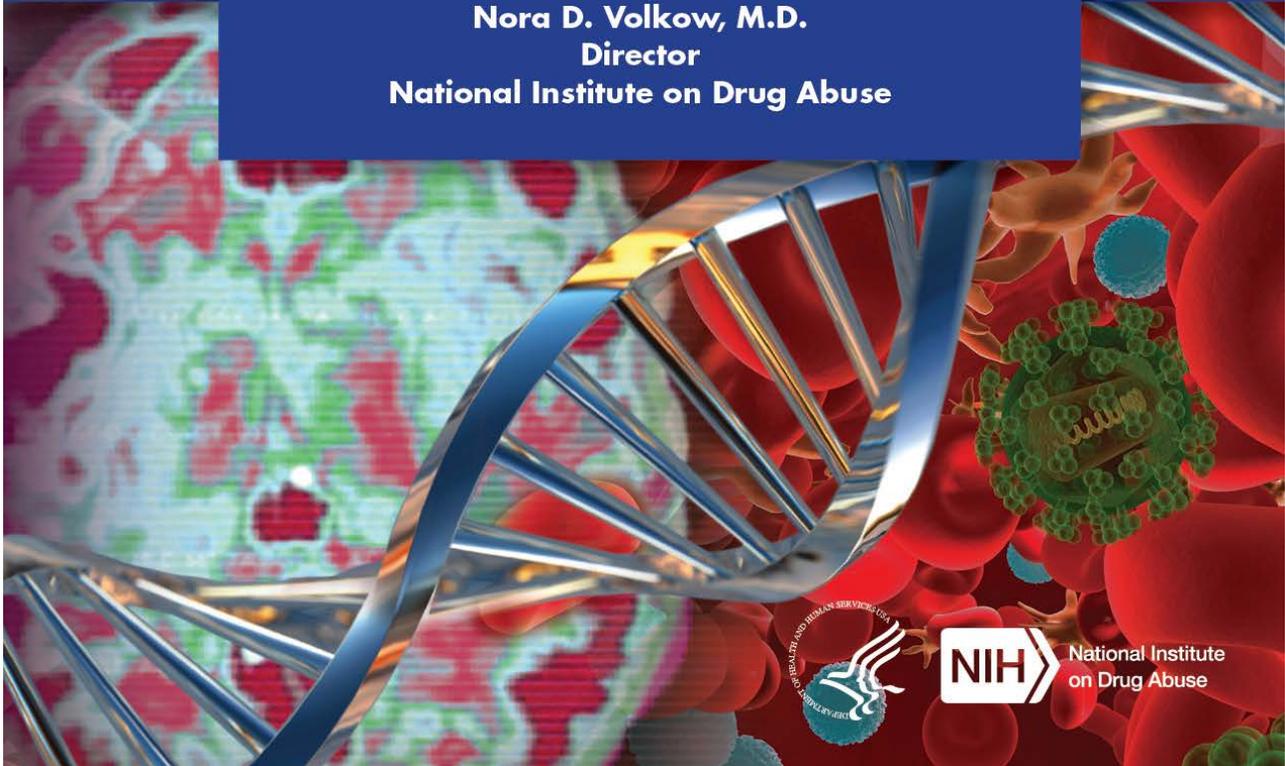




# DIRECTOR'S REPORT

————— *to the* —————  
National Advisory Council on Drug Abuse  
————— *May 2017* —————

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



National Institute  
on Drug Abuse



## TABLE OF CONTENTS

<b>RESEARCH HIGHLIGHTS.....</b>	<b>1</b>
<b>GRANTEE HONORS AND AWARDS.....</b>	<b>28</b>
<b>STAFF HONORS AND AWARDS.....</b>	<b>29</b>
<b>STAFF CHANGES.....</b>	<b>30</b>

## **RESEARCH HIGHLIGHTS**

### **BASIC AND BEHAVIORAL RESEARCH**

**Crystal Structure Of An LSD-Bound Human Serotonin Receptor** Wacker, Daniel; Wang, Sheng; McCorvy, John D; Betz, Robin M; Venkatakrishnan, A J; Levit, Anat; Lansu, Katherine; Schools, Zachary L; Che, Tao; Nichols, David E; Shoichet, Brian K; Dror, Ron O; Roth, Bryan L. *Cell*. 2017; 168(3): 377-389.e12.

The prototypical hallucinogen LSD acts via serotonin receptors, and here the authors describe the crystal structure of LSD in complex with the human serotonin receptor 5-HT<sub>2B</sub>. The complex reveals conformational rearrangements to accommodate LSD, providing a structural explanation for the conformational selectivity of LSD's key diethylamide moiety. LSD dissociates exceptionally slow from both 5-HT<sub>2BR</sub> and 5-HT<sub>2AR</sub>-a major target for its psychoactivity. Molecular dynamics (MD) simulations suggest that LSD's slow binding kinetics may be due to a "lid" formed by extracellular loop 2 (EL2) at the entrance to the binding pocket. A mutation predicted to increase the mobility of this lid greatly accelerates LSD's binding kinetics and selectively dampens LSD-mediated  $\beta$ -arrestin2 recruitment. This study thus reveals an unexpected binding mode of LSD; illuminates key features of its kinetics, stereochemistry, and signaling; and provides a molecular explanation for LSD's actions at human serotonin receptors.

**Cell- and Region-specific Expression Of Depression-related Protein P11 (S100a10) In The Brain** Milosevic, Ana; Liebmann, Thomas; Knudsen, Margarete; Schintu, Nicoletta; Svenningsson, Per; Greengard, Paul. *J Comp Neurol*. 2017; 525(4): 955-975.

P11 (S100a10), a member of the S100 family of proteins, has widespread distribution in the vertebrate body, including in the brain, where it has a key role in membrane trafficking, vesicle secretion, and endocytosis. Recently, the authors' laboratory has shown that a constitutive knockout of p11 (p11-KO) in mice results in a depressive-like phenotype. Furthermore, p11 has been implicated in major depressive disorder (MDD) and in the actions of antidepressants. Since depression affects multiple brain regions, and the role of p11 has only been determined in a few of these areas, a detailed analysis of p11 expression in the brain is warranted. Here the authors demonstrate that, although widespread in the brain, p11 expression is restricted to distinct regions, and specific neuronal and nonneuronal cell types. Furthermore, they provide comprehensive mapping of p11 expression using in situ hybridization, immunocytochemistry, and whole-tissue volume imaging. Overall, expression spans multiple brain regions, structures, and cell types, suggesting a complex role of p11 in depression. *J. Comp. Neurol.* 525:955-975, 2017.

**Loss Of  $\mu$  Opioid Receptor Signaling In Nociceptors, But Not Microglia, Abrogates Morphine Tolerance Without Disrupting Analgesia** Corder, Gregory; Tawfik, Vivianne L; Wang, Dong; Sypek, Elizabeth I; Low, Sarah A; Dickinson, Jasmine R; Sotoudeh, Chaudy; Clark, J David; Barres, Ben A; Bohlen, Christopher J; Scherrer, Grégory. *Nat Med*. 2017; 23(2): 164-173. Opioid pain medications have detrimental side effects including analgesic tolerance and opioid-induced hyperalgesia (OIH). Tolerance and OIH counteract opioid analgesia and drive dose escalation. The cell types and receptors on which opioids act to initiate these maladaptive processes remain disputed, which has prevented the development of therapies to maximize and sustain opioid analgesic efficacy. The authors found that  $\mu$  opioid receptors (MORs) expressed by primary afferent nociceptors initiate tolerance and OIH development. RNA sequencing and histological analysis revealed that MORs are expressed by nociceptors, but not by spinal microglia. Deletion of MORs

specifically in nociceptors eliminated morphine tolerance, OIH and pronociceptive synaptic long-term potentiation without altering antinociception. Furthermore, the authors found that co-administration of methylnaltrexone bromide, a peripherally restricted MOR antagonist, was sufficient to abrogate morphine tolerance and OIH without diminishing antinociception in perioperative and chronic pain models. Collectively, these data support the idea that opioid agonists can be combined with peripheral MOR antagonists to limit analgesic tolerance and OIH.

### **Effects Of Nucleus Accumbens Amphetamine Administration On Performance In A Delay Discounting Task**

Orsini, Caitlin A; Mitchell, Marci R; Heshmati, Sara C; Shimp, Kristy G; Spurrell, Megan S; Bizon, Jennifer L; Setlow, Barry. Behav Brain Res. 2017; 321(): 130-136. Chronic administration of cocaine can cause pronounced and enduring cognitive alterations such as increases in impulsive choice. Chronic cocaine can also result in enhanced dopamine (DA) release in the nucleus accumbens (NAc) in response to reward-related cues. It is possible that this enhanced DA release in the NAc is a mechanism by which cocaine increases impulsive choice. To date, however, the specific role of DA in the NAc in impulsive choice is unclear. To begin to address this, rats received acute microinjections of the indirect DA agonist amphetamine directly into the NAc prior to testing in a delay discounting task in which rats chose between a small, immediate and a large, delayed food reward. When delays to the large reward increased within test sessions, amphetamine increased choice of the large reward. When delays decreased within test sessions, however, amphetamine decreased choice of the large reward. These findings suggest that, rather than specifically mediating impulsive choice, DA neurotransmission in the NAc is necessary for flexible adaptation of choice strategies in the presence of shifting reward contingencies. These results further indicate that enhancements in NAc DA release likely do not account for lasting increases in impulsive choice caused by chronic cocaine.

### **In Silico Identification and In Vivo Validation Of MiR-495 As A Novel Regulator Of Motivation For Cocaine That Targets Multiple Addiction-related Networks In The Nucleus Accumbens**

Bastle, R M; Oliver, R J; Gardiner, A S; Pentkowski, N S; Bolognani, F; Allan, A M; Chaudhury, T; St Peter, M; Galles, N; Smith, C; Neisewander, J L; Perrone-Bizzozero, N I. Mol Psychiatry. 2017.

MicroRNAs (miRNAs) are important post-transcriptional regulators of gene expression and are implicated in the etiology of several neuropsychiatric disorders, including substance use disorders (SUDs). Using in silico genome-wide sequence analyses, we identified miR-495 as a miRNA whose predicted targets are significantly enriched in the Knowledgebase for Addiction Related Genes (ARG) database (KARG; <http://karg.cbi.pku.edu.cn>). This small non-coding RNA is also highly expressed within the nucleus accumbens (NAc), a pivotal brain region underlying reward and motivation. Using luciferase reporter assays, the authors found that miR-495 directly targeted the 3'UTRs of Bdnf, Camk2a and Arc. Furthermore, they measured miR-495 expression in response to acute cocaine in mice and found that it is downregulated rapidly and selectively in the NAc, along with concomitant increases in ARG expression. Lentiviral-mediated miR-495 overexpression in the NAc shell (NAcsh) not only reversed these cocaine-induced effects but also downregulated multiple ARG mRNAs in specific SUD-related biological pathways, including those that regulate synaptic plasticity. miR-495 expression was also downregulated in the NAcsh of rats following cocaine self-administration. Most importantly, the authors found that NAcsh miR-495 overexpression suppressed the motivation to self-administer and seek cocaine across progressive ratio, extinction and reinstatement testing, but had no effect on food reinforcement, suggesting that miR-495 selectively affects addiction-related behaviors. Overall, the authors' in silico search for post-transcriptional regulators identified miR-495 as a novel regulator of multiple ARGs that have a role

in modulating motivation for cocaine. *Molecular Psychiatry* advance online publication, 3 January 2017; doi:10.1038/mp.2016.238.

## **EPIDEMIOLOGY RESEARCH**

### **Developmental Course Of Non-medical Use Of Prescription Drugs From Adolescence To Adulthood In The United States: National Longitudinal Data**

McCabe, Sean Esteban; Kloska, Deborah D; Veliz, Philip; Jager, Justin; Schulenberg, John E. *Addiction*. 2016; 111(12): 2166-2176. The aim of this study was to identify the developmental course of non-medical use of four separate prescription drug classes (opioids, sedatives, stimulants and tranquilizers) by examining the general functional growth and related covariates during the transition from adolescence to adulthood in the United States. Nationally representative probability samples of high school seniors were followed longitudinally across five waves (waves 1, 2, 3, 4 and 5: modal ages 18, 19/20, 21/22, 23/24 and 25/26 years, respectively). Data were collected via self-administered questionnaires to high school seniors and young adults in the United States. The sample consisted of nearly 72,000 individuals in 30 cohorts (high school senior years of 1977-2006) who participated in at least one wave. Self-reports of annual non-medical use of prescription opioids, sedatives, stimulants, and tranquilizers. The annual non-medical use of prescription opioids, sedatives, stimulants and tranquilizers was highest at wave 1 over the five waves. There was a consistent descending path (linear and quadratic slopes,  $P < 0.001$ ) in annual non-medical use from baseline across all four prescription drug classes (e.g. opioids linear slope = -0.043 and opioids quadratic slope = 0.034,  $P < 0.001$ ). While the annual non-medical use of stimulants declined over time (linear slope = 0.063,  $P < 0.01$ ; quadratic slope = -0.133,  $P < 0.001$ ), the same decrease was not observed for the annual non-medical use of prescription opioids, sedatives or tranquilizers when controlling for socio-demographic and substance use behaviors at baseline. The covariates associated with the general functional growth differed across the four prescription drug classes. The non-medical use of prescription opioids, sedatives, stimulants and tranquilizers appears to peak during late adolescence, suggesting preventive intervention efforts should be initiated in early adolescence. The developmental course of non-medical use is not the same among all four classes of prescription drugs, suggesting that each drug class warrants individual research.

