DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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Director
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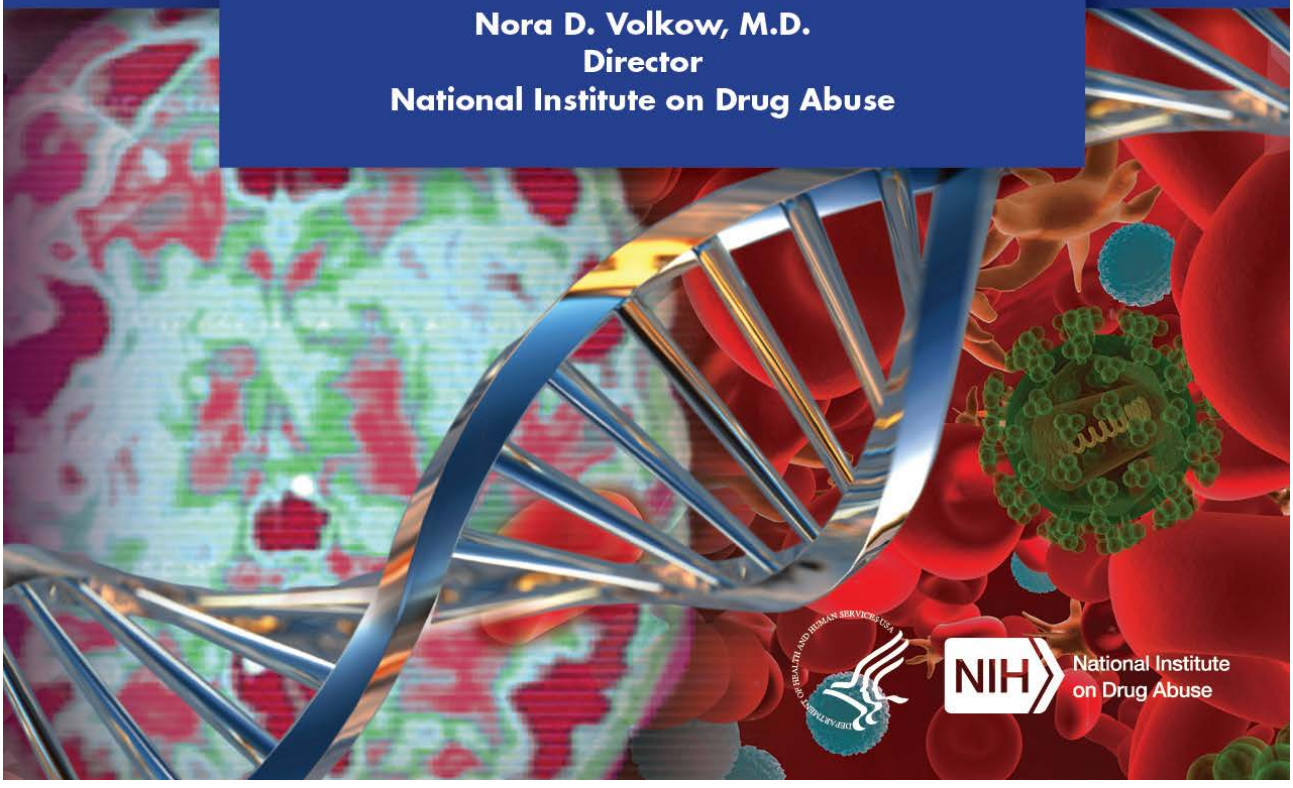

NIH National Institute on Drug Abuse

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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Self-administration Of the Anandamide Transport Inhibitor AM404 By Squirrel Monkeys
Schindler CW, Scherma M, Redhi GH, Vadivel SK, Makriyannis A, Goldberg S, Justinova Z. Psychopharmacology (Berl). 2016; [epub ahead of print].
N-(4-hydroxyphenyl)-arachidonamide (AM404) is an anandamide transport inhibitor shown to reduce rewarding and relapse-inducing effects of nicotine in several animal models of tobacco dependence. However, the reinforcing/rewarding effects of AM404 are not clear. The authors investigated whether AM404 maintains self-administration behavior or reinstates extinguished drug seeking in squirrel monkeys. In monkeys with a history of anandamide or cocaine self-administration, we substituted injections of AM404 (1-100 μg/kg/injection). Using a 10-response, fixed-ratio schedule, self-administration behavior was maintained by AM404. Dose-response curves had inverted U shapes, with peak response rates occurring at a dose of 10 μg/kg/injection. In anandamide-experienced monkeys, we also demonstrated self-administration of another anandamide transport inhibitor VDM11. In addition to supporting self-administration, priming injections of AM404 (0.03-0.3 mg/kg) reinstated drug-seeking behavior previously reinforced by cannabinoids (Δ(9)-tetrahydrocannabinol (THC) or anandamide) or cocaine. Both AM404 self-administration behavior and reinstatement of drug seeking by AM404 were reduced by treatment with the cannabinoid CB1 receptor antagonist/inverse agonist rimonabant (0.3 mg/kg). Moreover, the reinforcing effects of AM404 were potentiated by the treatment with the fatty acid amide hydrolase (FAAH) inhibitor URB597 (0.3 mg/kg) suggesting a major role of anandamide in these effects. Finally, AM404 (0.3 mg/kg) potentiated the reinforcing effects of anandamide but not those of cocaine.In non-human primates, AM404 effectively reinforced self-administration behavior and induced reinstatement of drug-seeking behavior in abstinent monkeys. These effects appeared to be mediated by cannabinoid CB1 receptors. Therefore, compounds that promote actions of endocannabinoids throughout the brain by inhibiting their membrane transport may have a potential for abuse.

Evidence Of Anhedonia and Differential Reward Processing In Prefrontal Cortex Among Post-withdrawal Patients With Prescription Opiate Dependence Huhn AS, Meyer RE, Harris JD, Ayaz H, Deneke E, Stankoski DM, Bunce SC. Brain Res Bull. 2015; [epub ahead of print].
Anhedonia is an important but understudied element of a neuroadaptive model underlying vulnerability to relapse in opioid dependence. Previous research using fMRI has shown reduced activation to pleasant stimuli in rostral prefrontal cortex among heroin-dependent patients in early recovery. This study evaluated the presence of anhedonia among recently withdrawn prescription opiate dependent patients (PODP) in residential treatment compared to control subjects. Anhedonia was assessed using self-report, affect-modulated startle response (AMSR), and a cue reactivity task during which participant's rostral prefrontal cortex (RPFC) and ventrolateral prefrontal cortex (VLPFC) was monitored with functional near infrared spectroscopy (fNIRS). The cue reactivity task included three distinct categories of natural reward stimuli: highly palatable food, positive social situations, and intimate (non-erotic) interactions. PODP reported greater anhedonia on self-report (Snaith-Hamilton Pleasure Scale), and showed reduced hedonic response to positive stimuli in the AMSR task relative to controls. PODP also exhibited reduced neural activation in bilateral

RPFC and left VLPFC in response to food images and reduced left VLPFC in response to images depicting positive social situations relative to controls. No differences were found for emotionally intimate stimuli. When patients were divided into groups based on the Snaith-Hamilton criteria for the presence or absence of anhedonia, patients endorsing anhedonia showed reduced neural responses to images depicting positive social stimuli and food relative to patients who did not endorse anhedonia. Activations were in areas of RPFC that support the retrieval of episodic memories. The results suggest the presence of anhedonia in a subsample of PODP.

Effects Of L-methamphetamine Treatment On Cocaine- and Food-maintained Behavior In Rhesus Monkeys Kohut SJ, Bergman J, Blough BE. Psychopharmacology (Berl). 2016; 233(6): 1067-1075.
Monoamine releasers with prominent dopaminergic actions, e.g., D-methamphetamine (D-MA), significantly reduce cocaine use and craving in clinical and preclinical laboratory studies. However, D-MA and related drugs also display high abuse potential, which limits their acceptability as agonist replacement medications for the management of Cocaine Use Disorder.The L-isomer of methamphetamine (L-MA), unlike D-MA, has preferential noradrenergic actions and is used medicinally with low, if any, abuse liability. The present study was conducted to determine whether L-MA could serve as an agonist replacement medication by both mimicking interoceptive effects of cocaine and decreasing intravenous (IV) cocaine self-administration. Separate groups (N = 4-5) of rhesus monkeys were studied to determine whether L-MA could (1) substitute for cocaine in subjects that discriminated intramuscular (IM) cocaine (0.4 mg/kg) from saline and (2) decrease IV cocaine self-administration under a second-order FR2(VR16:S) schedule of reinforcement. L-MA, like D-MA but with approximately 5-fold lesser potency, substituted for cocaine in drug discrimination experiments in a dose-dependent manner. In IV self-administration studies, 5-10-day treatments with continuously infused L-MA (0.032-0.32 mg/kg/h, IV) dose-dependently decreased cocaine-maintained responding; the highest dosage reduced cocaine intake to levels of saline self-administration without appreciable effects on food-maintained responding. These results indicate that L-MA both shares discriminative stimulus effects with cocaine and reduces cocaine self-administration in a behaviorally selective manner. L-MA and other compounds with a similar pharmacological profile deserve further evaluation for the management of Cocaine Use Disorder.

Astrocytes Assemble Thalamocortical Synapses By Bridging NRX1α And NL1 Via Hevin Singh SK, Stogsdill JA, Pulimood NS, Dingsdale H, Kim YH, Pilaz L-J, Kim IH, Manhaes AC, Rodrigues Jr, WS, Pamukcu A, Enustun E, Ertuz Z, Scheiffele P, Soderling SH, Silver DL, Ji R-R, Medina AE, Eroglu C. Cell. 2016; 164(1-2): 183-196.
Proper establishment of synapses is critical for constructing functional circuits. Interactions between presynaptic neurexins and postsynaptic neuroligins coordinate the formation of synaptic adhesions. An isoform code determines the direct interactions of neurexins and neuroligins across the synapse. However, whether extracellular linker proteins can expand such a code is unknown. Using a combination of in vitro and in vivo approaches, the authors found that hevin, an astrocyte-secreted synaptogenic protein, assembles glutamatergic synapses by bridging neurexin-1alpha and neuroligin-1B, two isoforms that do not interact with each other. Bridging of neurexin-1alpha and neuroligin-1B via hevin is critical for the formation and plasticity of thalamocortical connections in the developing visual cortex. These results show that astrocytes promote the formation of synapses by modulating neurexin/neuroligin adhesions through hevin secretion. These findings also provide

an important mechanistic insight into how mutations in these genes may lead to circuit dysfunction in diseases such as autism.

