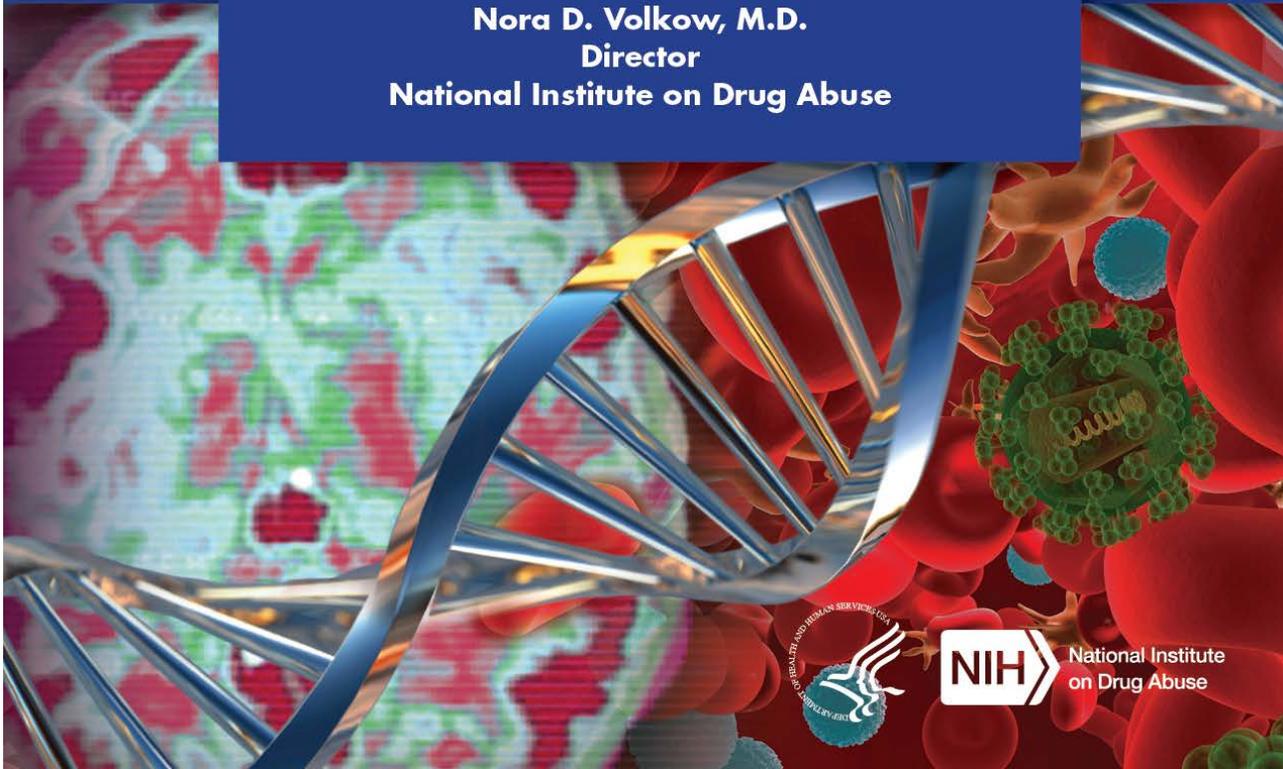




DIRECTOR'S REPORT

to the
National Advisory Council on Drug Abuse
February 2018

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National Institute
on Drug Abuse

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RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Genome-Wide Association Study Of Delay Discounting In 23,217 Adult Research Participants Of European Ancestry Sanchez-Roige S, Fontanillas P, Elson SL, Pandit A, Schmidt EM, Foerster JR, Abecasis GR, Gray JC, de Wit H, Davis LK, MacKillop J, Palmer AA; 23andMe Research Team. *Nat Neurosci.* 2018 Jan;21(1):16-18.

Delay discounting (DD), the tendency to discount the value of delayed versus current rewards, is elevated in a constellation of diseases and behavioral conditions. The authors performed a genome-wide association study of DD using 23,127 research participants of European ancestry. The most significantly associated single-nucleotide polymorphism was rs6528024 ($P = 2.40 \times 10^{-8}$), which is located in an intron of the gene GPM6B. They also showed that 12% of the variance in DD was accounted for by genotype and that the genetic signature of DD overlapped with attention-deficit/hyperactivity disorder, schizophrenia, major depression, smoking, personality, cognition and body weight.

Protraction Of Neuropathic Pain By Morphine Is Mediated By Spinal Damage Associated Molecular Patterns (DAMPs) In Male Rats Grace, Peter M; Strand, Keith A; Galer, Erika L; Rice, Kenner C; Maier, Steven F; Watkins, Linda R. *Brain Behav Immun.* 2017;[epub ahead of print].