### **E-Cigarette Use As A Predictor Of Cigarette Smoking: Results From A 1-Year Follow-Up Of A National Sample Of 12th Grade Students**

Miech R, Patrick ME, O'Malley PM, Johnston LD. *Tob Control*. 2017 Feb 6. [Epub ahead of print].

The objective of this study is to prospectively examine vaping as a predictor of future cigarette smoking among youth with and without previous cigarette smoking experience. A secondary aim is to investigate whether vaping may desensitize youth to the dangers of smoking. This was an analysis of prospective longitudinal panel data from the nationally representative Monitoring the Future study. The analysis is based on 347 12th grade students who were part of a randomly selected subsample that completed in-school surveys in 2014 and were resurveyed 1-year later. Among youth who had never smoked a cigarette by 12th grade, baseline, recent vapers were more than 4 times (relative risk (RR)=4.78) more likely to report past-year cigarette smoking at follow-up, even among youth who reported the highest possible level of perceived risk for cigarette smoking at baseline. Among 12th grade students who had smoked in the past but had not recently smoked at baseline, recent vapers were twice (RR=2.15) as likely to report smoking in the past 12 months at the follow-up. Vaping did not predict cessation of smoking among recent smokers at baseline. Among never-smokers at baseline, recent vapers were more than 4 times (RR=4.73) more

likely to move away from the perception of cigarettes as posing a 'great risk' of harm, a finding consistent with a desensitisation process. These results contribute to the growing body of evidence supporting vaping as a one-way bridge to cigarette smoking among youth. Vaping as a risk factor for future smoking is a strong, scientifically-based rationale for restricting youth access to e-cigarettes.

### **State Medical Marijuana Laws and The Prevalence Of Opioids Detected Among Fatally Injured Drivers**

Kim, June H; Santaella-Tenorio, Julian; Mauro, Christine; Wrobel, Julia; Cerdà, Magdalena; Keyes, Katherine M; Hasin, Deborah; Martins, Silvia S; Li, Guohua. Am J Public Health. 2016; 106(11): 2032-2037.

The aim of this study was to assess the association between medical marijuana laws (MMLs) and the odds of a positive opioid test, an indicator for prior use. The authors analyzed 1999-2013 Fatality Analysis Reporting System (FARS) data from 18 states that tested for alcohol and other drugs in at least 80% of drivers who died within 1 hour of crashing (n = 68 394). Within-state and between-state comparisons assessed opioid positivity among drivers crashing in states with an operational MML (i.e., allowances for home cultivation or active dispensaries) versus drivers crashing in states before a future MML was operational. State-specific estimates indicated a reduction in opioid positivity for most states after implementation of an operational MML, although none of these estimates were significant. When the authors combined states, they observed no significant overall association (odds ratio [OR] = 0.79; 95% confidence interval [CI] = 0.61, 1.03). However, age-stratified analyses indicated a significant reduction in opioid positivity for drivers aged 21 to 40 years (OR = 0.50; 95% CI = 0.37, 0.67; interaction P < .001). Operational MMLs are associated with reductions in opioid positivity among 21- to 40-year-old fatally injured drivers and may reduce opioid use and overdose.

### **US Traffic Fatalities, 1985-2014, and Their Relationship To Medical Marijuana Laws**

Santaella-Tenorio, Julian; Mauro, Christine M; Wall, Melanie M; Kim, June H; Cerdà, Magdalena; Keyes, Katherine M; Hasin, Deborah S; Galea, Sandro; Martins, Silvia S. Am J Public Health. 2017; 107(2): 336-342.

The aim of this study was to determine the association of medical marijuana laws (MMLs) with traffic fatality rates. Using data from the 1985-2014 Fatality Analysis Reporting System, the authors examined the association between MMLs and traffic fatalities in multilevel regression models while controlling for contemporaneous secular trends. They examined this association separately for each state enacting MMLs. They also evaluated the association between marijuana dispensaries and traffic fatalities. On average, MML states had lower traffic fatality rates than non-MML states. Medical marijuana laws were associated with immediate reductions in traffic fatalities in those aged 15 to 24 and 25 to 44 years, and with additional yearly gradual reductions in those aged 25 to 44 years. However, state-specific results showed that only 7 states experienced post-MML reductions. Dispensaries were also associated with traffic fatality reductions in those aged 25 to 44 years. Both MMLs and dispensaries were associated with reductions in traffic fatalities, especially among those aged 25 to 44 years. State-specific analysis showed heterogeneity of the MML-traffic fatalities association, suggesting moderation by other local factors. These findings could influence policy decisions on the enactment or repealing of MMLs and how they are implemented.

### **Non-medical Use Of Prescription Opioids Is Associated With Heroin Initiation Among US Veterans: A Prospective Cohort Study**

Banerjee, Geetanjoli; Edelman, E Jennifer; Barry, Declan T; Becker, William C; Cerdá, Magdalena; Crystal, Stephen; Gaither, Julie R; Gordon, Adam J; Gordon, Kirsha S; Kerns, Robert D; Martins, Silvia S; Fiellin, David A; Marshall, Brandon D L. *Addiction*. 2016; 111(11): 2021-2031.

The aim of this study was to estimate the influence of non-medical use of prescription opioids (NMUPO) on heroin initiation among US veterans receiving medical care. Using a multivariable Cox regression model, the authors analyzed data from a prospective, multi-site, observational study of HIV-infected and an age/race/site-matched control group of HIV-uninfected veterans in care in the United States. Approximately annual behavioral assessments were conducted and contained self-reported measures of NMUPO and heroin use. Veterans Health Administration (VHA) infectious disease and primary care clinics in Atlanta, Baltimore, New York, Houston, Los Angeles, Pittsburgh and Washington, DC. A total of 3396 HIV-infected and uninfected patients enrolled into the Veterans Aging Cohort Study who reported no life-time NMUPO or heroin use, had no opioid use disorder diagnoses at baseline and who were followed between 2002 and 2012. The primary outcome measure was self-reported incident heroin use and the primary exposure of interest was new-onset NMUPO. The authors' final model was adjusted for socio-demographics, pain interference, prior diagnoses of post-traumatic stress disorder and/or depression and self-reported other substance use. Using a multivariable Cox regression model, they found that non-medical use of prescription opioids NMUPO was associated positively and independently with heroin initiation [adjusted hazard ratio (AHR) = 5.43, 95% confidence interval (CI) = 4.01, 7.35]. New-onset non-medical use of prescription opioids (NMUPO) is a strong risk factor for heroin initiation among HIV-infected and uninfected veterans in the United States who reported no previous history of NMUPO or illicit opioid use.

### **Do College Students Improve Their Grades By Using Prescription Stimulants Nonmedically?**

Arria, Amelia M; Caldeira, Kimberly M; Vincent, Kathryn B; O'Grady, Kevin E; Cimini, M Dolores; Geisner, Irene M; Fossos-Wong, Nicole; Kilmer, Jason R; Larimer, Mary E. *Addict Behav*. 2017; 65: 245-249.

Many college students engage in nonmedical use of prescription stimulants (NPS) because they believe it provides academic benefits, but studies are lacking to support or refute this belief. Using a longitudinal design, 898 undergraduates who did not have an ADHD diagnosis were studied. Year 3 GPA (from college records) of four groups was compared: Abstainers (did not engage in NPS either year; 68.8%); Initiators (NPS in Year 3 but not Year 2; 8.7%); Desisters (NPS in Year 2 but not Year 3; 5.8%); and Persisters (NPS in both years; 16.7%). Generalized estimating equations regression was used to estimate the association between NPS and change in GPA, controlling for sex and Year 2 GPA. GPA increased significantly within Abstainers ( $p < 0.05$ ), but did not change significantly within the other groups. Overall, the relationship between NPS pattern group and change in GPA was not statistically significant ( $p = 0.081$ ). NPS was generally infrequent, but Persisters used more frequently than Desisters (11.7 versus 3.4 days in Year 2) and Initiators (13.6 versus 4.0 days in Year 3, both  $ps < 0.001$ ), controlling for sex and Year 2 GPA. We cannot rule out the possibility that NPS prevented declines in GPA, but we can conclude that students who engaged in NPS showed no increases in their GPAs and gained no detectable advantages over their peers. The results suggest that prevention and intervention strategies should emphasize that the promise of academic benefits from NPS is likely illusory.

### **Risky Driving and Sexual Behaviors As Developmental Outcomes Of Co-occurring Substance Use and Antisocial Behavior**

Luk, Jeremy W; Worley, Matthew J; Winiger, Evan; Trim, Ryan S; Hopfer, Christian J; Hewitt, John K; Brown, Sandra A; Wall, Tamara L. *Drug Alcohol Depend.* 2016; 169: 19-25.

The objective of their study was to examine the associations between substance use and antisocial behavior trajectories and seven risky behaviors over time. Data were collected from a high-risk sample of adolescents followed into young adulthood. Five trajectory classes, identified based on dual development of substance use and antisocial behavior symptoms, were used to predict three risky driving and four risky sexual behaviors. In this high-risk sample (n=530), participants reported notably high overall rates of reckless driving (55.5%) and unprotected sex under the influence (44.8%) in the past year. Risky behaviors that are typically of low base rates in population-based studies were also elevated, with 8.8% reporting past-year driving under the influence (DUI) charge, 17.6% reporting lifetime sexually transmitted infection (STI), and 10.4% reporting lifetime injection drug use. The Dual Chronic class had the highest levels of all seven risky behaviors, and were 3-4 times more likely to report risky driving, lifetime STI, and injection drug use than the Relatively Resolved class. Rates of past-year reckless driving and DUI were elevated among classes with persistent antisocial behavior, whereas rates of DUI, DUI charge, and unprotected sex under the influence were elevated among classes with persistent substance use. Young adults with persistent co-occurring substance use and antisocial behavior engage in multiple very costly risky behaviors. Differential associations between risky behaviors and trajectory classes highlight the need for targeted interventions.

### **Persistent Cannabis Dependence and Alcohol Dependence Represent Risks For Midlife Economic and Social Problems: A Longitudinal Cohort Study**

Cerdá, Magdalena; Moffitt, Terrie E; Meier, Madeline H; Harrington, HonaLee; Houts, Renate; Ramrakha, Sandhya; Hogan, Sean; Poulton, Richie; Caspi, Avshalom. *Clin Psychol Sci.* 2016; 4(6): 1028-1046.

With the increasing legalization of cannabis, understanding the consequences of cannabis use is particularly timely. The authors examined the association between cannabis use and dependence, prospectively assessed between ages 18-38, and economic and social problems at age 38. They studied participants in the Dunedin Longitudinal Study, a cohort (n=1,037) followed from birth to age 38. Study members with regular cannabis use and persistent dependence experienced downward socioeconomic mobility, more financial difficulties, workplace problems, and relationship conflict in early midlife. Cannabis dependence was not linked to traffic-related convictions. Associations were not explained by socioeconomic adversity, childhood psychopathology, achievement orientation, or family structure; cannabis-related criminal convictions; early onset of cannabis dependence; or comorbid substance dependence. Cannabis dependence was associated with more financial difficulties than alcohol dependence; no difference was found in risks for other economic or social problems. Cannabis dependence is not associated with fewer harmful economic and social problems than alcohol dependence.

### **A Bivariate Genetic Analysis Of Drug Abuse Ascertained Through Medical and Criminal Registries In Swedish Twins, Siblings and Half-Siblings**

Maes, Hermine H; Neale, Michael C; Ohlsson, Henrik; Zahery, Mahsa; Lichtenstein, Paul; Sundquist, Kristina; Sundquist, Jan; Kendler, Kenneth S. *Behav Genet.* 2016; 46(6): 735-741.

Using Swedish nationwide registry data, the authors investigated the correlation of genetic and environmental risk factors in the etiology of drug abuse as ascertained from medical and criminal registries by modeling twin and sibling data. Medical drug abuse was defined using public inpatient and outpatient records, while criminal drug abuse was ascertained through legal records. Twin, full

and half sibling pairs were obtained from the national twin and genealogical registers. Information about sibling pair residence within the same household was obtained from Statistics Sweden. Standard bivariate genetic structural equation modeling was applied to the population-based data on drug abuse ascertained through medical and crime registries, using OpenMx. Analyses of all possible pairs of twins (MZ: N = 4482; DZ: N = 9838 pairs), full- (N = 1,278,086) and half-siblings (paternal: N = 7767; maternal N = 70,553) who grew up together suggested that factors explaining familial resemblance for drug abuse as defined through medical or criminal registries were mostly the same. Results showed substantial heritability and moderate contributions of shared environmental factors to drug abuse; both were higher in males versus females, and higher for drug abuse ascertained through criminal than medical records. Because of the low prevalence of both assessments of drug abuse, having access to population data was crucial to obtain stable estimates. Using objective registry data, the authors found that drug abuse-whether ascertained through medical versus criminal records-was highly heritable. Furthermore, shared environmental factors contributed significantly to the liability of drug abuse. Genetic and shared environmental risk factors for these two forms of drug abuse were highly correlated.

## **PREVENTION RESEARCH**

### **Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study**

Deyo, Richard A; Hallvik, Sara E; Hildebran, Christi; Marino, Miguel; Dexter, Eve; Irvine, Jessica M; O'Kane, Nicole; Van Otterloo, Joshua; Wright, Dagan A; Leichtling, Gillian; Millet, Lisa M. J Gen Intern Med. 2017; 32(1): 21-27.