Nucleus Accumbens D2R Cells Signal Prior Outcomes and Control Risky Decision-Making Zalocusky KA, Ramakrishnan C, Lerner T, Davidson TJ, Knutson B, Deisseroth K. Nature. 2016; 531(7596): 642-646.
A marked bias towards risk aversion has been observed in nearly every species tested. A minority of individuals, however, instead seem to prefer risk (repeatedly choosing uncertain large rewards over certain but smaller rewards), and even risk-averse individuals sometimes opt for riskier alternatives. It is not known how neural activity underlies such important shifts in decision-making—either as a stable trait across individuals or at the level of variability within individuals. Here the authors describe a model of risk-preference in rats, in which stable individual differences, trial-by-trial choices, and responses to pharmacological agents all parallel human behaviour. By combining new genetic targeting strategies with optical recording of neural activity during behaviour in this model, the authors identify relevant temporally specific signals from a genetically and anatomically defined population of neurons. This activity occurred within dopamine receptor type-2 (D2R)-expressing cells in the nucleus accumbens (NAc), signalled unfavourable outcomes from the recent past at a time appropriate for influencing subsequent decisions, and also predicted subsequent choices made. Having uncovered this naturally occurring neural correlate of risk selection, the authors then mimicked the temporally specific signal with optogenetic control during decision-making and demonstrated its causal effect in driving risk-preference. Specifically, risk-preferring rats could be instantaneously converted to risk-averse rats with precisely timed phasic stimulation of NAc D2R cells. These findings suggest that individual differences in risk preference, as well as real-time risky decision-making, can be in large part explained by the encoding in D2R-expressing NAc cells of prior unfavourable outcomes during decision-making.

EPIDEMIOLOGY RESEARCH

Nonmedical Opioid Use and Heroin Use In A Nationally Representative Sample Of US High School Seniors Palamar JJ, Shearston JA, Dawson EW, Mateu-Gelabert P, Ompad DC. Drug Alcohol Depend. 2016; Jan; 158: 132-138.
Nonmedical use of opioids has become increasingly problematic in recent years with increases in overdoses, treatment admissions, and deaths. Use also appears to be contributing to heroin initiation, which has increased in recent years. Further research is needed to examine which adolescents are at highest risk for nonmedical use of opioids and heroin and to explore potential links between nonmedical opioid use and heroin use. Data were analyzed from a nationally representative sample of American high school seniors in the Monitoring the Future study (2009-2013, Weighted N=67,822). The authors examined associations between frequency and recency of nonmedical use of opioids and heroin. Sociodemographic correlates of use of each drug were also examined. 12.4% of students reported lifetime nonmedical opioid use and 1.2% reported lifetime heroin use. As frequency of lifetime nonmedical opioid use increased, so too did the odds for reporting heroin use, with over three-quarters (77. 3%) of heroin users reporting lifetime nonmedical opioid use. Recent (30-day) nonmedical opioid use was a robust risk factor for heroin use and almost a quarter (23. 2%) of students who reported using opioids ≥40 times reported lifetime heroin use. Black and Hispanic students were less likely to report nonmedical opioid or

heroin use than white students, but they were more likely to report heroin use in absence of nonmedical opioid use. Recent and frequent nonmedical opioid use are risk factors for heroin use among adolescents. Prevention needs to be targeted to those at highest risk.

Providing ART To HIV Seropositive Persons Who Use Drugs: Progress In New York City, Prospects For "Ending the Epidemic" Des Jarlais DC, Arasteh K, McKnight C, Feelemyer J, Hagan H, Cooper HLF, Campbell ANC, Tross S, Perlman DC. AIDS Behav. 2016; 20(2): 353-362.
New York City has experienced the largest HIV epidemic among persons who use psychoactive drugs. The authors examined progress in placing HIV seropositive persons who inject drugs (PWID) and HIV seropositive non-injecting drug users (NIDU) onto antiretroviral treatment (ART) in New York City over the last 15 years. The authors recruited 3511 PWID and 3543 NIDU from persons voluntarily entering drug detoxification and methadone maintenance treatment programs in New York City from 2001 to 2014. HIV prevalence declined significantly among both PWID and NIDU. The percentage who reported receiving ART increased significantly, from approximately 50 % (2001-2005) to approximately 75% (2012-2014). There were no racial/ethnic disparities in the percentages of HIV seropositive persons who were on ART. Continued improvement in ART uptake and TasP and maintenance of other prevention and care services should lead to an "End of the AIDS Epidemic" for persons who use heroin and cocaine in New York City.

Preliminary Findings Demonstrating Latent Effects Of Early Adolescent Marijuana Use Onset On Cortical Architecture Filbey FM, McQueeny T, DeWitt SJ, Mishra V. Dev Cogn Neurosci. 2015; Dec; 16: 16-22.
As the most commonly used illicit substance during early adolescence, long-term or latent effects of early adolescent marijuana use across adolescent developmental processes remain to be determined. The authors examined cortical thickness, gray/white matter border contrast (GWR) and local gyrification index (LGI) in 42 marijuana (MJ) users. Voxelwise regressions assessed early-onset (age <16) vs. late-onset (≥16 years-old) differences and relationships to continued use while controlling for current age and alcohol use. Although groups did not differ by onset status, groups diverged in their correlations between cannabis use and cortical architecture. Among early-onset users, continued years of MJ use and current MJ consumption were associated with thicker cortex, increased GWR and decreased LGI. Late-onset users exhibited the opposite pattern. This divergence was observed in all three morphological measures in the anterior dorsolateral frontal cortex ($p<.05$, FWE-corrected). Divergent patterns between current MJ use and elements of cortical architecture were associated with early MJ use onset. Considering brain development in early adolescence, findings are consistent with disruptions in pruning. However, divergence with continued use for many years thereafter suggests altered trajectories of brain maturation during late adolescence and beyond.

Psychometric Modeling Of Abuse and Dependence Symptoms Across Six Illicit Substances Indicates Novel Dimensions Of Misuse Clark SL, Gillespie NA, Adkins DE, Kendler KS, Neale MC. Addict Behav. 2016; Feb; 53: 132-140.
This study explored the factor structure of DSM III-R/IV symptoms for substance abuse and dependence across six illicit substance categories in a population-based sample of males. DSM III-R/IV drug abuse and dependence symptoms for cannabis, sedatives, stimulants, cocaine, opioids and hallucinogens from 4179 males born 1940-1970 from the population-based Virginia Adult

Twin Study of Psychiatric and Substance Use Disorders were analyzed. Confirmatory factor analyses tested specific hypotheses regarding the latent structure of substance misuse for a comprehensive battery of 13 misuse symptoms measured across six illicit substance categories (78 items). Among the models fit, the latent structure of substance misuse was best represented by a combination of substance-specific factors and misuse symptom-specific factors. The authors found no support for a general liability factor to illicit substance misuse. Results indicate that liability to misuse illicit substances is drug class specific, with little evidence for a general liability factor. Additionally, unique dimensions capturing propensity toward specific misuse symptoms (e. g., tolerance, withdrawal) across substances were identified. While this finding requires independent replication, the possibility of symptom-specific misuse factors, present in multiple substances, raises the prospect of genetic, neurobiological and behavioral predispositions toward distinct, narrowly defined features of drug abuse and dependence.

Impact Of Adolescent Marijuana Use On Intelligence: Results From Two Longitudinal Twin Studies Jackson NJ, Isen JD, Khoddam R, Irons D, Tuvblad C, Iacono WG, McGue M, Raine A, Baker LA. Proc Natl Acad Sci U S A. 2016; 113(5): E500-508.
Marijuana is one of the most commonly used drugs in the United States, and use during adolescence-when the brain is still developing-has been proposed as a cause of poorer neurocognitive outcome. Nonetheless, research on this topic is scarce and often shows conflicting results, with some studies showing detrimental effects of marijuana use on cognitive functioning and others showing no significant long-term effects. The purpose of the present study was to examine the associations of marijuana use with changes in intellectual performance in two longitudinal studies of adolescent twins (n = 789 and n = 2,277). The authors used a quasiexperimental approach to adjust for participants' family background characteristics and genetic propensities, helping us to assess the causal nature of any potential associations. Standardized measures of intelligence were administered at ages' 9-12 y, before marijuana involvement, and again at ages' 17-20 y. Marijuana use was self-reported at the time of each cognitive assessment as well as during the intervening period. Marijuana users had lower test scores relative to nonusers and showed a significant decline in crystallized intelligence between preadolescence and late adolescence. However, there was no evidence of a dose-response relationship between frequency of use and intelligence quotient (IQ) change. Furthermore, marijuana-using twins failed to show significantly greater IQ decline relative to their abstinent siblings. Evidence from these two samples suggests that observed declines in measured IQ may not be a direct result of marijuana exposure but rather attributable to familial factors that underlie both marijuana initiation and low intellectual attainment.

The Contribution Of Rare and Common Variants In 30 Genes To Risk Nicotine Dependence Yang J, Wang S, Yang Z, Hodgkinson CA, Iarikova P, Ma JZ, Payne TJ, Goldman D, Li MD. Mol Psychiatry. 2015; 20(11): 1467-1478.
Genetic and functional studies have revealed that both common and rare variants of several nicotinic acetylcholine receptor subunits are associated with nicotine dependence (ND). In this study, the authors identified variants in 30 candidate genes including nicotinic receptors in 200 sib pairs selected from the Mid-South Tobacco Family population with equal numbers of African Americans (AAs) and European Americans (EAs). The authors selected 135 of the rare and common variants and genotyped them in the Mid-South Tobacco Case-Control (MSTCC) population, which consists of 3088 AAs and 1430 EAs. None of the genotyped common variants

showed significant association with smoking status (smokers vs non-smokers), Fagerström Test for ND scores or indexed cigarettes per day after Bonferroni correction. Rare variants in NRXN1, CHRNA9, CHRNA2, NTRK2, GABBR2, GRIN3A, DNM1, NRXN2, NRXN3 and ARRB2 were significantly associated with smoking status in the MSTCC AA sample, with weighted sum statistic (WSS) P-values ranging from 2. 42 × 10(-3) to 1. 31 × 10(-4) after 10(6) phenotype rearrangements. The authors also observed a significant excess of rare nonsynonymous variants exclusive to EA smokers in NRXN1, CHRNA9, TAS2R38, GRIN3A, DBH, ANKK1/DRD2, NRXN3 and CDH13 with WSS P-values between 3. 5 × 10(-5) and 1 × 10(-6). Variants rs142807401 (A432T) and rs139982841 (A452V) in CHRNA9 and variants V132L, V389L, rs34755188 (R480H) and rs75981117 (N549S) in GRIN3A are of particular interest because they are found in both the AA and EA samples. A significant aggregate contribution of rare and common coding variants in CHRNA9 to the risk for ND (SKAT-C: P=0. 0012) was detected by applying the combined sum test in MSTCC EAs. Together, these results indicate that rare variants alone or combined with common variants in a subset of 30 biological candidate genes contribute substantially to the risk of ND.