The authors have recently reported that a short course of morphine, starting 10 days after sciatic chronic constriction injury (CCI), prolonged the duration of mechanical allodynia for months after morphine ceased. Maintenance of this morphine-induced persistent sensitization was dependent on spinal NOD-like receptor protein 3 (NLRP3) inflammasomes-protein complexes that proteolytically activate interleukin-1 β (IL-1 β) via caspase-1. However, it is still unclear how NLRP3 inflammasome signaling is maintained long after morphine is cleared. Here, the authors demonstrate that spinal levels of the damage associated molecular patterns (DAMPs) high mobility group box 1 (HMGB1) and biglycan are elevated during morphine-induced persistent sensitization in male rats; that is, 5 weeks after cessation of morphine dosing. They also show that HMGB1 and biglycan levels are at least partly dependent on the initial activation of caspase-1, as well as Toll like receptor 4 (TLR4) and the purinergic receptor P2X7R-receptors responsible for priming and activation of NLRP3 inflammasomes. Finally, pharmacological attenuation of the DAMPs HMGB1, biglycan, heat shock protein 90 and fibronectin persistently reversed morphine-prolonged allodynia. The authors conclude that after peripheral nerve injury, morphine treatment results in persistent DAMP release via TLR4, P2X7R and caspase-1, which are involved in formation/activation of NLRP3 inflammasomes. These DAMPs are responsible for maintaining persistent allodynia, which may be due to engagement of a positive feedback loop, in which NLRP3 inflammasomes are persistently activated by DAMPs signaling at TLR4 and P2X7R.

Prior Alcohol Use Enhances Vulnerability To Compulsive Cocaine Self-administration By Promoting Degradation Of HDAC4 and HDAC5 Griffin Jr, Edmund A; Melas, Philippe A; Zhou, Royce; Li, Yang; Mercado, Peter; Kempadoo, Kimberly A; Stephenson, Stacy; Colnaghi, Luca; Taylor, Kathleen; Hu, Mei-Chen; Kandel, Eric R; Kandel, Denise B. *Sci Adv.* 2017; 3(11): e1701682.

Addiction to cocaine is commonly preceded by experiences with legal or decriminalized drugs, such as alcohol, nicotine, and marijuana. The biological mechanisms by which these gateway drugs

contribute to cocaine addiction are only beginning to be understood. The authors report that in the rat, prior alcohol consumption results in enhanced addiction-like behavior to cocaine, including continued cocaine use despite aversive consequences. Conversely, prior cocaine use has no effect on alcohol preference. Long-term, but not short-term, alcohol consumption promotes proteasome-mediated degradation of the nuclear histone deacetylases HDAC4 and HDAC5 in the nucleus accumbens, a brain region critical for reward-based memory. Decreased nuclear HDAC activity results in global H3 acetylation, creating a permissive environment for cocaine-induced gene expression. The authors also find that selective degradation of HDAC4 and HDAC5, facilitated by the class II-specific HDAC inhibitor MC1568, enhances compulsive cocaine self-administration. These results parallel the authors' previously reported findings that the gateway drug nicotine enhances the behavioral effects of cocaine via HDAC inhibition. Together, these findings suggest a shared mechanism of action for the gateway drugs alcohol and nicotine, and reveal a novel mechanism by which environmental factors may alter the epigenetic landscape of the reward system to increase vulnerability to cocaine addiction.

Structure-Based Discovery Of New Antagonist and Biased Agonist Chemotypes For the Kappa Opioid Receptor Zheng, Zhong; Huang, Xi-Ping; Mangano, Thomas J; Zou, Rodger; Chen, Xin; Zaidi, Saheem A; Roth, Bryan L; Stevens, Raymond C; Katritch, Vsevolod. *J Med Chem.* 2017; 60(7): 3070-3081.

The ongoing epidemics of opioid overdose raises an urgent need for effective antiaddiction therapies and addiction-free painkillers. The κ -opioid receptor (KOR) has emerged as a promising target for both indications, raising demand for new chemotypes of KOR antagonists as well as G-protein-biased agonists. The authors employed the crystal structure of the KOR-JDTic complex and ligand-optimized structural templates to perform virtual screening of available compound libraries for new KOR ligands. The prospective virtual screening campaign yielded a high 32% hit rate, identifying novel fragment-like and lead-like chemotypes of KOR ligands. A round of optimization resulted in 11 new submicromolar KOR binders (best $K_i = 90$ nM). Functional assessment confirmed at least two compounds as potent KOR antagonists, while compound 81 was identified as a potent G_i biased agonist for KOR with minimal β -arrestin recruitment. These results support virtual screening as an effective tool for discovery of new lead chemotypes with therapeutically relevant functional profiles.