Long-term efficacy of opioids for non-cancer pain is unproven, but risks argue for cautious prescribing. Few data suggest how long or how much opioid can be prescribed for opioid-naïve patients without inadvertently promoting long-term use. The aim of this study was to examine the association between initial opioid prescribing patterns and likelihood of long-term use among opioid-naïve patients. This was a retrospective cohort study; data were from Oregon resident prescriptions linked to death certificates and hospital discharges. Patients filling opioid prescriptions between October 1, 2012, and September 30, 2013, with no opioid fills for the previous 365 days were examined. Subgroup analyses examined patients under age 45 who did not die in the follow-up year, excluding most cancer or palliative care patients. Data collected were numbers of prescription fills and cumulative morphine milligram equivalents (MMEs) dispensed during 30 days following opioid initiation ("initiation month") as well as the proportion of patients with six or more opioid fills during the subsequent year ("long-term users"). There were 536,767 opioid-naïve patients who filled an opioid prescription. Of these, 26,785 (5.0 %) became long-term users. Numbers of fills and cumulative MMEs during the initiation month were associated with long-term use. Among patients under age 45 using short-acting opioids who did not die in the follow-up year, the adjusted odds ratio (OR) for long-term use among those receiving two fills versus one was 2.25 (95 % CI: 2.17, 2.33). Compared to those who received < 120 total MMEs, those who received between 400 and 799 had an OR of 2.96 (95 % CI: 2.81, 3.11). Patients initiating with long-acting opioids had a higher risk of long-term use than those initiating with short-acting drugs. Early opioid prescribing patterns are associated with long-term use. While patient characteristics are important, clinicians have greater control over initial prescribing. These findings may help minimize the risk of inadvertently initiating long-term opioid use.

**Risk Factors For Substance Misuse and Adolescents' Symptoms Of Depression** Siennick, Sonja E; Widdowson, Alex O; Woessner, Mathew K; Feinberg, Mark E; Spoth, Richard L. *J Adolesc Health*. 2017; 60(1): 50-56.

Depressive symptoms during adolescence are positively associated with peer-related beliefs, perceptions, and experiences that are known risk factors for substance misuse. These same risk factors are targeted by many universal substance misuse prevention programs. This study examined whether a multicomponent universal substance misuse intervention for middle schoolers reduced the associations between depressive symptoms, these risk factors, and substance misuse. The study used data from a place-randomized trial of the Promoting School-Community-University Partnerships to Enhance Resilience model for delivery of evidence-based substance misuse programs for middle schoolers. Three-level within-person regression models were applied to four waves of survey, and social network data from 636 adolescents followed from sixth through ninth grades. When adolescents in control school districts had more symptoms of depression, they believed more strongly that substance use had social benefits, perceived higher levels of substance misuse among their peers and friends, and had more friends who misused substances, although they were not more likely to use substances themselves. Many of the positive associations of depressive symptoms with peer-related risk factors were significantly weaker or not present among adolescents in intervention school districts. The Promoting School-Community-University Partnerships to Enhance Resilience interventions reduced the positive associations of adolescent symptoms of depression with peer-related risk factors for substance misuse.

**Deficits In Autonomic Indices Of Emotion Regulation and Reward Processing Associated With Prescription Opioid Use and Misuse** Garland, Eric L; Bryan, Craig J; Nakamura, Yoshio; Froeliger, Brett; Howard, Matthew O. *Psychopharmacology (Berl)*. 2017; 234(4): 621-629.

Prescription opioid misuse and high-dose opioid use may result in allostatic dysregulation of hedonic brain circuitry, leading to reduced emotion regulation capacity. In particular, opioid misuse may blunt the ability to experience and upregulate positive affect from natural rewards. The purpose of this study was to examine associations between opioid use/misuse and autonomic indices of emotion regulation capability in a sample of chronic pain patients receiving prescription opioid pharmacotherapy. Chronic pain patients taking long-term opioid analgesics (N = 40) completed an emotion regulation task while heart rate variability (HRV) was recorded, and also completed self-report measures of opioid misuse, craving, pain severity, and emotional distress. Based on a validated cut-point on the Current Opioid Misuse Measure, participants were grouped as opioid misusers or non-misusers. Opioid misuse status and morphine equivalent daily dose (MEDD) were examined as predictors of HRV and self-reports of emotion regulation. Opioid misusers exhibited significantly less HRV during positive and negative emotion regulation, and significantly less positive effect, than non-misusers, after controlling for confounders including pain severity and emotional distress. MEDD was inversely associated with positive emotion regulation efficacy. Findings implicate the presence of reward processing deficits among chronic pain patients with opioid-misusing behaviors, and opioid dosage was associated with deficient emotion regulation, suggesting the presence of compromised top-down cognitive control over bottom-up hedonic processes. Emotion regulation among opioid misusers may represent an important treatment target

**Antisocial Peer Affiliation and Externalizing Disorders: Evidence For Gene × Environment × Development Interaction** Samek, Diana R; Hicks, Brian M; Keyes, Margaret A; Iacono, William G; McGue, Matt. *Dev Psychopathol*. 2017; 29(1): 155-172.

Gene × Environment interaction contributes to externalizing disorders in childhood and adolescence, but little is known about whether such effects are long lasting or present in adulthood.

The authors examined gene-environment interplay in the concurrent and prospective associations between antisocial peer affiliation and externalizing disorders (antisocial behavior and substance use disorders) at ages 17, 20, 24, and 29. The sample included 1,382 same-sex twin pairs participating in the Minnesota Twin Family Study. The authors detected a Gene  $\times$  Environment interaction at age 17, such that additive genetic influences on antisocial behavior and substance use disorders were greater in the context of greater antisocial peer affiliation. This Gene  $\times$  Environment interaction was not present for antisocial behavior symptoms after age 17, but it was for substance use disorder symptoms through age 29 (though effect sizes were largest at age 17). The results suggest adolescence is a critical period for the development of externalizing disorders wherein exposure to greater environmental adversity is associated with a greater expression of genetic risk. This form of Gene  $\times$  Environment interaction may persist through young adulthood for substance use disorders, but it appears to be limited to adolescence for antisocial behavior.

**Randomized Trial Of Parent Training To Prevent Adolescent Problem Behaviors During The High School Transition** Mason, W Alex; Fleming, Charles B; Gross, Thomas J; Thompson, Ronald W; Parra, Gilbert R; Haggerty, Kevin P; Snyder, James J. *J Fam Psychol.* 2016; 30(8):944-954.

This randomized controlled trial tested a widely used general parent training program, Common Sense Parenting (CSP), with low-income 8th graders and their families to support a positive transition to high school. The program was tested in its original 6-session format and in a modified format (CSP-Plus), which added 2 sessions that included adolescents. Over 2 annual cohorts, 321 families were enrolled and randomly assigned to either the CSP, CSP-Plus, or minimal-contact control condition. Pretest, posttest, 1-year follow-up, and 2-year follow-up survey data on parenting as well as youth school bonding, social skills, and problem behaviors were collected from parents and youth (94% retention). Extending prior examinations of posttest outcomes, intent-to-treat regression analyses tested for intervention effects at the 2 follow-up assessments, and growth curve analyses examined experimental condition differences in yearly change across time. Separate exploratory tests of moderation by youth gender, youth conduct problems, and family economic hardship also were conducted. Out of 52 regression models predicting 1- and 2-year follow-up outcomes, only 2 out of 104 possible intervention effects were statistically significant. No statistically significant intervention effects were found in the growth curve analyses. Tests of moderation also showed few statistically significant effects. Because CSP already is in widespread use, findings have direct implications for practice. Specifically, findings suggest that the program may not be efficacious with parents of adolescents in a selective prevention context and may reveal the limits of brief, general parent training for achieving outcomes with parents of adolescents.

**The Long-term Effectiveness Of The Family Check-Up On School-age Conduct Problems: Moderation By Neighborhood Deprivation** Shaw, Daniel S; Sitnick, Stephanie L; Brennan, Laurretta M; Choe, Daniel E; Dishion, Thomas J; Wilson, Melvin N; Gardner, Frances. *Dev Psychopathol.* 2016; 28(4pt2): 1471-1486.

Several studies suggest that neighborhood deprivation is a unique risk factor in child and adolescent development of problem behavior. The authors sought to examine whether previously established intervention effects of the Family Check-Up (FCU) on child conduct problems at age 7.5 would persist through age 9.5, and whether neighborhood deprivation would moderate these effects. In addition, the authors examined whether improvements in parent-child interaction during early childhood associated with the FCU would be related to later reductions in child aggression among families living in the highest risk neighborhoods. Using a multisite cohort of at-risk children identified on the basis of family, child, and socioeconomic risk and randomly assigned to the FCU,

intervention effects were found to be moderated by neighborhood deprivation, such that they were only directly present for those living at moderate versus extreme levels of neighborhood deprivation. In addition, improvements in child aggression were evident for children living in extreme neighborhood deprivation when parents improved the quality of their parent-child interaction during the toddler period (i.e., moderated mediation). Implications of the findings are discussed in relation to the possibilities and possible limitations in prevention of early problem behavior for those children living in extreme and moderate levels of poverty.

**The Dynamics Of Internalizing and Externalizing Comorbidity Across The Early School Years** Willner, Cynthia J; Gatzke-Kopp, Lisa M; Bray, Bethany C. *Dev Psychopathol.* 2016; 28(4pt1): 1033-1052.

High rates of comorbidity are observed between internalizing and externalizing problems, yet the developmental dynamics of comorbid symptom presentations are not yet well understood. This study explored the developmental course of latent profiles of internalizing and externalizing symptoms across kindergarten, first grade, and second grade. The sample consisted of 336 children from an urban, low-income community, selected based on relatively high (61%) or low (39%) aggressive/oppositional behavior problems at school entry (64% male; 70% African American, 20% Hispanic). Teachers reported on children's symptoms in each year. An exploratory latent profile analysis of children's scores on aggression/oppositionality, hyperactivity/inattention, anxiety, and social withdrawal symptom factors revealed four latent symptom profiles: comorbid (48% of the sample in each year), internalizing (19%-23%), externalizing (21%-22%), and well-adjusted (7%-11%). The developmental course of these symptom profiles was examined using a latent transition analysis, which revealed remarkably high continuity in the comorbid symptom profile (89% from one year to the next) and moderately high continuity in both the internalizing and externalizing profiles (80% and 71%, respectively). Internalizing children had a 20% probability of remitting to the well-adjusted profile by the following year, whereas externalizing children had a 25% probability of transitioning to the comorbid profile. These results are consistent with the hypothesis that a common vulnerability factor contributes to developmentally stable internalizing-externalizing comorbidity, while also suggesting that some children with externalizing symptoms are at risk for subsequently accumulating internalizing symptoms.

**Glucocorticoid Receptor (NR3C1) Gene Polymorphism Moderate Intervention Effects On The Developmental Trajectory Of African-American Adolescent Alcohol Abuse** Zheng, Yao; Albert, Dustin; McMahon, Robert J; Dodge, Kenneth; Dick, Danielle; Conduct Problems Prevention Research Group. *Prev Sci.* 2016; Nov. 6.

Accumulative evidence from recent genotype  $\times$  intervention studies suggests that individuals carrying susceptible genotypes benefit more from intervention and provides one avenue to identify subgroups that respond differentially to intervention. This study examined the moderation by glucocorticoid receptor (NR3C1) gene variants of intervention effects on the developmental trajectories of alcohol abuse through adolescence. Participants were randomized into Fast Track intervention and control groups self-reported past-year alcohol abuse annually from grade 7 through 2 years post-high school and provided genotype data at age 21 (69% males; European Americans [EAs] = 270, African-Americans [AAs] = 282). Latent growth curve models were fit to examine developmental trajectories of alcohol abuse. The interactions of 10 single nucleotide polymorphisms (SNPs) in NR3C1 with intervention were examined separately. Both EAs and AAs showed significant increases in past-year alcohol abuse with substantial inter-individual differences in rates of linear growth. AAs showed lower general levels and slower rates of linear growth than EAs. Adjusting for multiple tests, one NR3C1 SNP (rs12655166) significantly moderated

intervention effects on the developmental trajectories of alcohol abuse among AAs. Intervention effects on the rates of linear growth were stronger among AAs carrying minor alleles than those not carrying minor alleles. The findings highlight the importance of taking a developmental perspective on adolescent alcohol use and have implications for future intervention design and evaluation by identifying subgroups that could disproportionately benefit from intervention.

## **TREATMENT RESEARCH**

**[Digital Pills To Measure Opioid Ingestion Patterns In Emergency Department Patients With Acute Fracture Pain: A Pilot Study](#)** Chai, Peter R; Carreiro, Stephanie; Innes, Brendan J; Rosen, Rochelle K; O'Cleirigh, Conall; Mayer, Kenneth H; Boyer, Edward W. J Med Internet Res. 2017; 19(1): e19. rs

Nonadherence to prescribed regimens for opioid analgesic agents contributes to increasing opioid abuse and overdose death. Opioids are frequently prescribed on an as-needed basis, placing the responsibility to determine opioid dose and frequency with the patient. There is wide variability in physician prescribing patterns because of the lack of data describing how patients actually use as-needed opioid analgesics. Digital pill systems have a radiofrequency emitter that directly measures medication ingestion events, and they provide an opportunity to discover the dose, timing, and duration of opioid therapy. The purpose of this study was to determine the feasibility of a novel digital pill system to measure as-needed opioid ingestion patterns in patients discharged from the emergency department (ED) after an acute bony fracture. The authors used a digital pill with individuals who presented to a teaching hospital ED with an acute extremity fracture. The digital pill consisted of a digital radiofrequency emitter within a standard gelatin capsule that encapsulated an oxycodone tablet. When ingested, the gastric chloride ion gradient activated the digital pill, transmitting a radiofrequency signal that was received by a hip-worn receiver, which then transmitted the ingestion data to a cloud-based server. After a brief, hands-on training session in the ED, study participants were discharged home and used the digital pill system to ingest oxycodone prescribed as needed for pain for one week. The authors conducted pill counts to verify digital pill data and open-ended interviews with participants at their follow-up appointment with orthopedics or at one week after enrollment in the study to determine the knowledge, attitudes, beliefs, and practices regarding digital pills. They analyzed open-ended interviews using applied thematic analysis. The authors recruited 10 study participants and recorded 96 ingestion events (87.3%, 96/110 accuracy). Study participants reported being able to operate all aspects of the digital pill system after their training. Two participants stopped using the digital pill, reporting they were in too much pain to focus on the novel technology. The digital pill system detected multiple simultaneous ingestion events by the digital pill system. Participants ingested a mean 8 (SD 5) digital pills during the study period and four participants continued on opioids at the end of the study period. After interacting with the digital pill system in the real world, participants found the system highly acceptable (80%, 8/10) and reported a willingness to continue to use a digital pill to improve medication adherence monitoring (90%, 9/10). The digital pill is a feasible method to measure real-time opioid ingestion patterns in individuals with acute pain and to develop real-time interventions if opioid abuse is detected. Deploying digital pills is possible through the ED with a short instructional course. Patients who used the digital pill accepted the technology.