PREVENTION RESEARCH

An Adolescent Substance Prevention Model Blocks the Effect Of CHRNA5 Genotype On Smoking During High School Vandenbergh DJ, Schlomer GL, Cleveland HH, Schink AE, Hair KL, Feinberg ME, Neiderhiser JM, Greenberg MT, Spoth RL, Redmond C. Nicotine Tob Res. 2016; 18(2): 212-220.
Prevention intervention programs reduce substance use, including smoking, but not all individuals respond. The authors tested whether response to a substance use prevention/intervention program varies based upon a set of five markers (rs16969968, rs1948, rs578776, rs588765, and rs684513) within the cluster of nicotinic acetylcholine receptor subunit genes (CHRNA5/A3/B4). Participants (N = 424) were randomly assigned to either control condition, or a family-based intervention in grade 6 and a school-based drug preventive intervention in grade 7. Smoking in the past month was assessed in grades 9-12 using a four-point scale (0 = never smoked, 1 = smoked but not in last month, 2 = one or a few times, 3 = about once a week or more).There was a main effect of both the intervention (b = -0.24, P < .05) and genotype at rs16969968 (b = 0.14, P <.05) on high school smoking. Using dummy coding to allow for nonlinear effects, individuals with the A/A genotype smoked more often than those with G/G (b = 0.33, P <.05). A genotype × intervention effect was found with reduced smoking among those with A/A and G/A genotypes to levels similar to those with the G/G genotype (G/G vs. A/A: b = -0.67, P <.05; A/G vs. A/A: b = -0.61, P < .05; G/G vs. A/G ns). Results were nonsignificant for the other four markers. Preventive interventions can reduce the genetic risk for smoking from rs16969968.

A Family-based Intervention For Improving Children's Emotional Problems Through Effects On Maternal Depressive Symptoms Reuben JD, Shaw DS, Brennan LM, Dishion TJ, Wilson MN. J Consult Clin Psychol. 2015; 83(6): 1142-1148.
This study focused on whether a brief family-based intervention for toddlers, the Family Check-Up (FCU), designed to address parent management skills and prevent early conduct problems, would have collateral effects on maternal depressive symptoms and subsequent child emotional problems. Parents with toddlers were recruited from the Women, Infants, and Children Nutritional Supplement Program based on the presence of socioeconomic, family, and child risk (N = 731). Families were

randomly assigned to the FCU intervention or control group with yearly assessments beginning at child age 2. Maternal depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale at child ages 2 and 3. Child internalizing problems were collected from primary caregivers, alternative caregivers, and teachers using the Child Behavior Checklist at ages 7.5 and 8.5.Structural equation models revealed that mothers in families randomly assigned to the FCU showed lower levels of depressive symptoms at child age 3, which in turn were related to lower levels of child depressed/withdrawal symptoms as reported by primary caregivers, alternative caregivers, and teacher at ages 7.5-8.5.Findings suggest that a brief, preventive intervention improving maternal depressive symptoms can have enduring effects on child emotional problems that are generalizable across contexts. As there is a growing emphasis for the use of evidence-based and cost-efficient interventions that can be delivered in multiple delivery settings serving low-income families and their children, clinicians and researchers welcome evidence that interventions can promote change in multiple problem areas. The FCU appears to hold such promise.

How Does the Fast Track Intervention Prevent Adverse Outcomes In Young Adulthood? Sorensen LC, Dodge KA, Conduct Problems Prevention Research Group. Child Dev. 2015.
Numerous studies have shown that childhood interventions can foster improved outcomes in adulthood. Less well understood is precisely how-that is, through which developmental pathways-these interventions work. This study assesses mechanisms by which the Fast Track project (n = 891), a randomized intervention in the early 1990s for high-risk children in four communities (Durham, NC; Nashville, TN; rural PA; and Seattle, WA), reduced delinquency, arrests, and general and mental health service utilization in adolescence through young adulthood (ages 12-20). A decomposition of treatment effects indicates that about a third of Fast Track's impact on later crime outcomes can be accounted for by improvements in social and self-regulation skills during childhood (ages 6-11), such as prosocial behavior, emotion regulation, and problem solving. These skills proved less valuable for the prevention of general and mental health problems

Project QUIT (Quit Using Drugs Intervention Trial): A Randomized Controlled Trial Of A Primary Care-based Multi-component Brief Intervention To Reduce Risky Drug Use Gelberg L, Andersen RM, Afifi AA, Leake BD, Arangua L, Vahidi M, Singleton K, Yacenda-Murphy J, Shoptaw S, Fleming MF, Baumeister SE. Addiction. 2015; 110(11): 1777-1790.
The aim of this study was to assess the effect of a multi-component primary care delivered brief intervention for reducing risky psychoactive drug use (RDU) among patients identified by screening. Multicenter single-blind two-arm randomized controlled trial of patients enrolled from February 2011 to November 2012 with 3-month follow-up. Randomization and allocation to trial group were computer-generated. Primary care waiting rooms of five federally qualified health centers in Los Angeles County (LAC), USA. A total of 334 adult primary care patients (171 intervention; 163 control) with RDU scores (4-26) on the World Health Organization (WHO) Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) self-administered on tablet computers. 261 (78%) completed follow-up. Mean age was 41.7 years; 62.9% were male; 37.7% were Caucasian. Intervention patients received brief (typically 3-4 minutes) clinician advice to quit/reduce their drug use reinforced by a video doctor message, health education booklet and up to two 20-30-minute follow-up telephone drug use coaching sessions. Controls received usual care and cancer screening information. Primary outcome was patient self-reported use of highest scoring drug (HSD) at follow-up. Intervention and control patients reported equivalent baseline HSD use at 3-month follow-up. After adjustment for covariates, in the complete sample linear regression model,

intervention patients used their HSD on 3.5 fewer days in the previous month relative to controls (P<0.001), and in the completed sample model, intervention patients used their HSD 2.2 fewer days than controls (P < 0.005). No compensatory increases in use of other measured substances were found. A primary-care based, clinician-delivered brief intervention with follow-up coaching calls may decrease risky psychoactive drug use.

Inherited and Environmental Influences On A Childhood Co-occurring Symptom Phenotype: Evidence From An Adoption Study Roos LE, Fisher PA, Shaw DS, Kim HK, Neiderhiser JM, Reiss D, Natsuaki MN, Leve LD. Dev Psychopathol. 2016; 28(1): 111-125.
Risk factors for the childhood development of co-occurring internalizing and externalizing symptoms are not well understood, despite a high prevalence and poor clinical outcomes associated with this co-occurring phenotype. The authors examined inherited and environmental risk factors for co-occurring symptoms in a sample of children adopted at birth and their birth mothers and adoptive mothers (N = 293). Inherited risk factors (i.e., birth mothers' processing speed and internalizing symptoms) and environmental risk factors (i.e., adoptive mothers' processing speed, internalizing symptoms, and uninvolved parenting) were examined as predictors for the development of internalizing-only, externalizing-only, or co-occurring symptoms using structural equation modeling. Results suggested a unique pattern of predictive factors for the co-occurring phenotype, with risk conferred by adoptive mothers' uninvolved parenting, birth mothers' slower processing speed, and the birth mothers' slower processing speed in tandem with adoptive mothers' higher internalizing symptoms. Additional analyses indicated that when co-occurring-symptom children were incorporated into internalizing and externalizing symptom groups, differential risk factors for externalizing and internalizing symptoms emerged. The findings suggest that spurious results may be found when children with co-occurring symptoms are not examined as a unique phenotypic group.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders
Lee JD, Friedmann PD, Kinlock TW, Nunes EV, Boney TY, Hoskinson RA, Wilson D, McDonald R, Rotrosen J, Gourevitch MN, Gordon M, Fishman M, Chen DT, Bonnie RJ, Cornish JW, Murphy SM, O'Brien CP. N Engl J Med., March 31, 2016.
Extended-release naltrexone, a sustained-release monthly injectable formulation of the full mu-opioid receptor antagonist, is effective for the prevention of relapse to opioid dependence. Data supporting its effectiveness in U.S. criminal justice populations are limited. In this five-site, open-label, randomized trial, the authors compared a 24-week course of extended-release naltrexone (Vivitrol) with usual treatment, consisting of brief counseling and referrals for community treatment programs, for the prevention of opioid relapse among adult criminal justice offenders (i.e., persons involved in the U.S. criminal justice system) who had a history of opioid dependence and a preference for opioid-free rather than opioid maintenance treatments and who were abstinent from opioids at the time of randomization. The primary outcome was the time to an opioid-relapse event, which was defined as 10 or more days of opioid use in a 28-day period as assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 5 days of opioid use. Post-treatment follow-up occurred at weeks 27, 52, and 78. A total of 153 participants were assigned to extended-release naltrexone and 155 to usual treatment. During the

24-week treatment phase, participants assigned to extended-release naltrexone had a longer median time to relapse than did those assigned to usual treatment (10.5 vs. 5.0 weeks, P<0.001; hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.68), a lower rate of relapse (43% vs. 64% of participants, P<0.001; odds ratio, 0.43; 95% CI, 0.28 to 0.65), and a higher rate of opioid-negative urine samples (74% vs. 56%, P<0.001; odds ratio, 2.30; 95% CI, 1.48 to 3.54). At week 78 (approximately 1 year after the end of the treatment phase), rates of opioid-negative urine samples were equal (46% in each group, P=0.91). The rates of other prespecified secondary outcome measures--self-reported cocaine, alcohol, and intravenous drug use, unsafe sex, and reincarceration--were not significantly lower with extended-release naltrexone than with usual treatment. Over the total 78 weeks observed, there were no overdose events in the extended-release naltrexone group and seven in the usual-treatment group (P=0.02). In this trial involving criminal justice offenders, extended-release naltrexone was associated with a rate of opioid relapse that was lower than that with usual treatment. Opioid-use prevention effects waned after treatment discontinuation.

Lorcaserin Reduces The Discriminative Stimulus and Reinforcing Effects Of Cocaine In Rhesus Monkeys Collins GT, Gerak LR, Javors MA, France CP. J Pharmacol Exp Ther. 2016; 356(1): 85-95.