Menthol Enhances Nicotine Reward-Related Behavior By Potentiating Nicotine-Induced Changes In NACHR Function, NACHR Upregulation, and DA Neuron Excitability

Henderson, Brandon J; Wall, Teagan R; Henley, Beverley M; Kim, Charlene H; McKinney, Sheri; Lester, Henry A. *Neuropsychopharmacology.* 2017; 42(12): 2285-2291.

Understanding why the quit rate among smokers of menthol cigarettes is lower than non-menthol smokers requires identifying the neurons that are altered by nicotine, menthol, and acetylcholine. Dopaminergic (DA) neurons in the ventral tegmental area (VTA) mediate the positive reinforcing effects of nicotine. Using mouse models, the authors show that menthol enhances nicotine-induced changes in nicotinic acetylcholine receptors (nAChRs) expressed on midbrain DA neurons. Menthol plus nicotine upregulates nAChR number and function on midbrain DA neurons more than nicotine alone. Menthol also enhances nicotine-induced changes in DA neuron excitability. In a conditioned place preference (CPP) assay, the authors observed that menthol plus nicotine produces greater reward-related behavior than nicotine alone. These results connect changes in midbrain DA neurons to menthol-induced enhancements of nicotine reward-related behavior and may help explain how smokers of menthol cigarettes exhibit reduced cessation rates.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Prevalence and Attitudes Regarding Marijuana Use Among Adolescents Over the Past

Decade Miech R, Johnston L, O'Malley PM. Pediatrics Nov 2017, e20170982; DOI: 10.1542/peds.2017-0982.

Adolescent marijuana prevalence has not increased since 2005 despite a substantial decrease in the percentage of adolescents who believe marijuana use leads to great risk of harm. This finding calls into question the long-standing, inverse connection between marijuana prevalence and perceived risk of use, a connection central to many arguments opposing marijuana legalization. The authors tested 2 hypotheses for why marijuana prevalence did not increase after 2005: (1) decreases in adolescent use of cigarettes and alcohol reduced risk for marijuana use and counteracted the expected risk in marijuana prevalence, and/or (2) perceived risk of harm now plays a smaller role in marijuana use. Data came from the annual, nationally-representative Monitoring the Future study from 1991 to 2016, in which 1,100,000 US students in eighth, 10th, and 12th grade were surveyed. The entire sample was stratified into 3 mutually exclusive and exhaustive groups on the basis of cigarette and alcohol use. Within each of the 3 groups, marijuana prevalence increased from 2005 to 2016. Paradoxically, when the 3 groups were combined into 1 analysis pool, overall marijuana prevalence did not increase. The seeming paradox results from a decline in the percentage of adolescents who used cigarettes; as this group grew smaller, so too did its disproportionately large contribution to overall marijuana prevalence. Perceived risk of harm from marijuana remained a strong indicator of use throughout 2005 to 2016. Perceived risk of marijuana remains tightly associated with use, and adolescent marijuana prevalence today would be at or near record highs if cigarette use had not declined since 2005, according to study projections.

Injectable Naltrexone, Oral Naltrexone, and Buprenorphine Utilization and Discontinuation Among Individuals Treated For Opioid Use Disorder In A United States Commercially

Insured Population Jake R. Morgan, Bruce R. Schackman, Jared A. Leff, Benjamin P. Linas, Alexander Y. Walley Journal of Substance Abuse Treatment 2018 February; 85: 90-96.

The authors investigated prescribing patterns for four opioid use disorder (OUD) medications: 1) injectable naltrexone, 2) oral naltrexone, 3) sublingual or oral mucosal buprenorphine/naloxone, and 4) sublingual buprenorphine as well as transdermal buprenorphine (which is approved for treating pain, but not OUD) in a nationally representative claims-based database (Truven Health MarketScan®) of commercially insured individuals in the United States. They calculated the prevalence of OUD in the database for each year from 2010 to 2014 and the proportion of diagnosed patient months on OUD medication. The authors compared characteristics of individuals diagnosed with OUD who did and did not receive these medications with bivariate descriptive statistics. Finally, they fit a Cox proportional hazards model of time to discontinuation of therapy as a function of therapy type, controlling for relevant confounders. From 2010 to 2014, the proportion of commercially insured individuals diagnosed with OUD grew by fourfold (0.12% to 0.48%), but the proportion of diagnosed patient-months on medication decreased from 25% in 2010 (0.05% injectable naltrexone, 0.4% oral naltrexone, 23.1% sublingual or oral mucosal buprenorphine/naloxone, 1.5% sublingual buprenorphine, and 0% transdermal buprenorphine) to 16% in 2014 (0.2% injectable naltrexone, 0.4% oral naltrexone, 13.8% sublingual or oral mucosal buprenorphine/naloxone, 1.4% sublingual buprenorphine, and 0.3% transdermal buprenorphine). Individuals who received medication therapy were more likely to be male, younger, and have an additional substance use disorder compared with those diagnosed with OUD who did not receive medication therapy. Those prescribed injectable naltrexone were more often male, younger, and diagnosed with additional substance use disorders compared with those prescribed other

