite Lewis, OM
Patricia Ballerstadt, IRP

STAFF CHANGES

New Appointments/Employees

Joellen Austin, MPAff, MSM, joined NIDA as the new Associate Director for Management /Executive Officer on October 19, 2015. Joellen comes to NIDA with 26 years of NIH experience, most recently serving for 4 years as EO for the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. Prior to NIEHS, Joellen was the EO for the National Institute of Neurological Disorders and Stroke (NINDS). She received her Master of Science degree in Management upon graduation from the Sloan Fellows Program at the Graduate School of Business, Stanford University. She also holds a Master of Public Affairs degree from the Lyndon B. Johnson School of Public Affairs, University of Texas at Austin, and a Bachelor of Arts degree in Economics and Government from Skidmore College. She is a 2006 graduate of the HHS Senior Executive Service (SES) Candidate Development Program and was appointed to the SES in 2007.

Gayathri Dowling, Ph.D. rejoined NIDA on November 1, 2015 as the Director, Adolescent Brain and Cognitive Development (ABCD) Project, in the Division of Extramural Research. Prior to that, she served as the Deputy Director of the Office of Science Policy, Engagement, Education, and Communications (OSPEEC) at the National Heart, Lung, and Blood Institute (NHLBI). While at NHLBI, she helped to reorganize the functions of the Institute's policy and communications offices to create OSPEEC, a comprehensive, coordinated, and technology-supported office that provides scientifically-based information to patients and their family members, health professionals, researchers, policy makers, and other stakeholders to inform policy and promote the prevention and treatment of heart, lung, blood, and sleep disorders. Dr. Dowling was also the Chief of the Science Policy Branch in the Office of Science Policy and Communications at NIDA. There she helped to educate a variety of audiences about the science of drug abuse and addiction—developing, guiding, and targeting communications for many different audiences, including Congress, the White House Office of National Drug Control Policy, other Federal Agencies, constituency organizations, physicians, and the general public. Dr. Dowling earned a Ph.D. in Neurobiology from the University of California at Davis, where she studied the developing nervous system, and subsequently conducted research at the Parkinson's Institute in Sunnyvale, CA studying the role of nicotine in muscle cell degeneration and neuroprotection in a model of Parkinson's disease.

Katia Delrahim Howlett, Ph.D., M.P.P., M.B.A. joined NIDA as a Senior Scientific Program Manager in the Division of Extramural Research on November 1, 2015. She 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 those leading to Fetal Alcohol Spectrum Disorders. 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.

Bethany Deeds, Ph.D., is serving as Acting Chief of the Prevention Research Branch, Division of Epidemiology, Services and Prevention Research at NIDA.

Jessica Cotto, M.P.H. returned to the Science Policy Branch (SPB) in the Office of Science Policy and Communications (OSPC) in October 2015. Ms. Cotto left OSPC in October 2014, to serve as a Health Science Policy Analyst at NHLBI where she provided the Director and other NHLBI staff with reports on trends in morbidity, mortality, and care patterns for diseases within the Institute's mandate. Ms. Cotto originally joined SPB as an Epidemiologist in January 2009 where she was a tremendous asset to the team and we are thrilled to have her back. Her primary responsibilities include analyzing data and synthesizing information from disparate sources to identify trends related to substance use. Prior to NIDA, Ms. Cotto served as a Clinical Research Associate for The Children's National Medical Center, the National Institute of Allergy and Infectious Diseases, and the National Cancer Institute.

Carolyn Tucker has joined NIDA's Division of Extramural Research as an Extramural Support Assistant. With over a decade of government administrative support experience, she assisted in the coordination of divisions and institutional workgroups as well as logistical and planning operations. Her educational experience includes coursework in applied sciences at the University of the District of Columbia and additional training in management and program analysis. She has been a dedicated member of the NIDA Work Life Advisory Committee (WAC) and was recently appointed as the Secretary in 2016. As a proud parent advocate for children's individual education and health needs, she serves as the Secretary for the Parents of Children with Down syndrome of Prince George's County in Maryland.

Tracey Cain joined the NIDA Office of Management's Office of Acquisitions on January 10, 2016 as a NIDA R&D Contract Specialist. Tracey comes to NIDA from a position in the private sector.

Gweniffer Epps joined the NIDA Office of Management's Office of Acquisitions as a Contract Specialist on January 10, 2016. Gweniffer comes to NIDA from NCI.

Nancy Lamon-Kritikos joined the NIDA Office of Management's Office of Acquisitions as a Station Support Branch Lead Contract Specialist on November 29, 2015. Nancy comes to NIDA from NRC.

Mark McNally joined the NIDA Office of Management's Office of Acquisitions on September 20, 2015 as a NIDA R&D Contract Specialist.

Departures

Syreeta Evans, who has served as a key member of our DESPR operations and administrative team since 2008, accepted a position as Secretary at the Office of the Assistant Secretary for Health (OASH), within the Department of Health and Human Services. She will be supporting Dr. Nancy Lee, the Deputy Assistant Secretary of Health — Women's Health, and Director of the Office on Women's Health.

Cara Batenhorst, Contract Specialist in NIDA's Office of Management left NIDA on December 4, 2015.

Jesus Bonet, an IT Specialist in the NIDA Office of Management's Information & Resource Management Branch left NIDA on November 28, 2015 for a position at the SEC.

Paul Marsalese, a Contract Specialist in the NIDA Office of Management's Office of Acquisition's Station Support Branch left NIDA on October 3, 2015 for a position in the Office of the Secretary, DHHS

John Flannery, a Supervisory Contract Specialist in the NIDA Office of Management's Office of Acquisition's Station Support Branch left NIDA on October 31, 2015 for a position in the NIH Center for Information Technology.

Rodney Brooks, a Contract Specialist in the NIDA Office of Management's Office of Acquisition's Station Support Branch left NIDA on January 23, 2016 for a position in the Office of the Secretary, DHHS.

Retirements

Patricia Ballerstadt, IRP, retired from Federal service on October 1, 2015.

Jamie Biswas, Ph.D., retired from NIDA on December 31st, 2015. Jamie was the Chief of the Medications Research Grants Branch for 15 years. She was a Chemist by training and made significant contributions towards the development of medications to treat Substance Use Disorders. Ivan Montoya will serve as Acting Branch Chief.

Lynda Erinoff, Ph.D., OD, Associate Director, AIDS Research Program, retired on December 31, 2015 after 31 years of federal government service. She worked 2 years at the U.S. Environmental Protection Agency and 29 years at NIDA.

Diana Haikalis, a Grants Management Specialist in DER's Grants Management Branch, retired from Federal service on January 3, 2016 after serving for more than 36 years.

John Hamill, a NIDA R&D Supervisory Contract Specialist in NIDA's Office of Management, retired from Federal service on January 1, 2016.

Amy Siller, a Contract Specialist in NIDA's Office of Acquisitions, Office of Management retired from Federal service on October 2, 2015.

Hari Singh, Ph.D., a Chemist in DNB's Chemistry & Pharmacology Branch retired from Federal service on December 31, 2015.

Barbara Usher, Ph.D., a Program Analyst in DCNBR's Office of the Director, retired from Federal service on October 31, 2015.



National Institute
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