Cocaine abuse and obesity are serious public health problems, and studies suggest that both dopamine and serotonin systems are involved in regulating the consumption of drugs and food. Lorcaserin has serotonin (5-HT)2C receptor agonist actions, is approved by the U.S. Food and Drug Administration for treating obesity, and might be effective for treating cocaine abuse. These studies characterized the pharmacokinetic and behavioral profiles of lorcaserin (intragastric administration) and determined the effectiveness of lorcaserin to alter discriminative stimulus and reinforcing effects of cocaine (intravenous administration) in rhesus monkeys. Administered acutely, lorcaserin dose-dependently increased the occurrence of yawning while decreasing spontaneous activity and operant responding for food. These effects appeared within 30-60 minutes of administration and began to dissipate by 240 minutes, a time course closely matching plasma concentrations of lorcaserin. In monkeys discriminating cocaine from saline, lorcaserin alone did not occasion cocaine-appropriate responding but shifted the cocaine dose-response curve to the right and down in two of three monkeys. When administered acutely, lorcaserin dose-dependently decreased the rate at which monkeys responded for infusions of cocaine. When administered chronically, 3.2 mg/kg lorcaserin reduced the rate of cocaine-maintained responding by 50% for the duration of a 14-day treatment period. Together, these results show that lorcaserin attenuates the discriminative stimulus effects of cocaine after acute administration and the reinforcing effects of cocaine after acute and repeated administration, consistent with the view that it might have utility in treating cocaine abuse.

Blockade Of Nicotine and Cannabinoid Reinforcement and Relapse By a Cannabinoid CB1-Receptor Neutral Antagonist AM4113 and Inverse Agonist Rimonabant In Squirrel Monkeys Schindler CW, Redhi GH, Vemuri K, Makriyannis A, Le Foll B, Bergman J, Goldberg SR, Justinova Z. Neuropsychopharmacology. 2016.

Nicotine, the main psychoactive component of tobacco, and (-)-Δ(9)-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis, play major roles in tobacco and marijuana dependence as reinforcers of drug-seeking and drug-taking behavior. Drugs that act as inverse agonists of cannabinoid CB1 receptors in the brain can attenuate the rewarding and abuse-related effects of nicotine and THC, but their clinical use is hindered by potentially serious side effects. The recently developed CB1-receptor neutral antagonists may provide an alternative therapeutic

approach to nicotine and cannabinoid dependence. Here the authors compare attenuation of nicotine and THC reinforcement and reinstatement in squirrel monkeys by the CB1-receptor inverse agonist rimonabant and by the recently developed CB1-receptor neutral antagonist AM4113. Both rimonabant and AM4113 reduced two effects of nicotine and THC that play major roles in tobacco and marijuana dependence: (1) maintenance of high rates of drug-taking behavior, and (2) priming- or cue-induced reinstatement of drug-seeking behavior in abstinent subjects (models of relapse). In contrast, neither rimonabant nor AM4113 modified cocaine-reinforced or food-reinforced operant behavior under similar experimental conditions. However, both rimonabant and AM4113 reduced cue-induced reinstatement in monkeys trained to self-administer cocaine, suggesting the involvement of a common cannabinoid-mediated mechanism in the cue-induced reinstatement for different drugs of abuse. These findings point to CB1-receptor neutral antagonists as a new class of medications for treatment of both tobacco dependence and cannabis dependence. Neuropsychopharmacology advance online publication, 16 March 2016; doi:10.1038/npp.2016.27.

Effects Of Fatty Acid Amide Hydrolase (FAAH) Inhibitors On Working Memory In Rats
Panlilio LV, Thorndike EB, Nikas SP, Alapafuja SO, Bandiera T, Cravatt BF, Makriyannis A, Piomelli D, Goldberg SR, Justinova Z. Psychopharmacology (Berl). 2015.
Manipulations of the endocannabinoid system could potentially produce therapeutic effects with minimal risk of adverse cannabis-like side effects. Inhibitors of fatty acid amide hydrolase (FAAH) increase endogenous levels of the cannabinoid-receptor agonist, anandamide, and show promise for treating a wide range of disorders. However, their effects on learning and memory have not been fully characterized. The authors determined the effects of five structurally different FAAH inhibitors in an animal model of working memory known to be sensitive to impairment by delta-9 tetrahydrocannabinol (THC). A delayed nonmatching-to-position procedure was used in rats. Illuminated nosepoke holes were used to provide sample cues (left versus right) and record responses (correct versus incorrect) after delays ranging from 0 to 28 s. Various test drugs were given acutely up to two times per week before daily sessions. One FAAH inhibitor, AM3506 (3 mg/kg), decreased accuracy in the memory task. Four other FAAH inhibitors (URB597, URB694, PF-04457845, and ARN14633) and a monoacylglycerol lipase inhibitor (JZL184, which blocks the degradation of the endocannabinoid 2-arachidonoylglycerol) had no effect. Testing of AM3506 in combination with antagonists for receptors known to be affected by anandamide and other fatty acid amides indicated that the impairment induced by AM3506 was mediated by cannabinoid CB1 receptors, and not by alpha-type peroxisome proliferator-activated receptors (PPAR-alpha) or vanilloid transient receptor potential cation channels (TRPV1). FAAH inhibitors differ with respect to their potential for memory impairment, abuse liability, and probably other cannabis-like effects, and they should be evaluated individually for specific therapeutic and adverse effects.

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

The Impact Of Age, HIV Serostatus and Seroconversion On Methamphetamine Use Montoya JL, Cattie J, Morgan E, Woods SP, Cherner M, Moore DJ, Atkinson JH, Grant I, Translational Methamphetamine Aids Research Center Tmarc Group T. Am J Drug Alcohol Abuse. 2016 Feb 2:1-10. [Epub ahead of print].

Characterizing methamphetamine use in relation to age, HIV serostatus and seroconversion is pertinent given the increasingly older age of the population with HIV and the intertwined epidemics of methamphetamine use and HIV. Study aims were to investigate whether (i) methamphetamine use differs by age and HIV serostatus, and (ii) receiving an HIV diagnosis impacts methamphetamine use among younger and older persons with HIV. This study examined methamphetamine use characteristics among 217 individuals with a lifetime methamphetamine dependence diagnosis who completed an in-person study assessment.Multivariable regressions revealed that HIV serostatus uniquely attenuates methamphetamine use, such that persons with HIV report a smaller cumulative quantity ($\beta = -0.16$, $p = 0.01$) and a fewer number of days ($\beta = -0.18$, $p = 0.004$) of methamphetamine use than persons without HtV. Among the HIV+ sample, all participants persisted in methamphetamine use after receiving an HIV diagnosis, with about 20% initiating use after seroconversion. Repeated measures analysis of variance indicated that density of methamphetamine use (i.e. grams per day used) was greater among the younger, relative to the older, HIV+ group ($p = 0.02$), and increased for both age groups following seroconversion ($p < 0.001$). These analyses indicate that although HIV serostatus may attenuate methamphetamine use behaviors, many people with HIV initiate, or persist in, methamphetamine use after receiving an HIV diagnosis. These findings raise the question of whether tailoring of prevention and intervention strategies might reduce the impact of methamphetamine and HIV across the age continuum.

Dynamics Of The Human and Viral M6a RNA Methylomes During HIV-1 Infection Of T Cells Gianluigi L, Gao S, Saletore Y, Gonzalez GM, Bansal V, Wang Y, Mason CE, Rana TM. Nature Microbiology 2016 Published online: 22 February 2016.

*N*6-methyladenosine (m6A) is the most prevalent internal modification of eukaryotic mRNA. Very little is known of the function of m6A in the immune system or its role in host–pathogen interactions. Here, the authors investigate the topology, dynamics and bidirectional influences of the viral–host RNA methylomes during HIV-1 infection of human CD4 T cells. They show that viral infection triggers a massive increase in m6A in both host and viral mRNAs. In HIV-1 mRNA, we identified 14 methylation peaks in coding and noncoding regions, splicing junctions and splicing regulatory sequences. The authors also identified a set of 56 human gene transcripts that were uniquely methylated in HIV-1-infected T cells and were enriched for functions in viral gene expression. The functional relevance of m6A for viral replication was demonstrated by silencing of the m6A writer or the eraser enzymes, which decreased or increased HIV-1 replication, respectively. Furthermore, methylation of two conserved adenosines in the stem loop II region of HIV-1 Rev response element (RRE) RNA enhanced binding of HIV-1 Rev protein to the RRE *in vivo* and influenced nuclear export of RNA. These results identify a new mechanism for the control of HIV-1 replication and its interaction with the host immune system.

Mitochondrial Injury and Cognitive Function In HIV Infection and Methamphetamine Use Var SR, Day TRC, Vitomirov A, Smith DM, Soontornniyomkij V, Moore DJ, Achim CL, Mehta SR, Perez-Santiago M. AIDS 2016; 30:839–847.

In this work, the authors evaluated the association of human immunodeficiency virus (HIV) infection and methamphetamine (METH) use with mitochondrial injury in the brain and its implication on neurocognitive impairment. Mitochondria carry their genome (mtDNA) and play a critical role in cellular processes in the central nervous system. METH is commonly used in HIV-infected populations. HIV infection and METH use can cause damage to mtDNA and lead to neurocognitive morbidity. The authors evaluated HIV infection and METH use with mitochondrial

injury in the brain. They obtained white and gray matter from Brodmann areas 7, 8, 9, 46 of the following: HIV-infected individuals with history of past METH use (HIV.METH., n.16), HIV-infected individuals with no history of past METH use (HIV.METH, n.11), and HIV-negative controls (HIVMETH, n.30). The authors used the 'common deletion', a 4977 bp mutation, as a measurement of mitochondrial injury, and quantified levels of mtDNA and 'common deletion' by droplet digital PCR, and evaluated in relation to neurocognitive functioning [Global Deficit Score (GDS)]. Levels of mtDNA and mitochondrial injury were highest in white matter of Brodmann area 46. A higher relative proportion of mtDNA carrying the 'common deletion' was associated with lower GDS ($P<0.01$) in HIV.METH. but higher GDS ($P<0.01$) in HIV.METH. The authors conclude that increased mitochondrial injury was associated with worse neurocognitive function in HIV.METH individuals. Among HIV.METH. individuals, an opposite effect was seen.