**Anhedonia Is Associated With Poorer Outcomes In Contingency Management For Cocaine Use Disorder**

Wardle, Margaret C; Vincent, Jessica N; Suchting, Robert; Green, Charles E; Lane, Scott D; Schmitz, Joy M. *J Subst Abuse Treat.* 2017; 72: 32-39.

This study explored anhedonia (lack of interest or pleasure in non-drug rewards) as a potentially modifiable individual difference associated with the effectiveness of Contingency Management (CM). It also tested the hypothesis that a dopaminergic drug, levodopa (L-DOPA), would improve the effectiveness of CM, particularly in individuals high in anhedonia. The study was a single-site, randomized, double-blind, parallel group, 12-week trial comparing L-DOPA with placebo, with both medication groups receiving voucher-based CM targeting cocaine-negative urines. Participants were N=85 treatment-seeking adults with CUD. Anhedonia was measured at baseline using a validated self-report measure and a progressive ratio behavioral measure. Treatment Effectiveness Score (TES) was defined as the total number of cocaine-negative urines submitted. Analyses based on Frequentist general linear models were not significant, but Bayesian analyses indicated a high probability (92.6%) that self-reported anhedonia was associated with poor treatment outcomes (lower TES). L-DOPA did not significantly improve outcomes, nor was the effect of L-DOPA moderated by anhedonia. While the study failed to replicate positive findings from previous studies of L-DOPA in combination with CM, it does provide preliminary evidence that anhedonia may be a modifiable individual difference associated with poorer CM outcomes.

**Impact Of Cannabis Use On Treatment Outcomes Among Adults Receiving Cognitive-Behavioral Treatment For PTSD and Substance Use Disorders**

Ruglass, Lesia M; Shevorykin, Alina; Radoncic, Vanja; Smith, Kathryn M Z; Smith, Philip H; Galatzer-Levy, Isaac R; Papini, Santiago; Hien, Denise A. *J Clin Med.* 2017; 6(2).

Research has demonstrated a strong link between trauma, posttraumatic stress disorder PTSD and substance use disorders (SUDs) in general and cannabis use disorders in particular. Yet, few studies have examined the impact of cannabis use on treatment outcomes for individuals with co-occurring PTSD and SUDs. Participants were 136 individuals who received cognitive-behavioral therapies for co-occurring PTSD and SUD. Multivariate regressions were utilized to examine the associations between baseline cannabis use and end-of-treatment outcomes. Multilevel linear growth models were fit to the data to examine the cross-lagged associations between weekly cannabis use and weekly PTSD symptom severity and primary substance use during treatment. There were no significant positive nor negative associations between baseline cannabis use and end-of-treatment PTSD symptom severity and days of primary substance use. Cross-lagged models revealed that as cannabis use increased, subsequent primary substance use decreased and vice versa. Moreover, results revealed a crossover lagged effect, whereby higher cannabis use was associated with greater PTSD symptom severity early in treatment, but lower weekly PTSD symptom severity later in treatment. Cannabis use was not associated with adverse outcomes in end-of-treatment PTSD and primary substance use, suggesting independent pathways of change. The theoretical and clinical implications of the reciprocal associations between weekly cannabis use and subsequent PTSD and primary substance use symptoms during treatment are discussed.

**Guanfacine Alters The Effect Of Stress and Smoking On Heart Rate Variability In Regular Daily Smokers**

Verplaetse, Terril. L; Smith, Philip H.; Smith, Kathryn M. Z.; Oberleitner, Lindsay M.; McKee, Sherry A. *Psychopharmacology (Berl).* 2017; 234(5): 805-813.

The authors had previously demonstrated that guanfacine, an  $\alpha_2$ -adrenergic agonist, attenuated the effect of stress on smoking-lapse behavior in regular daily smokers. Heart rate variability (HRV), a measure of vagal activity, may be a potential mechanism underlying the relationship between stress,

smoking, and relapse. The authors examined whether guanfacine (0 mg/day vs. 3 mg/day; n = 26) altered changes in high-frequency heart rate variability (HF-HRV) following stress and ad-lib smoking using a validated laboratory analogue of smoking-lapse behavior. All participants completed a parent study evaluating the effects of guanfacine on stress-precipitated smoking. Each subject completed two laboratory sessions assessing the effects of guanfacine on HF-HRV following stress imagery (vs. neutral imagery; order counterbalanced) and smoking. Results demonstrated that guanfacine did not increase tonic levels of HF-HRV relative to placebo. Following the stress versus neutral imagery manipulation (prior to ad-lib smoking), there were no significant changes in HF-HRV in the placebo group. In contrast, guanfacine increased phasic HF-HRV following stress imagery and decreased HF-HRV following neutral imagery. Ad libitum smoking following both the stress and neutral conditions decreased HF-HRV in the placebo group across both imagery conditions. In contrast, guanfacine attenuated stress- and smoking-related decreases in phasic HF-HRV relative to the neutral imagery condition. This is the first demonstration that a noradrenergic target altered dynamic changes in HF-HRV in response to stress and smoking, suggesting that guanfacine alters HF-HRV response to stress. Findings support current theories which suggest that phasic changes in HRV are an important marker of the stress response.

**[Prescription Opioid Taper Support For Outpatients With Chronic Pain: A Randomized Controlled Trial](#)** Sullivan, Mark D; Turner, Judith A; DiLodovico, Cory; D'Appollonio, Angela; Stephens, Kari; Chan, Ya-Fen. *J Pain*. 2017; 18(3): 308-318.

Patients receiving long-term opioid therapy for chronic pain and interested in tapering their opioid dose were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N = 35). Assessments were conducted at baseline and 22 and 34 weeks after randomization. Using an intention to treat approach, the authors constructed linear regression models to compare groups at each follow-up. At 22 weeks, adjusted mean daily morphine-equivalent opioid dose in the past week (primary outcome) was lower in the taper support group, but this difference was not statistically significant (adjusted mean difference = -42.9 mg; 95% confidence interval, -92.42 to 6.62; P = .09). Pain severity ratings (0-10 numeric rating scale) decreased in both groups at 22 weeks, with no significant difference between groups (adjusted mean difference = -.68; 95% confidence interval, -2.01 to .64; P = .30). The taper support group improved significantly more than the usual care group in self-reported pain interference, pain self-efficacy, and prescription opioid problems at 22 weeks (all P-values < .05). This taper support intervention is feasible and shows promise in reducing opioid dose while not increasing pain severity or interference. In a pilot randomized trial comparing a prescription opioid taper support intervention to usual care, lower opioid doses and pain severity ratings were observed at 22 weeks in both groups. The groups did not differ significantly at 22 weeks in opioid dose or pain severity, but the taper support group improved significantly more in pain interference, pain self-efficacy, and perceived opioid problems. These results support the feasibility and promise of this opioid taper support intervention.

**[Long-Acting Injectable Naltrexone Induction: A Randomized Trial Of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine](#)** Sullivan, Maria; Bisaga, Adam; Pavlicova, Martina; Choi, C Jean; Mishlen, Kaitlyn; Carpenter, Kenneth M; Levin, Frances R; Dakwar, Elias; Mariani, John J; Nunes, Edward V. *Am J Psychiatry*. 2017.

At present there is no established optimal approach for transitioning opioid-dependent adults to extended-release injection naltrexone (XR-naltrexone) while preventing relapse. The authors

conducted a trial examining the efficacy of two methods of outpatient opioid detoxification for induction to XR-naltrexone. Participants were 150 opioid-dependent adults randomly assigned 2:1 to one of two outpatient detoxification regimens, naltrexone-assisted detoxification or buprenorphine-assisted detoxification, followed by an injection of XR-naltrexone. Naltrexone-assisted detoxification lasted 7 days and included a single day of buprenorphine followed by ascending doses of oral naltrexone along with clonidine and other adjunctive medications. Buprenorphine-assisted detoxification included a 7-day buprenorphine taper followed by a week-long delay before administration of XR-naltrexone, consistent with official prescribing information for XR-naltrexone. Participants from both groups received behavioral therapy focused on medication adherence and a second dose of XR-naltrexone. Compared with participants in the buprenorphine-assisted detoxification condition, participants assigned to naltrexone-assisted detoxification were significantly more likely to be successfully inducted to XR-naltrexone (56.1% compared with 32.7%) and to receive the second injection at week 5 (50.0% compared with 26.9%). Both models adjusted for primary type of opioid use, route of opioid administration, and morphine equivalents at baseline. These results demonstrate the safety, efficacy, and tolerability of low-dose naltrexone, in conjunction with single-day buprenorphine dosing and adjunctive nonopioid medications, for initiating adults with opioid dependence to XR-naltrexone. This strategy offers a promising alternative to the high rates of attrition and relapse currently observed with agonist tapers in both inpatient and outpatient settings.

**Maternal Buprenorphine Treatment and Fetal Neurobehavioral Development** Jansson, Lauren M; Velez, Martha; McConnell, Krystle; Spencer, Nancy; Tuten, Michelle; Jones, Hendree E; King, Van L; Gandotra, Neeraj; Milio, Lorraine A; Voegtline, Kristin; DiPietro, Janet A. *Am J Obstet Gynecol.* 2017.

Gestational opioid use/misuse is escalating in the United States, however, little is understood about the fetal effects of medications used to treat maternal opioid use disorders. The purpose of this study was to determine the effect of maternal buprenorphine administration on longitudinal fetal neurobehavioral development. Forty-nine buprenorphine-maintained women attending a substance use disorder treatment facility with generally uncomplicated pregnancies underwent fetal monitoring for 60 minutes at times of trough and peak maternal buprenorphine levels. Data were collected at 24, 28, 32, and 36 weeks gestation. Fetal neurobehavioral indicators (i.e., heart rate, motor activity and their integration (fetal movement-fetal heart rate coupling)) were collected via an actocardiograph, digitized and quantified. Longitudinal data analysis relied on hierarchical linear modeling. Fetal heart rate, heart rate variability and heart rate accelerations were significantly reduced at peak versus trough maternal buprenorphine levels. Effects were significant either by or after 28 weeks of gestation, and tended to intensify with advancing gestation. Fetal motor activity and fetal movement-fetal heart rate coupling were depressed from peak to trough at 36 weeks of gestation. Polysubstance-exposure did not significantly affect fetal neurobehavioral parameters, with the exception that fetuses of heavier smokers moved significantly less than those of lighter smokers at 36 weeks. By the end of gestation, higher maternal buprenorphine dose was related to depression of baseline fetal cardiac measures at trough. Maternal buprenorphine administration has acute suppressive effects on fetal heart rate and movement, and the magnitude of these effects increases as gestation progresses. Higher dose (> 13 mg) appears to exert greater depressive effects on measures of fetal heart rate and variability. These findings should be balanced against comparisons to gestational methadone effects, relatively good outcomes of buprenorphine-exposed infants, and recognition of the benefits of medication assisted treatment for pregnant women with opioid use disorders in optimizing pregnancy outcomes.

### **Pharmacokinetics and Safety Assessment Of L-Tetrahydropalmatine In Cocaine Users: A Randomized, Double-Blind, Placebo-Controlled Study**

Hassan, Hazem E; Kelly, Deanna; Honick, Moshe; Shukla, Sagar; Ibrahim, Ahmed; Gorelick, David A; Glassman, Matthew; McMahon, Robert P; Wehring, Heidi J; Kearns, Ann Marie; Feldman, Stephanie; Yu, Mingming; Bauer, Ken; Wang, Jia Bei. *J Clin Pharmacol.* 2017; 57(2): 151-160.

Cocaine use disorder (CUD) remains a significant public health challenge. l-Tetrahydro-palmatine (l-THP), a well-tolerated and nonaddictive compound, shows promise for the management of CUD. Its pharmacologic profile includes blockade at dopamine and other monoamine receptors and attenuation of cocaine self-administration, reinstatement, and rewarding properties in rats. This study evaluated the safety of l-THP in human cocaine users and its influence on the safety and pharmacokinetics (PK) of cocaine. Twenty-four cocaine-using adult men were randomized to receive l-THP (30 mg twice a day orally) or placebo double-blind for 4 days, with an intranasal cocaine (40 mg) challenge on the fourth day. Safety and tolerability were evaluated using vital signs, ECG, clinical laboratory tests, and standardized self-report instruments. Peripheral venous blood was collected periodically and later assayed for l-THP and cocaine using highly sensitive and specific ultraperformance liquid chromatography-fluorescence detection (UPLC-FLD) methods. Twenty subjects completed the study, of whom 19 provided complete PK data. The short 3.5-day course of l-THP was safe and well tolerated and did not affect cocaine's PK or its acute cardiovascular effects. The cocaine AUC<sub>0→∞</sub> was 211.5 and 261.4 h·ng/mL, and the C<sub>max</sub> was 83.3 and 104.5 ng/mL for the l-THP and placebo groups, respectively. In addition there were no significant differences in the number of side effects reported in each group (l-THP group 22 [48%], placebo group 24 [52%]) or vital signs including, heart rate, blood pressure, complete blood count, or ECG. These findings suggest that oral THP has promise for further development as a treatment for CUD.