medications for opioid use disorder (MOUDs). At 30 days after initiation, 52% for individuals treated with injectable naltrexone, 70% for individuals treated with oral naltrexone, 31% for individuals treated with sublingual or oral mucosal buprenorphine/naloxone, 58% for individuals treated with sublingual buprenorphine, and 51% for individuals treated with transdermal buprenorphine discontinued treatment. In the Cox proportional hazard model, use of injectable naltrexone, oral naltrexone, sublingual buprenorphine, and transdermal buprenorphine were all associated with significantly greater hazard of discontinuing therapy beginning N30 days after MOUD initiation (HR=2.17, 2.54, 1.15, and 2.21, respectively, 95% CIs 2.04–2.30, 2.45–2.64, 1.10–1.19, and 2.11–2.33), compared with the use of sublingual or oral mucosal buprenorphine/naloxone. This analysis demonstrates that the use of evidence-based medication therapies has not kept pace with increases in OUD diagnoses in commercially insured populations in the United States. Among those who have been treated, discontinuation rates N30 days after initiation are high. The proportion treated with injectable naltrexone, oral naltrexone, and transdermal buprenorphine grew over time but remains small, and the discontinuation rates are higher among those treated with these medications compared with those treated with sublingual or oral mucosal buprenorphine/naloxone. In the face of the opioid overdose and addiction crisis, new efforts are needed at the provider, health system, and policy levels so that MOUD availability and uptake keep pace with new OUD diagnoses and OUD treatment discontinuation is minimized.

Association Of Prescription Drug Monitoring Program Use With Opioid Prescribing and Health Outcomes: A Comparison Of Program Users and Non-Users Deyo, Richard A; Hallvik, Sara E; Hildebran, Christi; Marino, Miguel; Springer, Rachel; Irvine, Jessica M; O'Kane, Nicole; Van Otterloo, Joshua; Wright, Dagan A; Leichtling, Gillian; Millet, Lisa M; Carson, Jody; Wakeland, Wayne; McCarty, Dennis. *J Pain*. 2017; Oct. 17.

Prescription drug monitoring programs (PDMPs) are a response to the prescription opioid epidemic, but their impacts on prescribing and health outcomes remain unclear, with conflicting reports. The authors sought to determine if prescriber use of Oregon's prescription drug monitoring program (PDMP) led to fewer high-risk opioid prescriptions or overdose events. They conducted a retrospective cohort study from October 2011 through October 2014, using statewide PDMP data, hospitalization registry, and vital records. Early PDMP registrants (n=927) were matched with clinicians who never registered during the study period, using baseline prescribing metrics in a propensity score. Generalized estimating equations were used to examine prescribing trends following PDMP registration, using 2-month intervals. The authors found a statewide decline in measures of per capita opioid prescribing. However, compared with non-registrants, PDMP registrants did not subsequently have significantly fewer patients receiving high-dose prescriptions; overlapping opioid and benzodiazepine prescriptions, inappropriate prescriptions, prescriptions from multiple prescribers, or overdose events. At baseline, frequent PDMP users wrote fewer high-risk opioid prescriptions than infrequent users; this persisted during follow-up with few significant group differences in trend. Thus, although opioid prescribing declined statewide after implementing the PDMP, registrants did not demonstrate greater declines than non-registrants. Factors other than PDMP use may have had greater influence on prescribing trends. Refinements in the PDMP program and related policies may be necessary to increase PDMP impact.

Cumulative Contextual Risk At Birth and Adolescent Substance Initiation: Peer Mediation Tests Mason, W Alex; Patwardhan, Irina; Smith, Gail L; Chmelka, Mary B; Savolainen, Jukka; January, Stacy-Ann A; Miettunen, Jouko; Järvelin, Marjo-Riitta. *Drug Alcohol Depend*. 2017; 177(8): 291-298.