Prevalence Of Hepatitis C Virus Infection Among HIV. Men Who Have Sex With Men: A Systematic Review and Meta-Analysis Jordan AE, Perlman DC, Neurer J, Smith DJ, Des Jarlais DC, Hagan H. Int J STD AIDS OnlineFirst, published on January 28, 2016.
Since 2000, an increase in hepatitis C virus infection among HIV-infected (HIV.) men who have sex with men has been observed. Evidence points to blood exposure during sex as the medium of hepatitis C virus transmission. Hepatitis C virus prevalence among HIV.MSM overall and in relation to injection drug use is poorly characterized. In this study, a systematic review and meta-analysis examining global hepatitis C virus antibody prevalence and estimating active hepatitis C virus prevalence among HIV.MSM were conducted; 42 reports provided anti-hepatitis C virus prevalence data among HIV.MSM. Pooled prevalence produced an overall anti-hepatitis C virus prevalence among HIV.MSM of 8.1%; active HCV prevalence estimate was 5.3%–7.3%. Anti-hepatitis C virus prevalence among injection drug use and non-injection drug use HIV.MSM was 40.0% and 6.7%, respectively. Among HIV.MSM, hepatitis C virus prevalence increased significantly over time among the overall and non-injection drug use groups, and decreased significantly among injection drug use HIV.MSM. The author identified a moderate prevalence of hepatitis C virus among all HIV.MSM and among non-injection drug use HIV.MSM; for both, prevalence was observed to be increasing slightly. Pooled prevalence of hepatitis C virus among HIV.MSM was higher than that observed in the 1945–1965 US birth cohort. The modest but rising hepatitis C virus prevalence among HIV.MSM suggests an opportunity to control HCV among HIV.MSM; this combined with data demonstrating a rising hepatitis C virus incidence highlights the temporal urgency to do so.

Community Viral Load, Antiretroviral Therapy Coverage, and HIV Incidence In India: A Cross-Sectional, Comparative Study Solomon SS, Mehta SH, McFall AM, Srikrishnan AK, Saravanan S, Laeyendecker O, Balakrishnan P, Celentano DD, Solomon S, Lucas GM. Lancet HIV 2016 Published Online March 10, 2016.
HIV incidence is the best measure of treatment-programme effectiveness, but its measurement is difficult and expensive. The concept of community viral load as a modifiable driver of new HIV infections has attracted ubstantial attention. The authors set out to compare several measures of community viral load and antiretroviral therapy (ART) coverage as correlates of HIV incidence in high-risk populations. The authors analyzed data from a sample of people who inject drugs and men who have sex with men, who were participants of the baseline assessment of a cluster-randomized trial in progress across 22 cities in India (ClinicalTrials.gov number NCT01686750). The authors recruited the study population by use of respondent-driven sampling and did the baseline

assessment at 27 community-based sites (12 for men who have sex with men and 15 for people who inject drugs). The authors estimated HIV incidence with a multiassay algorithm and calculated five community-based measures of HIV control: mean log10 HIV RNA in participants with HIV in a community either engaged in care (in-care viral load), aware of their status but not necessarily in care (aware viral load), or all HIV-positive individuals whether they were aware, in care, or not (population viral load); participants with HIV in a community with HIV RNA more than 150 copies per mL (prevalence of viraemia); and the proportion of participants with HIV who self-reported ART use in the previous 30 days (population ART coverage). All participants were tested for HIV, with additional testing in HIV-positive individuals. The authors assessed correlations between the measures and HIV incidence with Spearman correlation coeffi cients and linear regression analysis. Between Oct 1, 2012, and Dec 19, 2013, the authors recruited 26,503 participants, 12,022 men who have sex with men and 14,481 people who inject drugs. Median incidence of HIV was 0.87% (IQR 0.40–1.17) in men who have sex with men and 1.43% (0.60–4.00) in people who inject drugs. Prevalence of viraemia was more strongly correlated with HIV incidence (correlation 0.81, 95% CI 0.62–0.91; p<0.0001) than all other measures, although correlation was signifi cant with aware viral load (0.59, 0.27–0.79; p=0.001), population viral load (0.51, 0.16–0.74; p=0.007), and population ART coverage (–0.54, –0.76 to –0.20; p=0.004). In-care viral load was not correlated with HIV incidence (0.29, –0.10 to 0.60; p=0.14). With regression analysis, the authors estimated that to reduce HIV incidence by 1 percentage point in a community, prevalence of viraemia would need to be reduced by 4.34%, and ART use in HIV-positive individuals would need to increase by 19.5%.

Ruptured Tendons In Anabolic-Androgenic Steroid Users: A Cross-Sectional Cohort Study
Kanayama G, DeLuca J, Meehan 3rd WP, Hudson JI, Isaacs S, Baggish A, Weiner R, Micheli L, Pope Jr, HG. Am J Sports Med. 2015; 43(11): 2638-2644.
Accumulating case reports have described tendon rupture in men who use anabolic-androgenic steroids (AAS). However, no controlled study has assessed the history of tendon rupture in a large cohort of AAS users and comparison nonusers. Men reporting long-term AAS abuse would report an elevated lifetime incidence of tendon rupture compared with non-AAS-using bodybuilders. Cohort study; Level of evidence, 3.Medical histories were obtained from 142 experienced male bodybuilders aged 35 to 55 years recruited in the course of 2 studies. Of these men, 88 reported at least 2 years of cumulative lifetime AAS use, and 54 reported no history of AAS use. In men reporting a history of tendon rupture, the circumstances of the injury, prodromal symptoms, concomitant drug or alcohol use, and details of current and lifetime AAS use (if applicable) were recorded. Surgical records were obtained for most participants. Nineteen (22%) of the AAS users, but only 3 (6%) of the nonusers, reported at least 1 lifetime tendon rupture. The hazard ratio for a first ruptured tendon in AAS users versus nonusers was 9.0 (95% CI, 2.5-32.3; P < .001). Several men reported 2 or more independent lifetime tendon ruptures. Interestingly, upper-body tendon ruptures occurred exclusively in the AAS group (15 [17%] AAS users vs 0 nonusers; risk difference, 0.17 [95% CI, 0.09-0.25]; P < .001 [hazard ratio not estimable]), whereas there was no significant difference between users and nonusers in risk for lower-body ruptures (6 [7%] AAS users, 3 [6%] nonusers; hazard ratio, 3.1 [95% CI, 0.7-13.8]; P = .13). Of 31 individual tendon ruptures assessed, only 6 (19%) occurred while weightlifting, with the majority occurring during other sports activities. Eight (26%) ruptures followed prodromal symptoms of nonspecific pain in the region. Virtually all ruptures were treated surgically, with complete or near-complete ultimate restoration of function. AAS abusers, compared with otherwise similar bodybuilders, showed a markedly increased risk of tendon ruptures, particularly upper-body tendon rupture.

Toward A More Accurate Estimate Of The Prevalence Of Hepatitis C In The United States
Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Hepatology. 2015; 62(5): 1353-1363.
Data from the 2003-2010 National Health and Nutrition Examination Survey (NHANES) indicate that about 3.6 million people in the United States have antibodies to the hepatitis C virus, of whom 2.7 million are currently infected. NHANES, however, excludes several high-risk populations from its sampling frame, including people who are incarcerated, homeless, or hospitalized; nursing home residents; active-duty military personnel; and people living on Indian reservations. The authors undertook a systematic review of peer-reviewed literature and sought out unpublished presentations and data to estimate the prevalence of hepatitis C in these excluded populations and in turn improve the estimate of the number of people with hepatitis C in the United States. The available data do not support a precise result, but the authors estimated that 1.0 million (range 0.4 million-1.8 million) persons excluded from the NHANES sampling frame have hepatitis C virus antibody, including 500,000 incarcerated people, 220,000 homeless people, 120,000 people living on Indian reservations, and 75,000 people in hospitals. Most are men. An estimated 0.8 million (range 0.3 million-1.5 million) are currently infected. Several additional sources of underestimation, including nonresponse bias and the underrepresentation of other groups at increased risk of hepatitis C that are not excluded from the NHANES sampling frame, were not addressed in this study. The number of US residents who have been infected with hepatitis C is unknown but is probably at least 4.6 million (range 3.4 million-6.0 million), and of these, at least 3.5 million (range 2.5 million-4.7 million) are currently infected; additional sources of potential underestimation suggest that the true prevalence could well be higher.

SERVICES RESEARCH

Catehol-o-Methyltransferase Gene Val158metPolymorphism as a Potential Predictor of Response to Computer-Assisted Delivery of Cognitive-Behavioral Therapy Among Cocaine-Dependent Individuals: Preliminary Findings from a Randomized Controlled Trial Carroll KM, Herman A, DeVito EE, Frankforter TL, Potenza MN, Sofuoglu M. Am J Addict. 2015; August; 24 (5): 443-451.
Findings from uncontrolled studies suggest that the COMT Val108/158Met polymorphism may affect response to cognitive behavioral therapy (CBT) in some populations. Using data from a randomized controlled trial evaluating computerized CBT (CBT4CBT), the authors evaluated treatment response by COMT genotype, with the a priori hypothesis that Val carriers would have improved response to computerized delivery of CBT. 101 cocaine-dependent individuals, of whom 81 contributed analyzable genetic samples, were randomized to standard methadone maintenance treatment plus CBT4CBT or standard treatment alone in an 8 week trial. There was a significant genotype by time effect on frequency of cocaine use from baseline to the end of the 6 month follow-up, suggesting greater reductions over time for Val carriers relative to individuals with the Met/Met genotype. There was a significant treatment condition by genotype interactions for rates of participants attaining 21 or more days of continuous abstinence as well as self-reported percent days of abstinence, suggesting less cocaine use among Val carriers when assigned to CBT compared to standard treatment. Exploration of possible mechanisms using measures of attentional biased also pointed to greater change over time in these measures among the Val carriers assigned to CBT. These are the first data from a randomized controlled trial indicating significant interactions of COMT polymorphism and behavioral therapy condition on treatment outcome, where Val carriers

appeared to respond particularly well to computerized CBT. These preliminary data point to a potential biomarker of response to CBT linked to its putative mechanism of action, enhanced cognitive control.