### **A Nanoparticle-based Nicotine Vaccine and The Influence Of Particle Size On Its Immunogenicity and Efficacy**

Zhao, Zongmin; Hu, Yun; Hoerle, Reece; Devine, Meaghan; Raleigh, Michael; Pentel, Paul; Zhang, Chenming. *Nanomedicine.* 2017; 13(2): 443-454.

Traditional haptent-protein conjugate nicotine vaccines have shown less than desired immunological efficacy due to their poor recognition and internalization by immune cells. The authors developed a novel lipid-polymeric hybrid nanoparticle-based nicotine vaccine to enhance the immunogenicity of the conjugate vaccine, and studied the influence of particle size on its immunogenicity and pharmacokinetic efficacy. The results demonstrated that the nanovaccines, regardless of size, could induce a significantly stronger immune response against nicotine compared to the conjugate vaccine. Particularly, a significantly higher anti-nicotine antibody titer was achieved by the 100 compared to the 500nm nanovaccine. In addition, both the 100 and 500nm nanovaccines reduced the distribution of nicotine into the brain significantly. The 100nm nanovaccine exhibited better pharmacokinetic efficacy than the 500nm nanovaccine in the presence of alum adjuvant. These results suggest that a lipid-polymeric nanoparticle-based nicotine vaccine is a promising candidate to treat nicotine dependence.

### **Role Of TAAR1 Within The Subregions Of The Mesocorticolimbic Dopaminergic System In Cocaine-Seeking Behavior**

Liu, Jian-Feng; Siemian, Justin N; Seaman Jr, Robert; Zhang, Yanan; Li, Jun-Xu. *J Neurosci.* 2017; 37(4): 882-892.

A novel G-protein coupled receptor, trace amine-associated receptor 1 (TAAR1), has been shown to be a promising target to prevent stimulant relapse. The authors' recent studies showed that systemic administration of TAAR1 agonists decreased abuse-related behaviors of cocaine. However, the role of TAAR1 in specific subregions of the reward system in drug addiction is unknown. Here, using a

local pharmacological activation method, they assessed the role of TAAR1 within the subregions of the mesocorticolimbic system: that is, the VTA, the prelimbic cortex (PrL), and infralimbic cortex of medial prefrontal cortex, the core and shell of NAc, BLA, and CeA, on cue- and drug-induced cocaine-seeking in the rat cocaine reinstatement model. The authors first showed that TAAR1 mRNA was expressed throughout these brain regions. Rats underwent cocaine self-administration, followed by extinction training. RO5166017 (1.5 or 5.0 µg/side) or vehicle was microinjected into each brain region immediately before cue- and drug-induced reinstatement of cocaine-seeking. The results showed that microinjection of RO5166017 into the VTA and PrL decreased both cue- and drug priming-induced cocaine-seeking. Microinjection of RO5166017 into the NAc core and shell inhibited cue- and drug-induced cocaine-seeking, respectively. Locomotor activity or food reinforced operant responding was unaffected by microinjection of RO5166017 into these brain regions. Cocaine-seeking behaviors were not affected by RO5166017 when microinjected into the substantia nigra, infralimbic cortex, BLA, and CeA. Together, these results indicate that TAAR1 in different subregions of the mesocorticolimbic system distinctly contributes to cue- and drug-induced reinstatement of cocaine-seeking behavior. TAAR1 has been indicated as a modulator of the dopaminergic system. Previous research showed that systemic administration of TAAR1 agonists could attenuate cocaine-related behaviors, suggesting that TAAR1 may be a promising drug target for the treatment of cocaine addiction. However, the specific role of TAAR1 in subregions of the mesocorticolimbic system in drug addiction is unknown. Here, we first showed that TAAR1 mRNA is expressed throughout the subregions of the mesocorticolimbic system. Then, by using a local pharmacological activation method, we demonstrated that TAAR1 in different subregions of the mesocorticolimbic system distinctly contributes to cue- and drug-induced reinstatement of cocaine-seeking behavior.

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

### **Cocaine Enhances DC to T-cell HIV-1 Transmission by Activating DC-SIGN/LARG/LSP1 Complex and Facilitating Infectious Synapse Formation**

Prasad, Anil; Kulkarni, Rutuja; Jiang, Shuxian; Groopman, Jerome E. *Scientific Reports* 2017; 7:40648. DOI: 10.1038/srep40648. DC-SIGN is a dendritic cell surface structure which participates in binding and transmission of HIV-1. Here, for the first time the authors demonstrate that cocaine induces over expression of DC-SIGN and significantly enhances virus transfer from DCs to T-cells by increasing the binding and internalization of HIV-1 in DCs. They found that cocaine activates a DC-SIGN mediated 'signalosome' complex by enhancing its association with LARG and LSP1. Further, LARG was observed to participate in DC-SIGN mediated internalization of HIV-1 in DCs. Intracellular trafficking studies of HIV-1 in cocaine treated DCs revealed increased co-localization of HIV-1 with endosomal or multi vesicular body (MVB) markers such as CD81 and VPS4 and decreased co-localization with the phagolysosomal marker LAMP1; this signified altered intracellular trafficking and decreased degradation of HIV-1 in cocaine treated DCs. Furthermore, the authors found that cocaine induced activation of LARG which in turn activated Rho A and the focal adhesion molecules FAK, Pyk2 and paxillin. This signaling cascade enhanced the formation of an infectious synapse between DCs and T-cells. This study provides insight into the molecular mechanisms of cocaine's contribution to key components in HIV pathogenesis and highlights novel targets for interrupting the virus life cycle in substance using hosts.

### **Getting To 90: Linkage To HIV Care Among Men Who Have Sex With Men and People Who Inject Drugs In India**

McFall, Allison M.; Mehtaa, Shruti H.; Srikrishnanb, Aylur K.; Lucasc, Gregory M.; Vasudevanb, Canjeevaram K.; Celentanoa, David D.; Kumarb, Muniratnam S.; Solomona, Suniti; Solomona, Sunil S. *AIDS Care*. 2016; 28(10): 1230–1239. doi:10.1080/09540121.2016.1168915.

UNAIDS set an ambitious target of “90-90-90” by 2020. The first 90 being 90% of those HIV-infected will be diagnosed; the second 90 being 90% of those diagnosed will be linked to medical care and on antiretroviral therapy (ART). While there has been dramatic improvement in HIV testing and ART use, substantial losses continue to occur at linkage-to-care following HIV diagnosis. Data on linkage among men who have sex with men (MSM) and people who inject drugs (PWID) are sparse, despite a greater burden of HIV in these populations. This cross-sectional study was conducted in 27 sites across India. Participants were recruited using respondent-driven sampling and had to be  $\geq 18$  years and self-identify as male and report sex with a man in the prior year (MSM) or injection drug use in the prior 2 years (PWID). Analyses were restricted to HIV-infected persons aware of their status. Linkage was defined as ever visiting a doctor for management of HIV after diagnosis. The authors explored factors that discriminated between those linked and not linked to care using multi-level logistic regression and area under the receiver operating curves (AUC), focusing on modifiable factors. Of 1726 HIV-infected persons aware of their status, 80% were linked to care. Modifiable factors around the time of diagnosis that best discriminated linkage included receiving assistance with HIV medical care (odds ratio [OR]: 10.0, 95% confidence interval [CI]: 5.6–18.2), disclosure of HIV-positive status (OR: 2.8; 95% CI: 2.4–6.1) and receiving information and counseling on management of HIV (OR: 2.3; 95% CI: 1.1–4.6). The AUC for these three factors together was 0.85, higher than other combinations of factors. The authors identified three simple modifiable factors around the time of diagnosis that could facilitate.

### **Peptide Targeted by Human Antibodies Associated with HIV Vaccine-Associated Protection Assumes a Dynamic $\alpha$ -Helical Structure**

Aiyegbo, Mohammed S.; Shmelkov, Evgeny; Dominguez, Lorenzo; Goger, Michael; Battacharya, Shibani; deCamp, Allan C.; Gilbert, Peter B.; Berman, Phillip W.; Cardozo, Timothy. *PLOS ONE* DOI:10.1371/journal.pone.0170530 January 20, 2017.

The only evidence of vaccine-induced protection from HIV acquisition in humans was obtained in the RV144 HIV vaccine clinical trial. One immune correlate of risk in RV144 was observed to be higher titers of vaccine-induced antibodies (Abs) reacting with a 23-mer non-glycosylated peptide with the same amino acid sequence as a segment in the second variable (V2) loop of the MN strain of HIV. The authors used NMR to analyze the dynamic 3D structure of this peptide. Distance restraints between spatially proximate inter-residue protons were calculated from NOE cross peak intensities and used to constrain a thorough search of all possible conformations of the peptide.  $\alpha$ -helical folding was strongly preferred by part of the peptide. A high-throughput structure prediction of this segment in all circulating HIV strains demonstrated that  $\alpha$ -helical conformations are preferred by this segment almost universally across all subtypes. Notably,  $\alpha$ -helical conformations of this segment of the V2 loop cluster cross-subtype-conserved amino acids on one face of the helix and the variable amino acid positions on the other in a semblance of an amphipathic  $\alpha$ -helix. Accordingly, some Abs that protected against HIV in RV144 may have targeted a specific, conserved  $\alpha$ -helical peptide epitope in the V2 loop of HIV's surface envelope glycoprotein.

### **Immortalization Of Primary Microglia: A New Platform To Study HIV Regulation In The Central Nervous System**

Garcia-Mesa, Yoelvis; Jay, Taylor R.; Checkley, Mary Ann; Lutge, Benjamin; Dobrowolski, Curtis; Valadkhan, Saba; Landreth, Gary E.; Karn, Jonathan; Alvarez-Carbonell, David. J. Neurovirol. 2017; 23:47–66. DOI 10.1007/s13365-016-0499-3

The major reservoirs for HIV in the CNS are in the microglia, perivascular macrophages, and to a lesser extent, astrocytes. To study the molecular events controlling HIV expression in the microglia, the authors developed a reliable and robust method to immortalize microglial cells from primary glia from fresh CNS tissues and commercially available frozen glial cells. Primary human cells, including cells obtained from adult brain tissue, were transformed with lentiviral vectors expressing SV40 T antigen or a combination of SV40 T antigen and hTERT. The immortalized cells have microgliallike morphology and express key microglial surface markers including CD11b, TGF $\beta$ R, and P2RY12. Importantly, these cells were confirmed to be of human origin by sequencing. The RNA expression profiles identified by RNA-seq are also characteristic of microglial cells. Furthermore, the cells demonstrate the expected migratory and phagocytic activity, and the capacity to mount an inflammatory response characteristic of primary microglia. The immortalization method has also been successfully applied to a wide range of microglia from other species (macaque, rat, and mouse). To investigate different aspects of HIV molecular regulation in CNS, the cells have been superinfected with HIV reporter viruses and latently infected clones have been selected that reactive HIV in response to inflammatory signals. The cell lines the authors have developed and rigorously characterized will provide an invaluable resource for the study of HIV infection in microglial cells as well as studies of microglial cell function.

### **Willingness To Use A Supervised Injection Facility Among Young Adults Who Use Prescription Opioids Non-Medically: A Crosssectional Study**

Bouvier, Benjamin A.; Elston, Beth; Hadland, Scott E.; Green, Traci C; Marshall, Brandon D. L. Harm Reduction Journal 2017; 14:13 DOI 10.1186/s12954-017-0139-0

Supervised injection facilities (SIFs) are legally sanctioned environments for people to inject drugs under medical supervision. SIFs currently operate in ten countries, but to date, no SIF has been opened in the USA. In light of increasing overdose mortality in the USA, this study evaluated willingness to use a SIF among youth who report non-medical prescription opioid (NMPO) use. Between January 2015 and February 2016, youth with recent NMPO use were recruited to participate in the Rhode Island Young Adult Prescription Drug Study (RAPiDS). The authors explored factors associated with willingness to use a SIF among participants who had injected drugs or were at risk of initiating injection drug use (defined as having a sex partner who injects drugs or having a close friend who injects). Among 54 eligible participants, the median age was 26 (IQR = 24–28), 70.4% were male, and 74.1% were white. Among all participants, when asked if they would use a SIF, 63.0% answered “Yes”, 31.5% answered “No”, and 5.6% were unsure. Among the 31 participants reporting injection drug use in the last six months, 27 (87.1%) reported willingness to use a SIF; 15 of the 19 (78.9%) who injected less than daily reported willingness, while all 12 (100.0%) of the participants who injected daily reported willingness. Compared to participants who were unwilling or were unsure, participants willing to use a SIF were also more likely to have been homeless in the last six months, have accidentally overdosed, have used heroin, have used fentanyl non-medically, and typically use prescription opioids alone. Among young adults who use prescription opioids non-medically and inject drugs or are at risk of initiating injection drug use, more than six in ten reported willingness to use a SIF. Established risk factors for overdose, including homelessness, history of overdose, daily injection drug use, heroin use, and fentanyl misuse, were associated with higher

SIF acceptability, indicating that young people at the highest risk of overdose might ultimately be the same individuals to use the facility. Supervised injection facilities merit consideration to reduce overdose mortality in the USA.