Children who experience multiple adversities, such as prenatal exposure to drugs and poverty, early in development are at increased risk for the early initiation of alcohol and cigarette use. However, studies that examine potentially malleable processes associated with substance use initiation in the context of exposure to cumulative stressors are scant. This study examined associations between cumulative contextual risk at birth and initiation of alcohol and cigarette use in adolescence, testing childhood peer marginalization and peer aggression and behavior problems as mediating mechanisms. Analyses further adjusted for fearfulness/inhibition and hyperactivity/distractibility to determine if the hypothesized mediating mechanisms were significant after accounting for temperamental characteristics associated with substance initiation. Participants were 6190 adolescents from the Northern Finland Birth Cohort 1986 Study. Data were collected on cumulative contextual risk (parent reports), substance initiation (adolescent reports), childhood peer processes and behavior problems (teacher reports), and temperamental characteristics (teacher reports). Novel discrete-time survival mediation analysis was conducted to test the hypothesized mediating mechanisms. Initial analyses showed that the associations between cumulative contextual risk and both alcohol and cigarette initiation were mediated by childhood peer processes and behavior problems; however, the indirect effects became statistically non-significant after adding the temperament variables, which themselves predicted substance initiation. Targeting peer processes may not be an effective way to interrupt pathways leading from early contextual risk to substance initiation. Instead, early screening and intervention efforts to delay substance initiation may need to be tailored to the individual temperamental characteristics of targeted participants.

[Time-Specific and Cumulative Effects Of Exposure To Parental Externalizing Behavior On Risk For Young Adult Alcohol Use Disorder](#) Edwards, Alexis C; Lönn, Sara L; Karriker-Jaffe, Katherine J; Sundquist, Jan; Kendler, Kenneth S; Sundquist, Kristina. *Addict Behav.* 2017; 72(9): 8-13.

Previous studies indicate that parental externalizing behavior (EB) is a robust risk factor for alcohol use disorder (AUD) in their children, and that this is due to both inherited genetic liability and environmental exposure. However, it remains unclear whether the effects of exposure to parental EB vary as a function of timing and/or chronicity. The authors identified biological parents with an alcohol use disorder, drug abuse, or criminal behavior, during different periods of their child's upbringing, using Swedish national registries. Logistic regression was used to determine whether the effect of parental EB exposure during different developmental periods differentially impacted children's risk for young adult AUD (ages 19-24). In addition, they tested how multiply affected parents and/or sustained exposure to affected parents impacted risk. While parental EB increased risk for young adult AUD, timing of exposure did not differentially impact risk. Having a second affected parent increased the risk of AUD additionally, and sustained exposure to parental EB across multiple periods resulted in a higher risk of young adult AUD than exposure in only one period. In this well-powered population study, there was no evidence of "sensitive periods" of exposure to national registry-ascertained parental EB with respect to impact on young adult AUD, but sustained exposure was more pathogenic than limited exposure. These findings suggest developmental timing does not meaningfully vary the impact, but rather there is a pervasive risk for development of young adult AUD for children and adolescents exposed to parental EB.

[A Developmental Etiological Model For Drug Abuse In Men](#) Kendler, Kenneth S; Ohlsson, Henrik; Edwards, Alexis C; Sundquist, Jan; Sundquist, Kristina. *Drug Alcohol Depend.* 2017; 179(10): 220-228.

The authors attempt to develop a relatively comprehensive structural model of risk factors for drug abuse (DA) in Swedish men that illustrates developmental and mediational processes. They

examined 20 risk factors for DA in 48,369 men undergoing conscription examinations in 1969-70 followed until 2011 when 2.34% (n=1134) of them had DA ascertained in medical, criminal and pharmacy registries. Risk factors were organized into four developmental tiers reflecting i) birth, ii) childhood/early adolescence, iii) late adolescence, and iv) young adulthood. Structural equational model fitting was performed using Mplus. The best fitting model explained 47.8% of the variance in DA. The most prominent predictors, in order, were: early adolescent externalizing behavior, early adult criminal behavior, early adolescent internalizing behavior, early adult unemployment, early adult alcohol use disorder, and late adolescent drug use. Two major inter-connecting pathways emerged reflecting i) genetic/familial risk and ii) family dysfunction and psychosocial adversity. Generated on a first and tested on a second random half of the sample, a model from these variables predicted DA with an ROC area under the curve of 83.6%. Fifty-nine percent of DA cases arose from subjects in the top decile of risk. DA in men is a highly multifactorial syndrome with risk arising from familial-genetic, psychosocial, behavioral and psychological factors acting and interacting over development. Among the multiple predisposing factors for DA, a range of psychosocial adversities, externalizing psychopathology and lack of social constraints in early adulthood are predominant.

Children's Brain Activation During Risky Decision-making: A Contributor To Substance Problems? Crowley, Thomas J; Dalwani, Manish S; Sakai, Joseph T; Raymond, Kristen M; McWilliams, Shannon K; Banich, Marie T; Mikulich-Gilbertson, Susan K. *Drug Alcohol Depend.* 2017; 178: 57-65.