Long-term Outcomes After Randomization To Buprenorphine/naloxone Versus Methadone In A Multi-site Trial Hser Y-I, Evans E, Huang D, Weiss R, Saxon A, Carroll KM, Woody G, Liu D, Wakim P, Matthews AG, Hatch-Maillette M, Jelstrom E, Wiest K, McLaughlin P, Ling W. Addiction. 2015; Nov 13.
The objective of this study was to compare long-term outcomes among participants randomized to buprenorphine or methadone. Follow-up was conducted in 2011-2014 of 1,080 opioid-dependent participants entering 7 opioid treatment programs in the USA between 2006 and 2009 and randomized (within each program) to receive open-label buprenorphine/naloxone or methadone for up to 24 weeks; 795 participants completed in-person interviews (~74% follow-up interview rate) covering on average 4.5 years. Outcomes were indicated by mortality and opioid use. Covariates included demographics, site, cocaine use, and treatment experiences. Mortality was not different between the two randomized conditions with 23 (3.6%) of 630 participants randomized to buprenorphine having died, versus 26 (5.8%) of 450 participants randomized to methadone. Opioid use at follow-up was higher among participants randomized to buprenorphine relative to methadone (42.8% vs. 31.7% positive opioid urine specimens, $p < .01$, effect size (h) = 0.23 [0.09, 0.38]; 5.8 days vs. 4.4 days of past 30-day heroin use, $p < .05$, effect size (d) = 0.14 [0.00, 0.28]). Opioid use over the follow-up period by randomization condition was also significant ($F(7,39600) = 3.16$; $p < .001$) mostly due to less treatment participation among participants randomized to buprenorphine than methadone. Less opioid use was associated with both buprenorphine and methadone treatment (relative to no treatment); no difference was found between the two treatments. Individuals who are white or used cocaine at baseline responded better to methadone than to buprenorphine. There are few differences in long-term outcomes between buprenorphine and methadone treatment for opioid dependence, and treatment with each medication is associated with a strong reduction in opioid use.

Bridging Waitlist Delays With Interim Buprenorphine Treatment: Initial Feasibility Sigmon SC, C Meyer A, Hruska B, Ochalek T, Rose G, Badger GJ, Brooklyn JR, Heil SH, Higgins ST, Moore BA, Schwartz RP. Addict Behav. 2015; 51: 136-142.
Despite the effectiveness of agonist maintenance for opioid dependence, individuals can remain on waitlists for months, during which they are at significant risk for morbidity and mortality. Interim dosing, consisting of daily medication without counseling, can reduce these risks. In this pilot study, the authors examined the initial feasibility of a novel technology-assisted interim buprenorphine treatment for waitlisted opioid-dependent adults. Following buprenorphine induction during Week 1, participants (n=10) visited the clinic at Weeks 2, 4, 6, 8, 10 and 12 to ingest their medication under staff observation, provide a urine specimen and receive their remaining doses via a computerized Med-O-Wheel Secure device. They also received daily monitoring via an Interactive Voice Response (IVR) platform, as well as random call-backs for urinalysis and medication adherence checks. The primary outcome was percent of participants negative for illicit opioids at each 2-week visit, with secondary outcomes of past-month drug use, adherence and acceptability. Participants achieved high levels of illicit opioid abstinence, with 90% abstinent at the Week 2 and 4 visits and 60% at Week 12. Significant reductions were observed in self-reported past-month illicit opioid use ($p<.001$), opioid withdrawal ($p<.001$), opioid craving ($p<.001$) and ASI Drug

composite score (p=.008). Finally, adherence with buprenorphine administration (99%), daily IVR calls (97%) and random call-backs (82%) was high. Interim buprenorphine treatment shows promise for reducing patient and societal risks during delays to conventional treatment. A larger-scale, randomized clinical trial is underway to more rigorously examine the efficacy of this treatment approach.

Successful Treatment Of Chronic Hepatitis C With Triple Therapy In An Opioid Agonist Treatment Program Litwin AH, Soloway IJ, Cockerham-Colas L, Reynoso S, Heo M, Tenore C, Roose RJ. Int J Drug Policy. 2015; 26(10): 1014-1019.
People who inject drugs (PWID) constitute 10 million people globally with hepatitis C virus, including many opioid agonist treatment patients. Little data exist describing clinical outcomes for patients receiving HCV treatment with direct-acting antiviral agents (DAAs) in opioid agonist treatment settings. In this retrospective observational study, the authors describe clinical outcomes for 50 genotype-1 patients receiving HCV treatment with triple therapy: telaprevir (n=42) or boceprevir (n=8) in combination with pegylated interferon and ribavirin on-site in an opioid agonist treatment program. Overall, 70% achieved an end of treatment response (ETR) and 62% achieved a sustained virological response (SVR). These treatment outcomes are nearly equivalent to previously published HCV outcomes shown in registration trials, despite high percentages of recent drug use prior to treatment (52%), ongoing drug use during treatment (45%) and psychiatric comorbidity (86%). Only 12% (n=6) discontinued antiviral treatment early for non-virological reasons. Four patients received a blood transfusion, and one discontinued telaprevir due to severe rash. These data demonstrate that on-site HCV treatment with direct-acting antiviral agents is effective in opioid agonist treatment patients including patients who are actively using drugs. Future interferon-free regimens will likely be even more effective. Opioid agonist treatment programs represent an opportunity to safely and effectively treat chronic hepatitis C, and PWID should have unrestricted access to DAAs.

Office-Based Opioid Treatment With Buprenorphine (OBOT-B): Statewide Implementation Of The Massachusetts Collaborative Care Model In Community Health Centers LaBelle CT, Han SC, Bergeron A, Samet JH. J Subst Abuse Treat. 2016; 60: 6-13.
The authors describe a Massachusetts Bureau of Substance Abuse Services' (BSAS) initiative to disseminate the office-based opioid treatment with buprenorphine (OBOT-B) Massachusetts Model from its development at Boston Medical Center (BMC) to its implementation at fourteen community health centers (CHCs) beginning in 2007. The Massachusetts Collaborative Care Model for the delivery of opioid agonist therapy with buprenorphine, in which nurses working with physicians play a central role in the evaluation and monitoring of patients, holds promise for the effective expansion of treatment for opioid use disorders. The training of and technical assistance for the OBOT nurses as well as a limited program assessment are described. Data spanning 6years (2007-2013) report patient demographics, prior treatment for opioid use disorders, history of overdose, housing, and employment. The expansion of OBOT to the fourteen CHCs increased the number of physicians who were "waivered" (i.e., enabling their prescribing of buprenorphine) by 375%, from 24 to 114, within 3years. During this period the annual admissions of OBOT patients to CHCs markedly increased. Dissemination of the Massachusetts Model of the Office-Based Opioid Treatment with Buprenorphine employing a collaborative care model with a central role for nursing enabled implementation of effective treatment for patients with an opioid use disorder at community

health centers throughout Massachusetts while effectively engaging primary care physicians in this endeavor.

CTN-RELATED RESEARCH

Gender Differences in Internalizing Symptoms and Suicide Risk Among Men and Women Seeking Treatment for Cannabis Use Disorder from Late Adolescence to Middle Adulthood Foster KT, Li N, McClure EA, Sonne SC, Gray KM. J Subst Abuse Treat 2016 Jul; 66:16-22. Cannabis continues to rise in popularity as the perception of its harmfulness decreases and evidence of its deleterious developmental effect increases. While internalizing distress and suicide risk have been linked with cannabis use problems [DSM-5 cannabis use disorder (CUD); DSM-IV cannabis abuse and dependence] it remains unclear how this association varies over the course of development in treatment-seeking men and women. The current study utilized the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) to conduct a cross-sectional comparison of internalizing distress and suicide risk among men (n = 437) and women (n = 163) spanning ages – 50 who met DSM-5 criteria for CUD. Interactions between gender and developmental stage (i.e., late adolescence, early adulthood, and middle adulthood) were observed for suicide risk and anxiety but not depression problems. Specifically, women seeking CUD treatment in late adolescence and middle adulthood exhibited significantly higher rates of anxiety and suicide risk compared to men seeking treatment during the same developmental stages. Internalizing distress and suicide risk did not differ between treatment-seeking men and women in the early adult stage. Overall, results suggest that the structure of risk for CUD may differ in men and women across the lifespan and that women presenting for CUD treatment during late adolescence and middle adulthood may uniquely benefit from intervention designed to address these elevations in anxiety and suicide risk.

Cost-Effectiveness Of An Internet-Delivered Treatment For Substance Abuse: Data From A Multisite Randomized Controlled Trial Murphy SM, Campbell AN, Ghitza UE, Kyle TL, Bailey GL, Nunes EV, Polsky D. Drug Alcohol Depend. 2016 Apr 1; 161:119-126. Epub 2016 Jan 30. Substance misuse and excessive alcohol consumption are major public health issues. Internet-based interventions for substance use disorders (SUDs) are a relatively new method for addressing barriers to access and supplementing existing care. This study examines cost-effectiveness in a multisite, randomized trial of an internet-based version of the community reinforcement approach (CRA) with contingency management (CM) known as the Therapeutic Education System (TES). This was an economic evaluation of the 12-week trial with follow-up at 24 and 36 weeks. 507 individuals who were seeking therapy for alcohol or other substance use disorders at 10 outpatient community-based treatment programs were recruited and randomized to either treatment as usual (TAU) or TES+TAU. Sub-analyses were completed on participants with a poorer prognosis (i.e., those not abstinent at study entry). From the provider's perspective, TES+TAU as it was implemented in this study costs $278 (SE=87) more than TAU alone after 12 weeks. The quality-adjusted life years gained by TES+TAU and TAU were similar; however, TES+TAU has at least a 95% chance of being considered cost-effective for providers and payers with willingness-to-pay thresholds as low as $20,000 per abstinent year. Findings for the subgroup not abstinent at study entry are slightly more favorable. With regard to the clinical outcome of abstinence, the authors'cost-effectiveness findings of TES+TAU compare favorably to those found elsewhere in the CM literature. The

analyses performed here serve as an initial economic framework for future studies integrating technology into SUD therapy.

Buprenorphine + Naloxone plus Naltrexone for the Treatment of Cocaine Dependence: The Cocaine Use Reduction with Buprenorphine (CURB) Study Ling W, Hillhouse MP, Saxon AJ, Mooney LJ, Thomas CM, Ang A, Matthews AG, Hasson A, Annon J, Sparenborg S, Liu DS, McCormack J, Church S, Swafford W, Drexler K, Schuman C, Ross S, Wiest K, Korthuis P, Lawson W, Brigham GS, Knox PC, Dawes M, Rotrosen J. Addiction. 2016 Mar 7. [Epub ahead of print].