**Phylogenetic Analysis Of Full-length, Early Infection, Hepatitis C Virus Genomes Among People With Intravenous Drug Use: The InC(3) Study**

Rodrigo, C; Eltahla, A A; Bull, R A; Luciani, F; Grebely, J; Dore, G J; Applegate, T; Page, K; Bruneau, J; Morris, M D; Cox, A L; Osburn, W; Kim, A Y; Shoukry, N H; Lauer, G M; Maher, L; Schinkel, J; Prins, M; Hellard, M; Lloyd, A R; InC3 Collaborative. *J Viral Hepat.* 2017; 24(1): 43-52.

Cross-continental phylogenetic analysis is important to understand subtle molecular differences of currently circulating hepatitis C virus (HCV) subtypes. Existence of such differences can be crucial in pursuing a universal hepatitis C vaccine. The authors characterized molecular epidemiology of early HCV infections identified across nine cohorts [North America (n=4), Australia (n=4) and Europe (n=1)] in the International Collaborative of Incident HIV and Hepatitis C in Injecting Cohorts (InC(3)). One hundred and ninety-two full-length HCV genomes were amplified from plasma of incident infections and subjected to next generation sequencing to establish the largest cross-continental, full-length acute HCV genomic data set available to date. Genomes from the most common subtypes (1a: n=94, 2b: n=15 and 3a: n=68) were used in phylogenetic analysis. Using full genome trees, 78 sequences (44%) were found to lie within 29 phylogenetic clusters/pairs defined on the basis of molecular similarity of consensus sequences. Of these, 26 each had exclusively Australian or North American sequences indicating a strong geographical bias for molecular similarity. On further analysis of behavioural and demographic associations, binary logistic regression analysis showed that older age and non-Caucasian ethnicity were significantly associated with clustering. HCV probably evolves in micro-epidemics within geographically isolated communities.

**Higher Incidence Of HCV In Females Compared To Males Who Inject Drugs: A Systematic Review and Meta-analysis**

Esmaili, A; Mirzazadeh, A; Carter, G M; Esmaili, A; Hajarizadeh, B; Sacks, H S; Page, K A. *J Viral Hepat.* 2017; 24(2): 117-127.

Women who inject drugs have been shown to have higher incidence of HIV and risk behaviours than men, but there are conflicting reports about hepatitis C virus (HCV) incidence. The authors systematically reviewed the literature to examine the female-to-male (F:M) HCV incidence in female and male persons who inject drugs (PWID), and also to explore the heterogeneity (i.e. methodological diversity) in these differences. They searched PubMed and EMBASE for studies published between 1989 and March 2015 for research that reported incidence of HCV infection by sex or HCV incidence F:M rate ratio. A total of 28 studies, which enrolled 9325 PWID, were included. The overall pooled HCV incidence rate (per 100 person-years observation) was 20.36 (95% CI: 13.86, 29.90) and 15.20 (95% CI: 10.52, 21.97) in females and males, respectively. F:M ratio was 1.36:1 (95% CI: 1.13, 1.64) with substantial heterogeneity (I-squared=71.6%). The F:M ratio varied by geographic location from 4.0 (95% CI: 1.80, 8.89) in China to 1.17 (95% CI: 0.95, 1.43) in the U.S. In studies which recruited participants from community settings, the F:M ratio was 1.24 (95% CI: 1.03, 1.48), which was lower than that reported in the clinical settings (1.72, 95% CI: 0.86, 3.45). The number of studies included provided sufficient statistical power to detect sex differences in this analysis. These findings raise questions and concerns regarding sex differences with respect to the risk of HCV. Both behavioural and biological studies are needed to investigate causes and potential mechanisms as well as sex-specific prevention approaches to HCV infection.

### **White Matter Abnormalities In Long-term Anabolic-androgenic Steroid Users: A Pilot Study**

Seitz, Johanna; Lyall, Amanda E; Kanayama, Gen; Makris, Nikos; Hudson, James I; Kubicki, Marek; Pope Jr, Harrison G; Kaufman, Marc J. *Psychiatry Res.* 2017; 260: 1-5.

Recent studies of long-term anabolic-androgenic steroid (AAS) users reported amygdala structural and functional connectivity abnormalities. The authors assessed white matter microstructure in the inferior-fronto-occipital fasciculus (IFOF), a major associative bundle of the amygdala network. Diffusion weighted images acquired from 9 male long-term AAS users and 8 matched controls aged 36-51 years old were processed using a standardized pipeline (Tract-Based Spatial Statistics). Group differences were examined using linear regression with adjustment for age and current testosterone level. Compared to nonusers, AAS users exhibited significantly higher fractional anisotropy (FA) in the IFOF. Users showed markedly greater FA than nonusers on the left IFOF but only a modest, nonsignificant difference on the right IFOF. Moreover, FA was positively associated with lifetime cumulative AAS dose. The authors' results suggest that long-term AAS use alters IFOF white matter organization and integrity, which in turn might affect amygdala-related processes such as reward system function. Accordingly, further studies are needed to replicate findings in larger subject groups to determine the functional significance of the FA abnormality.

### **Failure To Get Into Substance Abuse Treatment** Fisher, Dennis G; Reynolds, Grace L; D'Anna, Laura H; Hosmer, David W; Hardan-Khalil, Kholoud. *J Subst Abuse Treat.* 2017; 73: 55-62.

Among substance abusers in the US, the discrepancy in the number who access substance abuse treatment and the number who need treatment is sizable. This results in a major public health problem of access to treatment. The purpose of this study was to examine characteristics of Persons Who Use Drugs (PWUDs) that either hinder or facilitate access to treatment. 2646 participants were administered the Risk Behavior Assessment (RBA) and the Barratt Impulsiveness Scale. The RBA included the dependent variable which was responses to the question "During the last year, have you ever tried, but been unable, to get into a drug treatment or detox program?" In multivariate analysis, factors associated with being unable to access treatment included: Previously been in drug treatment (OR=4.51), number of days taken amphetamines in the last 30days (OR=1.18), traded sex for drugs (OR=1.53), homeless (OR=1.73), Nonplanning subscale of the Barratt Impulsiveness Scale (OR=1.19), age at interview (OR=0.91), and sexual orientation, with bisexual men and women significantly more likely than heterosexuals to have tried but been unable to get into treatment. The answers to the question on "why were you unable to get into treatment" included: No room, waiting list; not enough money, did not qualify, got appointment but no follow through, still using drugs, and went to jail before program start. As expected, findings suggest that limiting organizational and financial obstacles to treatment may go a long way in increasing drug abuse treatment accessibility to individuals in need. Additionally, this study points to the importance of developing approaches for increasing personal planning skills/reducing Nonplanning impulsivity among PWUDs when they are in treatment as a key strategy to ensure access to additional substance abuse treatment in the future.

### **Higher Prevalence Of Detectable Troponin I Among Cocaine-users Without Known Cardiovascular Disease** Riley, Elise D; Hsue, Priscilla Y; Vittinghoff, Eric; Wu, Alan H B; Coffin, Phillip O; Moore, Peter K; Lynch, Kara L. *Drug Alcohol Depend.* 2017; 172: 88-93.

While cocaine use is an established risk factor for acute cardiovascular complications, associations between cocaine use and markers of cardiac injury outside of acute hospital presentation remain poorly characterized. The authors leveraged advances in cardiac troponin (cTnI) testing to assess low but clinically meaningful levels of cardiac injury among cocaine users and non-users. They conducted a case control study comparing cTnI levels by the presence of cocaine among patients

presenting for non-cardiac care in an urban safety net hospital. Samples were chosen sequentially among those for which urine drug screens were ordered by providers hospital-wide. During 2015, 14% of all hospital drug screens ordered were cocaine-positive. Among unique persons providing cocaine-positive (N=100) and cocaine-negative (N=100) samples, 37% were female, 45% were African-American and the median age was 51. Detectable cTnI (> 0.02ng/mL) was observed in 21 samples (11%). It was more common in subjects using cocaine (Adjusted OR=2.81; 95% CI=1.03-7.65), but not other drugs. Moreover, there was a significant correlation between concentrations of cTnI and the cocaine metabolite, benzoylecgonine (Spearman Correlation=0.34, p<0.01). Among urban safety net hospital patients, 11% had detectable cTnI, and cTnI concentration was significantly correlated with benzoylecgonine concentration. While these preliminary results require additional confirmation, they suggest the potential utility of considering cocaine use as more than just an episodic exposure leading to acute cardiac events. The consideration of cocaine use as an ongoing chronic exposure leading to subclinical cardiac injury may improve risk-stratification and patient outcomes in populations where cocaine use is high.

## **SERVICES RESEARCH**

**[Demographic Trends Among Older Cannabis Users In The United States, 2006-13](#)** Han, Benjamin H; Sherman, Scott; Mauro, Pia M; Martins, Silvia S; Rotenberg, James; Palamar, Joseph J. *Addiction*. 2017; 112(3): 516-525.

The ageing US population is providing an unprecedented population of older adults who use recreational drugs. The authors aimed to estimate the trends in the prevalence of past-year use of cannabis, describe the patterns and attitudes and determine correlates of cannabis use by adults age 50 years and older. This was a secondary analysis of the National Survey on Drug Use and Health survey from 2006 to 2013, a cross-sectional survey given to a nationally representative probability sample of populations living in US households. A total of 47,140 survey respondents aged  $\geq 50$  years. Estimates and trends of past-year use of cannabis. The prevalence of past-year cannabis use among adults aged  $\geq 50$  increased significantly from 2006/07 to 2012/13, with a 57.8% relative increase for adults aged 50-64 (linear trend  $P < 0.001$ ) and a 250% relative increase for those aged  $\geq 65$  (linear trend  $P = 0.002$ ). When combining data from 2006 to 2013, 6.9% of older cannabis users met criteria for cannabis abuse or dependence, and the majority of the sample reported perceiving no risk or slight risk associated with monthly cannabis use (85.3%) or weekly use (79%). Past-year users were more likely to be younger, male, non-Hispanic, not have multiple chronic conditions and use tobacco, alcohol or other drugs compared with non-past-year cannabis users. The prevalence of cannabis use has increased significantly in recent years among US adults aged  $\geq 50$  years.

**[Criminally Involved Parents Who Misuse Substances and Children's Odds Of Being Arrested As A Young Adult: Do Drug Treatment Courts Mitigate The Risk?](#)** Gifford, Elizabeth J;

Eldred, Lindsey M; Evans, Kelly E; Sloan, Frank A. *J Child Fam Stud*. 2016; 25(8): 2447-2457.

This paper examined (1) the association between parents who are convicted of a substance-related offense and their children's probability of being arrested as a young adult and (2) whether or not parental participation in an adult drug treatment court program mitigated this risk. The analysis relied on state administrative data from North Carolina courts (2005-2013) and from birth records (1988-2003). The dependent variable was the probability that a child was arrested as a young adult (16-21). Logistic regression was used to compare groups and models accounted for the clustering of

multiple children with the same mother. Findings revealed that children whose parents were convicted on either a substance-related charge or a non-substance-related charge had twice the odds of being arrested as young adults, relative to children whose parents had not been observed having a conviction. While a quarter of children whose parents participated in a drug treatment court program were arrested as young adults, parental completion of this program did not reduce this risk. In conclusion, children whose parents were convicted had an increased risk of being arrested as young adults, irrespective of whether or not the conviction was on a substance-related charge. However, drug treatment courts did not reduce this risk. Reducing intergenerational links in the probability of arrest remains a societal challenge.

**[The Costs Of Crime During and After Publicly-funded Treatment For Opioid Use Disorders: A Population-level Study For The State Of California](#)** Krebs, Emanuel; Urada, Darren; Evans, Elizabeth; Huang, David; Hser, Yih-Ing; Nosyk, Bohdan. *Addiction*. 2016; Dec. 15

Treatment for opioid use disorders (OUD) reduces the risk of mortality and infectious disease transmission; however, opportunities to quantify the potential economic benefits of associated decreases in drug-related crime are scarce. This paper aimed to estimate the costs of crime during and after periods of engagement in publicly-funded treatment for OUD to compare total costs of crime over a hypothetical 6-month period following initiation of opioid agonist treatment (OAT) versus detoxification. Retrospective, administrative data-based cohort study with comprehensive information on drug treatment and criminal justice systems interactions. Publicly-funded drug treatment facilities in California, USA (2006-2010). 31,659 individuals admitted for the first time to treatment for OUD, and who were linked with criminal justice and mortality data, were followed during a median 2.3 years. Median age at first treatment admission was 32, 35.8% were women, and 37.1% primarily used prescription opioids. Daily costs of crime (2014\$US) were calculated from a societal perspective and were composed of the costs of policing, court, corrections, and criminal victimization. The authors estimated the average marginal effect of treatment engagement in OAT or detoxification adjusting for potential fixed and time-varying confounders, including drug use and criminal justice system involvement prior to treatment initiation. Daily costs of crime during treatment compared with after treatment were \$126 lower for OAT (95% CI: \$116, \$136) and \$144 lower for detoxification (\$135, \$154). Summing the costs of crime during and after treatment over a hypothetical 6-month period using the observed median durations of OAT (161 days) and detoxification (19 days), the authors estimated that enrolling an individual in OAT as opposed to detoxification would save \$17,550 (\$16,840, \$18,383). In publicly-funded drug treatment facilities in California USA, engagement in treatment for opioid use disorders is associated with lower costs of crime in the six months following initiation of treatment, and the economic benefits were far greater for individuals receiving time-unlimited treatment.

**CTN-RELATED RESEARCH**

**[Feasibility and Safety of Extended-Release Naltrexone Treatment of Opioid and Alcohol Use Disorder in HIV Clinics: A Pilot/Feasibility Randomized Trial](#)** Korthuis PT, Lum PJ, Vergara-

Rodriguez P, Ahamad K, Wood E, Kunkel LE, Oden NL, Lindblad R, Sorensen JL, Arenas V, Ha D, Mandler RN, McCarty D; CTN-0055 CHOICES Investigators. *Addiction*. 2017 Jan 6. doi: 10.1111/add.13753. [Epub ahead of print].