Among young children excessive externalizing behaviors often predict adolescent conduct and substance use disorders. Adolescents with those disorders show aberrant brain function when choosing between risky or cautious options. The authors therefore asked whether similarly aberrant brain function during risky decision-making accompanies excessive externalizing behaviors among children, hypothesizing an association between externalizing severity and regional intensity of brain activation during risky decision-making. Fifty-eight (58) 9-11 year-old children (both sexes), half community-recruited, half with substance-treated relatives, had parent-rated Child Behavior Checklist Externalizing scores. During fMRI, children repeatedly chose between doing a cautious behavior earning 1 point or a risky behavior that won 5 or lost 10 points. Conservative permutation-based whole-brain regression analyses sought brain regions where, during decision-making, activation significantly associated with externalizing score, with sex, and with their interaction. Before risky responses higher externalizing scores were significantly, negatively associated with neural activation (t 's: 2.91-4.76) in regions including medial prefrontal cortex (monitors environmental reward-punishment schedules), insula (monitors internal motivating states, e.g., hunger, anxiety), dopaminergic striatal and midbrain structures (anticipate and mediate reward), and cerebellum (where injuries actually induce externalizing behaviors). Before cautious responses there were no significant externalizing: activation associations (except in post hoc exploratory analyses), no significant sex differences in activation, and no significant sex-by-externalizing interactions. Among children displaying more externalizing behaviors extensive decision-critical brain regions were hypoactive before risky behaviors. Such neural hypoactivity may contribute to the excessive real-life risky decisions that often produce externalizing behaviors. Substance exposure, minimal here, was a very unlikely cause.

Initial Validation of a Proxy Indicator of Functioning as a Potential Tool for Establishing a Clinically Meaningful Cocaine Use Outcome Kiluk, Brian D.; Babuscio, Theresa A., Nich, Charla; Carroll, Kathleen M. *Drug and Alcohol Dependence.* 2017; Available Online 14 August.

Establishing a non-abstinence cocaine use outcome as clinically meaningful has been elusive, in part due to the lack of association between cocaine use outcomes and meaningful indicators of long-term functioning. Using data pooled across 7 clinical trials evaluating treatments for cocaine (N=718), a dichotomous indicator of functioning was created to represent a meaningful outcome ('problem-free functioning' – PFF), defined as the absence of problems across non-substance-related domains on the Addiction Severity Index. Its validity was evaluated at multiple time points (baseline, end-of-treatment, terminal follow-up) and used to explore associations with cocaine use. The percentage of participants meeting PFF criteria increased over time (baseline =18%; end-of-treatment =32%; terminal follow-up =37%). At each time point, ANOVAs indicated those who met PFF criteria reported significantly less distress on the Brief Symptom Inventory and less perceived stress on the Perceived Stress Scale. Generalized linear models indicated categorical indices of self-reported cocaine use at the end of treatment were predictive of the probability of meeting PFF criteria during follow-up ($\beta=-0.01$, $p < 0.01$; 95% CI: -0.008 to -0.003), with those reporting 0 days or 1–4 days ('occasional' use) in the final month of treatment showing an increased likelihood of achieving PFF. Initial validation of a proxy indicator of problem-free functioning demonstrated criterion validity and sensitivity to change over time. Frequency of cocaine use in the final month of treatment was associated with PFF during follow-up, with strongest associations between PFF and abstinence or 'occasional' use.

[Pathways To Preventing Substance Use Among Youth In Foster Care](#) Kim, Hyoun K; Buchanan, Rohanna; Price, Joseph M. *Prev Sci.* 2017; 18(5): 567-576.

Substance use problems are highly prevalent among youth in foster care. Such problems in adolescence have long-lasting implications for subsequent adjustment throughout adulthood and even across generations. Although several programs have demonstrated positive results in reducing substance use in at-risk youth, few studies have systemically examined how such programs work for foster youth and whether they are effective for both genders. This study examined the efficacy of KEEP SAFE, a family-based and skill-focused program designed to prevent substance use and other related health risking behaviors among youth in foster care. The authors hypothesized that improving the caregiver-youth relationship would lead to later reductions in youth's involvement with deviant peers, which subsequently would lead to less substance use, and that this mechanism would work comparably for both genders. A sample of 259 youth (154 girls, ages 11-17 years) in foster care and their caregivers participated in a randomized controlled trial and was followed for 18 months post-baseline. Results indicated that the intervention significantly reduced substance use in foster youth at 18 months post-baseline and that the intervention influenced substance use through two processes: youth's improved quality of relationships with caregivers at 6 months post-baseline and fewer associations with deviant peers at 12 months post-baseline. This suggests that these two processes may be fruitful immediate targets in substance use prevention programs for foster youth. The authors also found little gender differences in direct and mediating effects of the intervention, suggesting KEEP SAFE may be effective for both genders in foster care.

[Collaborative Care For Opioid and Alcohol Use Disorders In Primary Care: The SUMMIT Randomized Clinical Trial](#) Watkins, Katherine E; Ober, Allison J; Lamp, Karen; Lind, Mimi; Setodji, Claude; Osilla, Karen Chan; Hunter, Sarah B; McCullough, Colleen M; Becker, Kirsten; Iyiewuare, Praise O; Diamant, Allison; Heinzerling, Keith; Pincus, Harold Alan. *JAMA Intern Med.* 2017.