The aims of this study were to examine the safety and effectiveness of buprenorphine + naloxone sublingual tablets (BUP, as Suboxone®) provided after administration of extended-release injectable naltrexone (XR-NTX, as Vivitrol®) to reduce cocaine use in participants who met DSM-IV criteria for cocaine dependence and past or current opioid dependence or abuse. This multi-centered, double-blind, placebo-controlled study, conducted under the auspices of the National Drug Abuse Treatment Clinical Trials Network, randomly assigned 302 participants at sites in California, Oregon, Washington, Colorado, Texas, Georgia, Ohio, New York, and Washington D.C., USA to 1 of 3 conditions provided with XR-NTX: 4 mg/day BUP (BUP4, n = 100), 16 mg/day BUP (BUP16, n = 100), or no buprenorphine (placebo; PLB, n = 102). Participants received pharmacotherapy for 8 weeks, with 3 clinic visits per week. Cognitive Behavioral Therapy was provided weekly. Follow-up assessments occurred at 1 and 3 months post-intervention. The planned primary outcome was urine drug screen (UDS)-corrected, self-reported cocaine use during the last 4 weeks of treatment. Planned secondary analyses assessed cocaine use by UDS, medication adherence, retention, and adverse events. No group differences were found between groups for the primary outcome (BUP4 vs. PLB, p = 0.262; BUP16 vs PLB, p = 0.185). Longitudinal analysis of UDS data during the evaluation period using generalized linear mixed equations found a statistically significant difference between BUP16 and PLB (p = 0.022, OR = 1.71) but not for BUP4 (p = 0.105, OR = 1.05). No secondary outcome differences across groups were found for adherence, retention, or adverse events. Buprenorphine + naloxone, used in combination with naltrexone, may be associated with reductions in cocaine use among people who meet DSM-IV criteria for cocaine dependence and past or current opioid dependence or abuse.

Decision-Making Processes As Predictors Of Relapse and Subsequent Use In Stimulant-Dependent Patients Adinoff B, Carmody TJ, Walker R, Donovan DM, Brigham GS, Winhusen T. Am J Drug Alcohol Abuse. 2016 Jan 8:1-10. [Epub ahead of print].

Decision-making processes have been posited to affect treatment outcome in addicted patients. The present multi-site study assessed whether two measures of decision-making predicted relapse and subsequent use in stimulant-dependent patients. A total of 160 methamphetamine- or cocaine-dependent patients participating in a multi-site clinical trial evaluating a modified 12-step facilitation intervention for stimulant-dependent patients (STAGE-12) were assessed. Decision-making processes of risk and delay (Iowa Gambling Task [IGT]) and response reversal (Wisconsin Card Sorting Task [WCST]) were obtained shortly after treatment admission followed by assessment of stimulant use over the next six months. The relationships of the IGT and WCST (Perseverative Errors) with relapse (yes/no) and days of stimulant use during the 6-month period following post-randomization were evaluated. Performance on the IGT and WCST did not significantly predict relapse status or time to relapse. Unexpectedly, worse performance on the IGT was associated with a fewer number of stimulant use days (p = 0.001). In contrast, worse

performance on the WCST (fewer perseverative errors) was associated with a greater number of stimulant use days ($p = 0.0003$). The predictive effects of perseverative errors on subsequent use were confined to methamphetamine-dependent and Minority participants. Decision-making processes, as measured in the current study, do not uniformly predict relapse or subsequent use. A decrease in the salience attribution of non-drug reinforcers may explain the positive relationship between IGT performance and post-relapse use. More comprehensive and global measures of impulsiveness may better assess relapse risk and use.

Pain Volatility and Prescription Opioid Addiction Treatment Outcomes In Patients With Chronic Pain Worley MJ, Heinzerling KG, Shoptaw S, Ling W. Exp Clin Psychopharmacol. 2015 Dec;23(6):428-35. Epub 2015 Aug 24.
The combination of prescription opioid dependence and chronic pain is increasingly prevalent and hazardous to public health. Variability in pain may explain poor prescription opioid addiction treatment outcomes in persons with chronic pain. This study examined pain trajectories and pain volatility in patients with chronic pain receiving treatment for prescription opioid addiction. The authors conducted secondary analyses of adults with chronic pain ($n = 149$) who received buprenorphine/naloxone (BUP/NLX) and counseling for 12 weeks in an outpatient, multisite clinical trial. Good treatment outcome was defined as urine-verified abstinence from opioids at treatment endpoint (Week 12) and during at least 2 of the previous 3 weeks. Pain severity significantly declined over time during treatment ($b = -0.36$, $p < .001$). Patients with greater pain volatility were less likely to have a good treatment outcome (odds ratio = 0.55, $p < .05$), controlling for baseline pain severity and rate of change in pain over time. A 1 standard deviation increase in pain volatility was associated with a 44% reduction in the probability of endpoint abstinence. The significant reduction in subjective pain during treatment provides observational support for the analgesic effects of BUP/NLX in patients with chronic pain and opioid dependence. Patients with greater volatility in subjective pain during treatment have increased risk of returning to opioid use by the conclusion of an intensive treatment with BUP/NLX and counseling. Future research should examine underlying mechanisms of pain volatility and identify related therapeutic targets to optimize interventions for prescription opioid addiction and co-occurring chronic pain.

INTRAMURAL RESEARCH

Integrative Neuroscience Research Branch
Neuronal Networks Section

Glutamatergic Efferents From the Ventral Tegmental Area To Nucleus Accumbens Drive Aversion By Acting On GABAergic Interneurons Qi J, Zhang S, Wang HL, Barker DJ, Miranda-Barrientos J and Morales M. Nat Neurosci 2016; Mar 28. doi: 10.1038/nn.4281. [Epub ahead of print].
The ventral tegmental area (VTA) is best known for its dopamine neurons, some of which project to nucleus accumbens (nAcc). However, the VTA also has glutamatergic neurons that project to nAcc. The function of the mesoaccumbens-glutamatergic pathway remains unknown. Here, the authors report that nAcc photoactivation of mesoaccumbens-glutamatergic fibers promotes aversion. Although they found that these mesoaccumbens-glutamate-fibers lack GABA, the aversion evoked by their photoactivation depends on glutamate and GABA receptor signaling, and not on dopamine

receptor signaling. The authors found that mesoaccumbens-glutamatergic-fibers establish multiple asymmetric synapses on single parvalbumin-GABAergic interneurons, and that nAcc photoactivation of these fibers drives AMPA-mediated cellular firing of parvalbumin-GABAergic interneurons. These parvalbumin-GABAergic-interneurons, in turn, inhibit nAcc medium spiny output neurons, as such, controlling inhibitory neurotransmission within nAcc. The mesoaccumbens-glutamatergic pathway is the first glutamatergic input to nAcc shown to mediate aversion, instead of reward, and the first pathway shown to establish excitatory synapses on nAcc parvalbumin-GABAergic interneurons.

Cellular Neurobiology Research Branch
Behavioral Neurophysiology Research Section

Neural Estimates Of Imagined Outcomes In Basolateral Amygdala Depend On Orbitofrontal Cortex Lucantonio F, Gardner MP, Mirenzi A, Newman LE, Takahashi YK, Schoenbaum G. Journal of Neuroscience 2015; 35:16521-16530.
Reciprocal connections between the orbitofrontal cortex (OFC) and the basolateral nucleus of the amygdala (BLA) provide a critical circuit for guiding normal behavior when information about expected outcomes is required. Recently, the authors reported that outcome signaling by OFC neurons is also necessary for learning in the face of unexpected outcomes during a Pavlovian over-expectation task. Key to learning in this task is the ability to build on prior learning to infer or estimate an amount of reward never previously received. OFC was critical to this process. Notably, in parallel work, the authors found that BLA was not necessary for learning in this setting. This suggested a dissociation in which the BLA might be critical for acquiring information about the outcomes but not for subsequently using it to make novel predictions. Here we evaluated this hypothesis by recording single-unit activity from BLA in rats during the same Pavlovian over-expectation task used previously. The authors found that spiking activity recorded in BLA in control rats did reflect novel outcome estimates derived from the integration of prior learning, however consistent with a model in which this process occurs in the OFC, these correlates were entirely abolished by ipsilateral OFC lesions. These data indicate that this information about these novel predictions is represented in the BLA, supported via direct or indirect input from the OFC, even though it does not appear to be necessary for learning.

Cellular Neurobiology Research Branch
Synaptic Plasticity Section

Role Of Ventral Subiculum In Context-Induced Relapse To Alcohol Seeking After Punishment-Imposed Abstinence Marchant NJ, Campbell EJ, Whitaker LR, Harvey BK, Kaganovsky K, Adhikary S, Hope BT, Heins RC, Prisinzano TE, Vardy E, Bonci A, Bossert JM, Shaham Y. J Neurosci. 2016 Mar 16;36(11):3281-3294
In many human alcoholics, abstinence is self-imposed because of the negative consequences of excessive alcohol use, and relapse is often triggered by exposure to environmental contexts associated with prior alcohol drinking. The authors recently developed a rat model of this human condition in which we train alcohol-preferring P rats to self-administer alcohol in one context (A), punish the alcohol-reinforced responding in a different context (B), and then test for relapse to

alcohol seeking in Contexts A and B without alcohol or shock. Here, we studied the role of projections to nucleus accumbens (NAc) shell from ventral subiculum (vSub), basolateral amygdala, paraventricular thalamus, and ventral medial prefrontal cortex in context-induced relapse after punishment-imposed abstinence. First, the authors measured double-labeling of the neuronal activity marker Fos with the retrograde tracer cholera toxin subunit B (injected in NAc shell) and demonstrated that context-induced relapse is associated with selective activation of the vSub→NAc shell projection. Next, the authors reversibly inactivated the vSub with GABA receptor agonists (muscimol+baclofen) before the context-induced relapse tests and provided evidence for a causal role of vSub in this relapse. Finally, they used a dual-virus approach to restrict expression of the inhibitory κ opioid-receptor based DREADD (KORD) in vSub→NAc shell projection neurons. The authors found that systemic injections of the KORD agonist salvinorin B, which selectively inhibits KORD-expressing neurons, decreased context-induced relapse to alcohol seeking. These results demonstrate a critical role of vSub in context-induced relapse after punishment-imposed abstinence and further suggest a role of the vSub→NAc projection in this relapse.

GRANTEE HONORS AND AWARDS

The Breakthrough Prize Foundation announced that Howard Hughes Medical Institute (HHMI) investigators **Dr. Karl Deisseroth** of Stanford University and **Dr. Ed Boyden** of MIT are among five scientists awarded the Breakthrough Prizes in Life Sciences. The prizes honor transformative advances toward understanding living systems and extending human life. It's a $3M prize.

Dr. Robert Heimer of Yale University was awarded a Jefferson Science Fellowship by the U.S. National Academy of Sciences, March 3, 2016, Washington, D.C. Dr. Heimer, who has a successful international and domestic drug abuse, AIDS and related infectious disease research portfolio, will be working with the U.S. Department of State on international security and biological issues. Preeminent in these includes the threat of emerging syndemics of infectious diseases. NIDA support to Dr. Heimer's research has played an important part in advancing our understanding of such threats.

Dr. John Lowe has been selected to receive the 2016 American Nurses Association Luther Christman Award in recognition of contributions that individual men in nursing have made to the profession. He will be recognized at a reception on June 23, 2016 before the ANA Membership Assembly.

Courtney Miller (Scripps Florida) was the recipient of a prestigious PECASE Award. (Presidential Early Career Awards for Scientists and Engineers).