HIV-infected persons with substance use disorders are least likely to benefit from advances in HIV treatment. Integration of extended-release naltrexone (XR-NTX) into HIV clinics may increase engagement in the HIV care continuum by decreasing substance use. The authors aimed to compare

1) XR-NTX treatment initiation, 2) retention, and 3) safety of XR-NTX versus treatment as usual (TAU) for treating opioid use disorder (OUD) and/or alcohol use disorder (AUD) in HIV clinics. This was a non-blinded randomized trial of XR-NTX versus pharmacotherapy carried out in HIV primary care clinics in Vancouver, BC, Canada and Chicago, IL, USA. Participants were 51 HIV-infected patients seeking treatment for OUD (n = 16), AUD (n = 27) or both OUD and AUD (n = 8). Primary outcomes were XR-NTX initiation (receipt of first injection within 4 weeks of randomization) and retention at 16 weeks. Secondary outcomes generated point estimates for change in substance use, HIV viral suppression (HIV RNA per < 200 copies/mL), and safety. Two-thirds (68%) of participants assigned to XR-NTX initiated treatment, and 88% of these were retained on XR-NTX at 16 weeks. In comparison, 96% of TAU participants initiated treatment, but only 50% were retained on medication at 16 weeks. Mean days of opioid use in past 30 days decreased from 19 to 10 for TAU (n = 12) and from 18 to 13 for XR-NTX (n = 10). Mean heavy drinking days decreased from 18 to 7 for TAU (n = 11) and 13 to 6 for XR-NTX (n = 12). Among those with OUD, HIV suppression improved from 67% to 80% for XR-NTX and 58% to 75% for TAU. XR-NTX was well-tolerated, with no precipitated withdrawals and 1 serious injection site reaction. The authors conclude that extended-release naltrexone (XR-NTX) is feasible and safe for treatment of opioid use disorder and alcohol use disorder in HIV clinics. Treatment initiation appears to be lower and retention greater for XR-NTX compared with treatment as usual. (clinicaltrials.gov [NCT01908062](https://clinicaltrials.gov/ct2/show/study/NCT01908062)).

**[Randomized Controlled Trial Comparing Exercise to Health Education for Stimulant Use Disorder: Results From the CTN-0037 STimulant Reduction Intervention Using Dosed Exercise \(STRIDE\) Study](#)**

Trivedi MH, Greer TL, Rethorst CD, Carmody T, Grannemann BD, Walker R, Warden D, Shores-Wilson K, Stoutenberg M, Oden N, Silverstein M, Hodgkins C, Love L, Seamans C, Stotts A, Causey T, Szucs-Reed RP, Rinaldi P, Myrick H, Straus M, Liu D, Lindblad R, Church T, Blair SN, Nunes EV. J Clin Psychiatry. 2017 Feb 14. doi: 10.4088/JCP.15m10591. [Epub ahead of print].

The objective of this study was to evaluate exercise as a treatment for stimulant use disorders. The STimulant Reduction Intervention using Dosed Exercise (STRIDE) study was a randomized clinical trial conducted in 9 residential addiction treatment programs across the United States from July 2010 to February 2013. Of 497 adults referred to the study, 302 met all eligibility criteria, including DSM-IV criteria for stimulant abuse and/or dependence, and were randomized to either a dosed exercise intervention (Exercise) or a health education intervention (Health Education) control, both augmenting treatment as usual and conducted thrice weekly for 12 weeks. The primary outcome of percent stimulant abstinent days during study weeks 4 to 12 was estimated using a novel algorithm adjustment incorporating self-reported Timeline Followback (TLFB) stimulant use and urine drug screen (UDS) data. Mean percent of abstinent days based on TLFB was 90.8% (SD = 16.4%) for Exercise and 91.6% (SD = 14.7%) for Health Education participants. Percent of abstinent days using the eliminate contradiction (ELCON) algorithm was 75.6% (SD = 27.4%) for Exercise and 77.3% (SD = 25.1%) for Health Education. The primary intent-to-treat analysis, using a mixed model controlling for site and the ELCON algorithm, produced no treatment effect (P = .60). In post hoc analyses controlling for treatment adherence and baseline stimulant use, Exercise participants had a 4.8% higher abstinence rate (78.7%) compared to Health Education participants (73.9%) (P = .03, number needed to treat = 7.2).

The primary analysis indicated no significant difference between exercise and health education. Adjustment for intervention adherence showed modestly but significantly higher percent of abstinent days in the exercise group, suggesting that exercise may improve outcomes for stimulant

users who have better adherence to an exercise dose. TRIAL REGISTRATION: ClinicalTrials.gov identifier: [NCT01141608](https://clinicaltrials.gov/ct2/show/study/NCT01141608).

### **Identifying Substance Misuse in Primary Care: TAPS Tool Compared to the WHO ASSIST**

Schwartz RP, McNeely J, Wu LT, Sharma G, Wahle A, Cushing C, Nordeck CD, Sharma A, O'Grady KE, Gryczynski J, Mitchell SG, Ali RL, Marsden J, Subramaniam GA. *J Subst Abuse Treat.* 2017 May;76:69-76. doi: 10.1016/j.jsat.2017.01.013. Epub 2017 Jan 31.

There is a need for screening and brief assessment instruments to identify primary care patients with substance use problems. This study's aim was to examine the performance of a two-step screening and brief assessment instrument, the TAPS Tool, compared to the WHO ASSIST.

Two thousand adult primary care patients recruited from five primary care clinics in four Eastern US states completed the TAPS Tool followed by the ASSIST. The ability of the TAPS Tool to identify moderate- and high-risk use scores on the ASSIST was examined using sensitivity and specificity analyses. The interviewer and self-administered computer tablet versions of the TAPS Tool generated similar results. The interviewer-administered version (at cut-off of 2), had acceptable sensitivity and specificity for high-risk tobacco (0.90 and 0.77) and alcohol (0.87 and 0.80) use. For illicit drugs, sensitivities were >0.82 and specificities >0.92. The TAPS (at a cut-off of 1) had good sensitivity and specificity for moderate-risk tobacco use (0.83 and 0.97) and alcohol (0.83 and 0.74). Among illicit drugs, sensitivity was acceptable for moderate-risk of marijuana (0.71), while it was low for all other illicit drugs and non-medical use of prescription medications. Specificities were 0.97 or higher for all illicit drugs and prescription medications.

The TAPS Tool identified adult primary care patients with high-risk ASSIST scores for all substances as well moderate-risk users of tobacco, alcohol, and marijuana, although it did not perform well in identifying patients with moderate-risk use of other drugs or non-medical use of prescription medications. The advantages of the TAPS Tool over the ASSIST are its more limited number of items and focus solely on substance use in the past 3months.

### **Chronic Pain Among Patients With Opioid Use Disorder: Results From Electronic Health Records Data**

Hser YI, Mooney LJ, Saxon AJ, Miotto K, Bell DS, Huang D. *J Subst Abuse Treat.* 2017 Mar;77:26-30 (published online March 9, 2017).

The purpose of this study was to examine the prevalence of comorbid chronic pain among patients with opioid use disorder (OUD) and to compare other comorbidities (substance use disorder (SUD), mental health disorders, health/disease conditions) among patients in four categories: no chronic pain (No Pain), OUD prior to pain (OUD First), OUD and pain at the same time (Same Time), or pain condition prior to OUD (Pain First). Using an electronic health record (EHR) database from 2006–2015, the study assessed 5307 adult patients with OUD in a large healthcare system; 35.6% were No Pain, 9.7% were OUD First, 14.9% were Same Time, and 39.8% were Pain First. Most OUD patients (64.4%) had chronic pain conditions, and among them 61.8% had chronic pain before their first OUD diagnosis. Other SUDs occurred more frequently among OUD First patients than among other groups in terms of alcohol (33.4% vs. 25.4% for No Pain, 20.7% for Same Time, and 20.3% for Pain First), cocaine (19.0%, vs. 13.8%, 9.4%, 7.1%), and alcohol or drug-induced disorders. OUD First patients also had the highest rates of HIV (4.7%) and hepatitis C virus (HCV; 28.2%) among the four groups. Pain First patients had the highest rates of mental disorder (81.7%), heart disease (72.0%), respiratory disease (68.4%), sleep disorder (41.8%), cancer (23.4%), and diabetes (19.3%). The authors conclude that the alarming high rates of chronic pain conditions occurring before OUD and the associated severe mental health and physical health conditions require better models of assessment and coordinated care plans to address these complex medical conditions.

**Distinctive Trajectories of Opioid Use Over an Extended Follow-up of Patients in a Multisite Trial on Buprenorphine+Naloxone and Methadone**

Hser YI, Huang D, Saxon AJ, Woody G, Moskowitz AL, Matthews AG, Ling W. *J Addict Med.* 2017 Jan/Feb;11(1):63-69. doi: 10.1097/ADM.0000000000000274.

Uncovering heterogeneities in longitudinal patterns (trajectories) of opioid use among individuals with opioid use disorder can increase our understanding of disease progression and treatment responses to improve care. The present study aims to identify distinctive opioid use trajectories and factors associated with these patterns among participants randomized to treatment with methadone (MET) or buprenorphine+naloxone (BUP). Growth mixture modeling was applied to identify distinctive opioid use trajectories among 795 opioid users after their enrollment in a multisite trial during 2006 to 2009, with follow-up interviews conducted during 2011 to 2014. Four distinctive trajectories were identified based on opioid use over the follow-up period: low use (42.0%), high use (22.3%), increasing use (17.1%), and decreasing use (18.6%). Greater odds of being in the high use group (relative to low use) was associated with Hispanics (relative to African American, odds ratio [OR] 3.21), injection drug use (OR 2.12), higher mental health functioning at baseline (OR 1.23), location on the West Coast (vs East Coast, OR 2.15), and randomization to BUP (relative to MET, OR 1.53). High use and increasing use groups had greater severity in problems related to drug, employment, legal, and social/family relationships, and worsened mental health functioning at follow-up. Participation in treatment significantly accounted for both within and between-group differences in opioid use. The authors conclude that continued treatment is necessary to reduce risk for opioid use and related adverse consequences, particularly among individuals (eg, injecting drug) at risk for consistently high level of opioid use.

**INTRAMURAL RESEARCH**

**The Novel Modafinil Analog, JJC8-016, as a Potential Cocaine Abuse Pharmacotherapeutic**

Zhang HY, Bi GH, Yang HJ, He Y, Xue G, Cao JJ, Tanda G, Gardner EL, Newman AH, Xi ZX. *Neuropsychopharmacology*, 2017 Mar 7. doi: 10.1038/npp.2017.41. [Epub ahead of print].

(±)Modafinil ((±)MOD) and its R-enantiomer (R-modafinil; R-MOD) have been investigated for their potential as treatments for psychostimulant addiction. The authors recently reported a series of (±)MOD analogues, of which JJC8-016 (N-(2-((bis(4-fluorophenyl)methyl)thio)ethyl)-3-phenylpropan-1-amine) was selected for further development. JJC8-016 and R-MOD were evaluated for binding across ~70 receptors, transporters and enzymes. Although at a concentration of 10 µM, there were many hits for JJC8-016, binding affinities in the range of its DAT affinity were only observed at the serotonin transporter (SERT), dopamine D2-like and sigma1 receptors. R-MOD was more selective, but had much lower affinity at the DAT (Ki=3 µM) than JJC8-016 (Ki=116 nM). In rats, systemic administration of R-MOD alone (10–30 mg/kg i.p.) dose-dependently increased locomotor activity and electrical brain-stimulation reward, while JJC8-016 (10–30 mg/kg i.p.) did not produce these effects. Strikingly, pretreatment with JJC8-016 dose-dependently inhibited cocaine-enhanced locomotion, cocaine self-administration, and cocaine-induced reinstatement of drug-seeking behavior, while R-MOD inhibited cocaine-induced reinstatement only at the high dose of 100 mg/kg. Notably, JJC8-016 alone neither altered extracellular dopamine in the nucleus accumbens, nor maintained self-administration. It also failed to induce reinstatement of drug-seeking behavior. These findings suggest that JJC8-016 is a unique DAT inhibitor that has no cocaine-like abuse potential by itself. Moreover, pretreatment with JJC8-016 significantly inhibits cocaine-taking and cocaine-seeking behavior likely by interfering with cocaine binding to DAT. In addition, off target actions may also contribute to its potential

therapeutic utility in the treatment of cocaine abuse.

**Circuit Specificity In The Inhibitory Architecture Of The VTA Regulates Cocaine-Induced Behavior** Edwards NJ, Tejada HA, Pignatelli M, Zhang S, McDevitt RA Wu J, Bass CE, Bettler B Morales M, Bonci A. *Nat Neurosci*. 2017 Mar;20(3):438-448.

Afferent inputs to the ventral tegmental area (VTA) control reward-related behaviors through regulation of dopamine neuron activity. The nucleus accumbens (NAc) provides one of the most prominent projections to the VTA; however, recent studies have provided conflicting evidence regarding the function of these inhibitory inputs. Using optogenetics, cell-specific ablation, whole cell patch-clamp and immuno-electron microscopy, the authors found that NAc inputs synapsed directly onto dopamine neurons, preferentially activating GABAB receptors. GABAergic inputs from the NAc and local VTA GABA neurons were differentially modulated and activated separate receptor populations in dopamine neurons. Genetic deletion of GABAB receptors from dopamine neurons in adult mice did not affect general or morphine-induced locomotor activity, but markedly increased cocaine-induced locomotion. Collectively, these findings demonstrate notable selectivity in the inhibitory architecture of the VTA and suggest that long-range GABAergic inputs to dopamine neurons fundamentally regulate behavioral responses to cocaine.