Primary care offers an important and underutilized setting to deliver treatment for opioid and/or alcohol use disorders (OAUD). Collaborative care (CC) is effective but has not been tested for OAUD. The objective of this study was to determine whether CC for OAUD improves delivery of

evidence-based treatments for OAUD and increases self-reported abstinence compared with usual primary care. This was a randomized clinical trial of 377 primary care patients with OAUD conducted in 2 clinics in a federally qualified health center. Participants were recruited from June 3, 2014 to January 15, 2016 and followed for 6 months. Of the 377 participants, 187 were randomized to CC and 190 were randomized to usual care; 77 (20.4%) of the participants were female, of whom 39 (20.9%) were randomized to CC and 38 (20.0%) were randomized to UC. The mean (SD) age of all respondents at baseline was 42 (12.0) years, 41(11.7) years for the CC group, and 43 (12.2) years for the UC group. Collaborative care was a system-level intervention, designed to increase the delivery of either a 6-session brief psychotherapy treatment and/or medication-assisted treatment with either sublingual buprenorphine/naloxone for opioid use disorders or long-acting injectable naltrexone for alcohol use disorders. Usual care participants were told that the clinic provided OAUD treatment and given a number for appointment scheduling and list of community referrals. The primary outcomes were use of any evidence-based treatment for OAUD and self-reported abstinence from opioids or alcohol at 6 months. The secondary outcomes included the Healthcare Effectiveness Data and Information Set (HEDIS) initiation and engagement measures, abstinence from other substances, heavy drinking, health-related quality of life, and consequences from OAUD. At 6 months, the proportion of participants who received any OAUD treatment was higher in the CC group compared with usual care (73 [39.0%] vs 32 [16.8%]; logistic model adjusted OR, 3.97; 95% CI, 2.32-6.79; $P < .001$). A higher proportion of CC participants reported abstinence from opioids or alcohol at 6 months (32.8% vs 22.3%); after linear probability model adjustment for covariates ($\beta = 0.12$; 95% CI, 0.01-0.23; $P = .03$). In secondary analyses, the proportion meeting the HEDIS initiation and engagement measures was also higher among CC participants (initiation, 31.6% vs 13.7%; adjusted OR, 3.54; 95% CI, 2.02-6.20; $P < .001$; engagement, 15.5% vs 4.2%; adjusted OR, 5.89; 95% CI, 2.43-14.32; $P < .001$) as was abstinence from opioids, cocaine, methamphetamines, marijuana, and any alcohol (26.3% vs 15.6%; effect estimate, $\beta = 0.13$; 95% CI, 0.03-0.23; $P = .01$). Among adults with OAUD in primary care, the SUMMIT collaborative care intervention resulted in significantly more access to treatment and abstinence from alcohol and drugs at 6 months, than usual care.clinicaltrials.gov Identifier: NCT01810159.

Major Depressive Disorder, Suicidal Thoughts and Behaviours, and Cannabis Involvement In Discordant Twins: A Retrospective Cohort Study

Agrawal, Arpana; Nelson, Elliot C; Bucholz, Kathleen K; Tillman, Rebecca; Grucza, Richard A; Statham, Dixie J; Madden, Pamela Af; Martin, Nicholas G; Heath, Andrew C; Lynskey, Michael T. *Lancet Psychiatry*. 2017; 4(9): 706-714. Early and frequent cannabis use are associated with an increased likelihood of major depressive disorder (MDD) as well as suicidal thoughts and behaviours. The authors identify associations between aspects of cannabis use, MDD, and suicidal thoughts and behaviours and examine whether such associations persist after accounting for those predisposing factors, including genetic liability and early family environment, that are shared by identical twins who are discordant for cannabis exposure. Any residual association in such identical pairs might be indicative of individual-specific pathways that might be of a causal nature. The authors did a logistic regression analysis of cannabis use from retrospective data on same-sex male and female twin pairs drawn from 3 studies that had recruited twins from the Australian Twin Registry, 1992-93 (sample 1), 1996-2000 (sample 2), and 2005-09 (sample 3). They studied associations between early use and frequent use of cannabis and MDD, suicidal ideation (ever and persistent), and suicide plan and attempt in the full sample as well as in pairs of monozygotic and dizygotic twins that were discordant for each measure of cannabis involvement at a single timepoint. Significant monozygotic associations were further adjusted for covariates, such as early alcohol or nicotine use, early dysphoric or anhedonic mood, conduct disorder, and childhood sexual abuse. Interactions between each cannabis measure and sex, sample