Dr. James L. Sorensen received the **Miracles Tribute award**, honoring a professional for lifetime achievement and outstanding service in the treatment of addiction and co-occurring disorders, from the Alta Mira Recovery program located in Sausalito, California. The award was presented on Friday, November 6, 2015 at the third Annual Miracles Breakfast, held at the Olympic Club in San Francisco. Dr. Sorensen has made **significant contributions to the treatment of addiction and co-occurring disorders** over the past thirty years. He continues to serve as professor in residence in the UCSF Department of Psychiatry at Langley Porter Psychiatric Institute as well as part of the medical staff at San Francisco General Hospital in which he dedicates much of his research to treatment and services in substance abuse and community mental health. He also serves as co-director, with Dr. Dennis McCarty of Oregon Health & Science University (OHSU), of the Western States Node of the National Drug Abuse Treatment Clinical Trials Network (CTN). In addition to his own research and his work in the CTN, he continues to mentor many budding researchers who also have an interest in working in these fields. Dr. Sorensen's contribution collectively enables the progression of treatment in addiction and co-occurring disorders, and inspires current and future researchers in doing the same.

Dr. Cathy Spatz Widom, Distinguished Professor of Psychology at John Jay College of Criminal Justice- CUNY, was selected by the international jury for the Stockholm Prize in Criminology in recognition of advancing knowledge about how parents and peers shape successes, or failures, in preventing adult violence and crime. She will receive the award at a ceremony in Stockholm, Sweden in June, 2016.

STAFF HONORS AND AWARDS

STAFF AWARDS

Dr. Cheryl Anne Boyce, received an NIA Director's Award as part of the planning team for the workshop "Multiple Approaches to Understanding and Preventing Elder Abuse and Mistreatment" held in October, 2015 in response to a strong recommendation for follow-up to the White House Conference on Aging. The workshop succeeded in illuminating both the accomplishments and the weaknesses of elder abuse research, and provided valuable input for the development of future program emphases for NIH.

Dr. Peter Hartsock, DESPR, was inducted as a Fellow in to the College of Physicians of Philadelphia (CPP), Nov. 20, 2015.

Dr. Yu "Woody" Lin received the Presidential Commendation from the American Academy of Pain Medicine (AAPM) for bringing together the National Institutes of Health and the AAPM membership through a better understanding of the NIH grant programs.

Dr. Minda Lynch was selected to be the 2016 recipient of the College on Problems in Drug Dependence's J. Michael Morrison Award.

Dr. Cora Lee Wetherington is being honored with the *Outstanding Contributions to Advancing the Understanding of Addictions Award for 2016* from Division 50 (which is the Society of Addiction Psychology) of the American Psychological Association

Dr. Lorenzo Leggio, IRP, received the 2016 NIAAA Director Mentoring Award.

Ms. Lisa Farinelli (Manager in Dr. Leggio's CPN lab) received the 2016 NIAAA Director's Operational Excellence Award.

Dr. Mehdi Farokhnia (postdoctoral fellow in Dr. Leggio's CPN lab) received a 2016 New Investigator Award from the International Society for CNS Clinical Trials and Methodology (ISCTM), Washington DC.

Dr. Kenner Rice, IRP, was named recipient of the 2016 Mentorship Award given annually to a member of the College on Problems of Drug Dependence who has been an exemplary mentor to developing researchers in the field of drug dependence.

Dr. Anna Li, IRP, a post-doc in Dr. Shaham's group, has received a K99/R00 award.

Dr. Bruce Hope, IRP, received tenure in September 2015.

Dr. Yuji Takahashi, IRP, was promoted to Staff Scientist.

STAFF CHANGES

New Appointments/Employees

Dr. Kevin Walton was recently appointed Chief of the Clinical Research Grants Branch of DTMC. He replaced Dr. Jamie Biswas who retired last December. Kevin received his PhD in Pharmacology from the Johns Hopkins University School of Medicine. After his postdoc and several years as an Assistant Professor at the University of Michigan, Kevin spent 15 years in neuroscience drug discovery, most recently at Pfizer where he worked on developing novel medications for neurological and psychiatric disorders. Kevin has been at NIH since 2010 and joined NIDA in 2013 as a Project Officer. He has made significant contributions to NIH, such as addressing the research opportunities and challenges of electronic cigarettes, including collaborations to develop a Drug Master File with the FDA and a research electronic cigarette for use by investigators. Kevin will now be responsible for leading the grant-funded clinical research of pharmacological and non-pharmacological treatments for substance use disorders

Dr. Roger Sorensen succeeds Dr. Nancy Pilotte as the Branch Chief of the Integrative Neuroscience Branch in the Division of Neuroscience and Behavior. Dr. Sorensen joined NIDA as a Project Officer in 2007. Dr. Sorensen's programmatic interests broadly concern studies of the neurobiological mechanisms underlying the functional changes in neuronal excitability, synaptic plasticity, homeostasis, and communication within neural circuits and networks as a consequence of substance abuse and addiction. Of additional interest are the effects of psychoactive drugs on the functional interactions between neurons and glial cells in their regulation of neuronal activity. Dr. Sorensen manages the Pathways to Independence Award [K99/R00] program in basic research, and is co-Chair of the NIDA-NIAAA Neuroscience Workgroup. He contributes to various programs and planning activities across the NIH including the NIH Blueprint for Neuroscience and BRAIN Initiative programs.

Dr. Lorenzo Leggio, IRP, was appointed as the Associate Director for Clinical Research in the Medication Development Program (MDP, Director: Dr. Amy Newman) of NIDA IRP.

Dr. Eric Bow joined the Section on Drug Design and Synthesis, IRP, as an IRTA Postdoctoral Fellow.

Mr. Adrian Guerrero joined the Medicinal Chemistry Section, IRP, in February 2016 as an IRTA post-baccalaureate fellow. Adrian is the recipient of the NIDA SD Fellowship for Diversity in Research.

Dr. Anver Basha Shaik joined the Medicinal Chemistry Section, IRP, in February 2016 as a visiting post-doctoral fellow.

In April 2016, **Harold (Marcus) Brown** joined the Office of Management's Administrative Management and Analysis Branch as an Administrative Officer. Marcus comes to NIDA from the National Cancer Institute.

In January 2016, **Tracey Cain** joined the Office of Acquisitions as a Contract Specialist. Tracey comes to NIDA from the private sector.

In March 2016, **Amy Connolly** joined the Grants Management Branch of the Division of Extramural Research as a Grants Management Specialist. Amy comes to NIDA from the National Heart, Lung and Blood Institute.

In January 2016, **Gweniffer Epps** joined the Office of Acquisitions as a Contract Specialist. Gweniffer comes to NIDA from the National Cancer Institute.

In April 2016, **Kenneth Janosko** joined the Office of Acquisitions' NIDA R&D Branch as a Contract Specialist. Kenneth comes to NIDA from a position with the Department of the Navy.

In April 2016, **Ejinwaemeonu Ndidi Okeag** joined the Office of Acquisitions' NIDA R&D Branch as a Contract Specialist. Ejinwaemeonu comes to NIDA from a position in the private sector.

In March 2016, **Stacey Polk** joined the Office of Acquisitions Station Support Branch as a Contract Specialist. Stacey comes to NIDA from the NIH Clinical Center.

Departures

Dr. Joni Rutter left to take a position in the Precision Medicine Initiative as Director, Personalized Medicine Initiative (PMI) Programs & Strategic Implementation. In October 2015 Dr. Rutter began a detail to the PMI initiative and helped lead the program from FOA development to issuing awards in a period of only 4 months. She was offered a full time leadership position in March of 2016.

Dr. Cheryl Anne Boyce will begin a new position in May 2016 as Chief of the Implementation Science Branch within the Center for Translation Research and Implementation Science (CTRIS) at the National Heart, Lung, and Blood Institute (NHLBI). In this role, she will advance translational research programs to accelerate the adoption and sustained appropriate use of drugs, therapeutics, diagnostics, and effective interventions that more fully utilize scientific discoveries and result in better health for diverse and global populations.

Dr. Tom Radman left the Integrative Neuroscience Branch to take a position in the lab of Holly Lisenby at the NIMH intramural research program. Tom joined NIDA in 2014 and led our program in Big Data Science and Computational Neurobiology in the Integrative Neuroscience Branch. He was a leader in a Strategic Working Group on Big Data Science in 2015 and a liaison for DNB and NIDA to many trans-NIH efforts including the BRAIN intiative and Big Data to Knowledge.

In April 2016, **Megan Ault**, a Contract Specialist with the Office of Management's Station Support Branch left NIDA for a position with the Department of Energy

In April 2016, **Matthew Antonin**i, a Contract Specialist in the Office of Management's Office of Acquisitions left NIDA for a position with the private sector.

In February 2016, **Renata Baginski**, an Administrative Officer with the Office of Management's Administrative Management and Analysis Branch left NIDA for a position with the Smithsonian Institution.

In January 2016, **Rodney Brooks**, a Contract Specialist in the Office of Management's Station Support Branch left NIDA for a position with the HHS Office of the Secretary.

In April 2016, **Mark Caulder**, a Health Program Specialist (Genetics) in the Division of Neuroscience and Behavior left NIDA for a position with the NIH Office of the Director.

In January 2016, **Dawnya Jordan**, a Program Specialist in the Division of Neuroscience and Behavior left NIDA for a position with the Food and Drug Administration.

In March 2016, **Samantha Kelly**, a Contract Specialist with the Office of Management's Station Support Branch left NIDA for a position with the Defense Information Systems Agency.

Retirements

Dr. Nancy Pilotte, Chief of the Integrative Neuroscience [formerly the Functional Neuroscience Research] Branch, within the Division of Neuroscience and Behavior [DNB], officially retired on 29 February 2016. Nancy had a long, illustrious career at NIDA. She joined the Intramural Research Program at NIDA in 1987. She subsequently moved to a position within NIDA's Medication Development division prior to becoming Branch Chief. Nancy was passionate about the basic research being supported by NIDA. In particular, she promoted and nurtured work studying neurotransmitters, dopamine release, and neural circuitry to better understand the neurobiology underlying drug abuse and addiction. She encouraged the development and use of research tools such as optogenetics and DREADDS to study central nervous system function. She was a proponent for studying stress circuits, neuroendocrine influences, and sex differences in addiction. Nancy also made major contributions to a variety of activities and programs across NIDA and the NIH, including the NIH Blueprint for Neuroscience Research, and the Office of Research on Women's Health.

Michele Straus, MS, RPh retired from NIDA/CCTN and federal government service in February 2016.

National Institute
on Drug Abuse