**Synaptic Plasticity Onto Dopamine Neurons Shapes Fear Learning** Pignatelli M, Umanah GK, Ribeiro SP, Chen R, Karuppagounder SS, Yau HJ, Eacker S, Dawson VL, Dawson TM, Bonci A. *Neuron*. 2017 Jan 18;93(2):425-440.

Fear learning is a fundamental behavioral process that requires dopamine (DA) release. Experience-dependent synaptic plasticity occurs on DA neurons while an organism is engaged in aversive experiences. However, whether synaptic plasticity onto DA neurons is causally involved in aversion learning is unknown. Here, the authors show that a stress priming procedure enhances fear learning by engaging VTA synaptic plasticity. Moreover, they took advantage of the ability of the ATPase Thorase to regulate the internalization of AMPA receptors (AMPA receptors) in order to selectively manipulate glutamatergic synaptic plasticity on DA neurons. Genetic ablation of Thorase in DAT+ neurons produced increased AMPAR surface expression and function that lead to impaired induction of both long-term depression (LTD) and long-term potentiation (LTP). Strikingly, animals lacking Thorase in DAT+ neurons expressed greater associative learning in a fear conditioning paradigm. In conclusion, these data provide a novel, causal link between synaptic plasticity onto DA neurons and fear learning.

**Functional  $\mu$ -Opioid-Galanin Receptor Heteromers in the Ventral Tegmental Area** Moreno E, Quiroz C, Rea W, Cai NS, Mallol J, Cortés A, Lluís C, Canela EI, Casadó V, Ferré S. *J Neurosci*. 2017;37(5):1176-1186.

The neuropeptide galanin has been shown to interact with the opioid system. More specifically, galanin counteracts the behavioral effects of the systemic administration of  $\mu$ -opioid receptor (MOR) agonists. Yet the mechanism responsible for this galanin-opioid interaction has remained elusive. Using biophysical techniques in mammalian transfected cells, the authors found evidence for selective heteromerization of MOR and the galanin receptor subtype Gal1 (Gal1R). Also in transfected cells, a synthetic peptide selectively disrupted MOR-Gal1R heteromerization as well as specific interactions between MOR and Gal1R ligands: a negative cross talk, by which galanin counteracted MAPK activation induced by the endogenous MOR agonist endomorphin-1, and a cross-antagonism, by which a MOR antagonist counteracted MAPK activation induced by galanin. These specific interactions, which represented biochemical properties of the MOR-Gal1R heteromer, could then be identified in situ in slices of rat ventral tegmental area (VTA) with MAPK

activation and two additional cell signaling pathways, AKT and CREB phosphorylation. Furthermore, in vivo microdialysis experiments showed that the disruptive peptide selectively counteracted the ability of galanin to block the dendritic dopamine release in the rat VTA induced by local infusion of endomorphin-1, demonstrating a key role of MOR-Gal1R heteromers localized in the VTA in the direct control of dopamine cell function and their ability to mediate antagonistic interactions between MOR and Gal1R ligands. The results also indicate that MOR-Gal1R heteromers should be viewed as targets for the treatment of opioid use disorders.

**Lateral Habenula Involvement in Impulsive Cocaine Seeking** Zapata A, Hwang EK, Lupica CR. *Neuropsychopharmacology*. 2017 Apr;42(5):1103-1112. doi: 10.1038/npp.2016.286. Epub 2016 Dec 27.

The lateral habenula (LHb) is a brain structure receiving inputs from limbic forebrain areas and innervating major midbrain monoaminergic nuclei. Evidence indicates LHb involvement in sleep control, reward-based decision making, avoidance of punishment, and responses to stress. Additional work has established that the LHb mediates negative feedback in response to aversive events. As a hallmark of drug addiction is the inability to limit drug use despite negative consequences, the authors hypothesize that LHb dysfunction may have a role in the lack of control over drug seeking. Here they examine the effects of LHb inactivation in control over drug seeking in several cocaine self-administration (SA) paradigms in rats. They find that inhibition of the LHb with GABAergic agonists did not alter cocaine SA under progressive ratio or seeking/taking chained reinforcement schedules, or during punishment-induced suppression of cocaine-reinforced responding. In contrast, LHb inhibition increased cocaine seeking when the drug was not available in rats trained to discriminate its presence using an environmental cue. This effect of LHb inhibition was selective for cocaine, as it did not impair responding for sucrose reinforcement. The effect of LHb injection of GABA agonists was mimicked by intra-LHb muscarinic cholinergic (mACh) antagonist injection, and activation of mACh receptors excited a majority of LHb neurons in in vitro electrophysiology experiments. These results indicate that the LHb participates in the suppression of impulsive responding for cocaine through the activation of a cholinergic circuit, and they suggest that LHb dysfunction may contribute to impaired impulse control associated with drug addiction.

## **GRANTEE HONORS AND AWARDS**

### **CTN Pacific Northwest Node**

One of the Node's Community Treatment Program (CTP) directors, **Dr. Molly Carney**, of Evergreen Treatment Services, will be receiving the Excellence in Advocacy - Individual Achievement award at the National Council for Behavioral Health meeting this April in Seattle. The National Council for Behavioral Health is the unifying voice of America's mental health and addictions treatment organizations. Its annual Awards of Excellence honor the advocates and leaders advancing public policies that support improved quality of and access to care, organizations that promote excellence and build health communities, and the achievements of individuals with mental illnesses and addictions, their family members, and the professionals who care for them. Molly Carney, Ph.D., MBA, is trained as a clinical psychologist and has worked in substance use disorder treatment since 1986, most recently as director of Evergreen Treatment Services, a private, nonprofit agency offering medication-assisted treatment for adults with opioid use disorders since

## **STAFF HONORS AND AWARDS**

**Dr. Aidan Hampson**, DPMC, received the **2016 Mitchell B. Balter Award**, from the Journal of Clinical Psychopharmacology, for the publication, “A pharmacokinetic study examining acetazolamide as a novel adherence marker for clinical trials”. The complete reference is: A Pharmacokinetic Study Examining Acetazolamide as a Novel Adherence Marker for Clinical Trials Hampson, Aidan J.; Babalonis, Shanna; Lofwall, Michelle R.; Nuzzo, Paul A.; Krieter, Phillip; Walsh, Sharon L Journal of Clinical Psychopharmacology . 36(4):324-332, August 2016.

**Dr. Antonello Bonci**, Director, IRP, received the Distinguished Scientist Award, University of North Carolina-Chapel Hill.

**Dr. Antonello Bonci** became a member of the Jacob P. Waletzky Award Selection Committee, Society for Neuroscience and the Dana Alliance for Brain Initiatives (DABI).

**Dr. Sofia Bouhlal**, IRP, was selected for a New Investigator Award from the American Society for Clinical Psychopharmacology (ASCP).

**Lisa Farinelli**, IRP, was selected among many applicants from NIH and other federal agencies to participate in the 2016-2017 Leaders Mentoring Program (LMP), League of United Latin American Citizens (LULAC). She was also unanimously nominated by the faculty of the LMP program to speak at the graduation ceremony, representing the LMP cohort.

**Dr. Lorenzo Leggio**, IRP, was promoted to Full Professor (Adjunct) at Brown University

**Drs. Alessandro Bonifazi, Rachel Slack, and Anver Shaik**, IRP, received travel awards to present their research at the Behavior, Biology, and Chemistry Meeting in San Antonio, TX.

**Andrew Kesner**, IRP, received a 2017 NIH Graduate Student Research Award (NGSRA) for having one of the best posters presented at the 13th Annual NIH Graduate Student Research Symposium.

**Trinity Russell**, IRP, received a NIDA SD Fellowship for Diversity in Research and will start her post-baccalaureate fellowship in June.

**Dr. Yavin Shaham**, IRP, received the 2017 European Behavioral Pharmacology Society Distinguished Achievement Award.

## STAFF CHANGES

### New Appointments/Employees

**Rita Valentino, Ph.D.**, joined NIDA as the new Director of the Division of Neuroscience and Behavior on April 16, 2017. Dr. Valentino's career spans 26 years of academic, research, and leadership experience in pharmacology, psychiatry, and neurobiology. Dr. Valentino received her B.S. in Pharmacy with highest distinction from the University of Rhode Island and her Ph.D. in Pharmacology from the University of Michigan. She completed her postdoctoral fellowship in neurobiology at the University of North Carolina (1980-1981) and The Salk Institute (1981-1983). From 1983 to present, Dr. Valentino received academic appointments at some of the most prestigious research and education institutions in the U.S., including George Washington University Medical School and Hahnemann University/Allegheny University. She is currently a Professor of Anesthesiology and Critical Care at the University of Pennsylvania School of Medicine. She is also serving as the Director of Stress Neurobiology and a Stokes Investigator at the Children's Hospital of Philadelphia.

**Michelle Corbin, MBA**, joined the Public Information and Liaison Branch (PILB), Office of Science Policy and Communications, in January 2017, as a Public Health Analyst, where she will focus on strategic planning and coordination of activities to expand NIDA's outreach to clinicians. Prior to joining PILB, she was a Public Health Analyst at HRSA, coordinating communications and recruitment efforts for the National Health Service Corps. She has also served as a Public Affairs specialist at HRSA for more than 7 years. Michelle has an MBA with a marketing specialty from American University.

**Tara Garwood** joined the Digital Communications Branch (DCB), Office of Science Policy and Communications, in January 2017, as a Social Media Specialist. Prior to joining DCB, she was a video/multimedia production specialist with the U.S. Secret Service and prior to that with the Food and Drug Administration.

**Emily Jones, Ph.D., M.P.P.**, joined the Science Policy Branch (SPB), Office of Science Policy and Communications, in January 2017, as Deputy Branch Chief. Prior to joining SPB, she worked at the HHS Office of the Assistant Secretary for Planning and Evaluation to launch and evaluate policy initiatives to increase access to quality, affordable mental health and substance use disorder treatment. Before that, she was Team Lead for HITECH Act evaluation at the HHS Office of the National Coordinator for Health IT, and part of the team implementing the Affordable Care Act in federally-qualified health centers at the Health Resources and Services Administration. Emily also served as the Assistant Director of the Outstanding Scholar Program in the Bureau of Competition at the Federal Trade Commission; she has over 10 years of federal experience. She gained research experience at the Urban Institute, the Georgetown Health Policy Institute, and the George Washington University Department of Health Policy, where she served as Associate Director of the Geiger Gibson/RCHN Foundation Research Collaborative. She earned her doctorate in public policy and public administration from George Washington University and a master's degree in Public Policy from Georgetown.

**Jinhee Lee, Pharm.D.**, joined the Public Information and Liaison Branch (PILB), Office of Science Policy and Communications (OSPC) in February 2017, as the Director of Content Management where she works with NIDA's communications and digital staffers, the OSPC scientific team and other NIDA experts to ensure scientific accuracy of our public facing science based materials. Dr. Lee previously worked at the Center for Substance Abuse Treatment at the Substance Abuse and Mental Health Services Administration (SAMHSA) where she was the Managing Editor of the 2016 Surgeon General's Report on Alcohol, Drugs and Health. Prior to her six years at SAMHSA, Dr. Lee was at the Food and Drug Administration for close to ten years. She holds a Doctor of Pharmacy degree from University of Illinois and completed a pharmacy practice residency at the MedStar Washington Hospital Center, as well as an Executive Patient Safety Fellowship from Virginia Commonwealth University. Dr. Lee is a Commander in the U.S. Public Health Service Commissioned Corps.

### **Separations**

**Phil Skolnick, Ph.D., D.Sc. (hon.)**, Director of the Division of Therapeutics and Medical Consequences (DTMC) of NIDA, resigned on February 2<sup>nd</sup>, 2017 after 7 years in this position. Prior to joining NIDA, Dr. Skolnick had 10 years of experience in medications development at DOV Pharmaceutical and Eli Lilly & Company. From 1972 to 1997, Dr. Skolnick had several positions at NIH, including Chief of the Neurobiology Section and Chief Laboratory of Neuroscience at NIDDK. Some of his studies initiated at the NIH more and continued at Lilly Research Laboratories, provided the foundation for the development of compounds ranging from ketamine to rapastinel and, most recently LY 3020371. The development of glutamate-based antidepressants, and indeed, the bases for the clinical study of NMDA antagonists such as ketamine in depression, can be directly attributed to the studies conducted in Skolnick's laboratory. His laboratory also reported that chronic antidepressant treatments downregulate the expression of NMDA receptor NR2 subunits in an agent and region-specific fashion. The fundamental importance of these studies to the pathophysiology of depression and the potential for the development of novel antidepressant agents was recognized by an Anna Monika Prize in 1995. At NIDA, Phil reinvigorated the government-based model of drug discovery and development by securing funding for large and transformative projects that brought compounds closer to FDA approval. He made significant contributions to NIDA's science by leading multiple collaboration with the pharmaceutical sector, one them resulted in the FDA approval of Nasal Narcan® for opioid overdose. Dr. Skolnick is now the Chief Scientific Officer of Opiant Pharmaceuticals, Inc. a specialty pharmaceutical company developing pharmacological treatments for substance use, addictive and eating disorders.

### **Retirements**

**Joseph Frascella, Ph.D.**, Senior Scientific Advisor to the NIDA director, and former director of NIDA's Clinical Neuroscience and Behavioral Research Division comprising a broad drug abuse and addiction program of translational research and research training in clinical neuroscience, human development and behavioral treatment retired from Federal service on March 31, 2017.



National Institute  
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