or study effects, and birth year category were also examined as covariates. In 13,986 twins (6181 monozygotic and 7805 dizygotic), cannabis use ranged from 1345 (30.4%) of 4432 people in sample 1 to 2275 (69.0%) of 3299 in sample 3. Mean age of first cannabis use ranged from 17.9 years (SD 3.3) in sample 3 to 21.1 years (5.2) in sample 1, and frequent use (≥ 100 times) was reported by 214 (15.9%) of 1345 users in sample 1 and 499 (21.9%) of 2275 in sample 3. The prevalence of suicidal ideation ranged from 1102 (24.9%) of 4432 people in sample 1 to 1644 (26.3%) of 6255 people in sample 2 and 865 (26.2%) of 3299 people in sample 3. Prevalence of MDD ranged from 901 (20.3%) people in sample 1 to 1773 (28.3%) in sample 2. The monozygotic twin who used cannabis frequently was more likely to report MDD (odds ratio 1.98, 95% CI 1.11-3.53) and suicidal ideation (2.47, 1.19-5.10) compared with their identical twin who had used cannabis less frequently, even after adjustment for covariates. For early cannabis use, the monozygotic point estimate was not significant but could be equated to the significant dizygotic estimate, suggesting a possible association with suicidal ideation. The increased likelihood of MDD and suicidal ideation in frequent cannabis users cannot be solely attributed to common predisposing factors

Trends In Receipt Of Buprenorphine and Naltrexone For Opioid Use Disorder Among Adolescents and Young Adults, 2001-2014

Hadland, Scott E; Wharam, J Frank; Schuster, Mark A; Zhang, Fang; Samet, Jeffrey H; Larochelle, Marc R. JAMA Pediatr. 2017; 171(8): 747-755. Opioid use disorder (OUD) frequently begins in adolescence and young adulthood. Intervening early with pharmacotherapy is recommended by major professional organizations. No prior national studies have examined the extent to which adolescents and young adults (collectively termed youth) with OUD receive pharmacotherapy. The objective of this study was to identify time trends and disparities in receipt of buprenorphine and naltrexone among youth with OUD in the United States. A retrospective cohort study was conducted using deidentified data from a national commercial insurance database. Enrollment and complete health insurance claims of 9.7 million youth, aged 13 to 25 years were analyzed, identifying individuals who received a diagnosis of OUD between January 1, 2001, and June 30, 2014, with final follow-up date December 31, 2014. Analysis was conducted from April 25 to December 31, 2016. Time trends were identified and multivariable logistic regression was used to determine sociodemographic factors associated with medication receipt. Sex, age, race/ethnicity, neighborhood education and poverty levels, geographic region, census region, and year of diagnosis. Dispensing of a medication (buprenorphine or naltrexone) within 6 months of first receiving an OUD diagnosis. Among 20,822 youth diagnosed with OUD (0.2% of the 9.7 million sample), 13,698 (65.8%) were male and 17,119 (82.2%) were non-Hispanic white. Mean (SD) age was 21.0 (2.5) years at the first observed diagnosis. The diagnosis rate of OUD increased nearly 6-fold from 2001 to 2014 (from 0.26 per 100,000 person-years to 1.51 per 100,000 person-years). Overall, 5580 (26.8%) youth were dispensed a medication within 6 months of diagnosis, with 4976 (89.2%) of medication-treated youth receiving buprenorphine and 604 (10.8%) receiving naltrexone. Medication receipt increased more than 10-fold, from 3.0% in 2002 (when buprenorphine was introduced) to 31.8% in 2009, but declined in subsequent years (27.5% in 2014). In multivariable analyses, younger individuals were less likely to receive medications, with adjusted probability for age 13 to 15 years, 1.4% (95% CI, 0.4%-2.3%); 16 to 17 years, 9.7% (95% CI, 8.4%-11.1%); 18 to 20 years, 22.0% (95% CI, 21.0%-23.0%); and 21 to 25 years, 30.5% (95% CI, 30.0%-31.5%) ($P < .001$ for difference). Females (7124 [20.3%]) were less likely than males (13,698 [24.4%]) to receive medications ($P < .001$), as were non-Hispanic black (105 [14.8%]) and Hispanic (1165 [20.0%]) youth compared with non-Hispanic white (17,119 [23.1%]) youth ($P < .001$). In this first national study of buprenorphine and naltrexone receipt among youth,

dispensing increased over time. Nonetheless, only 1 in 4 commercially insured youth with OUD received pharmacotherapy, and disparities based on sex, age, and race/ethnicity were observed.

TREATMENT RESEARCH

Effects Of Nicotine Versus Placebo E-cigarette Use On Symptom Relief During Initial

Tobacco Abstinence Perkins, Kenneth A; Karelitz, Joshua L; Michael, Valerie C. *Exp Clin Psychopharmacol.* 2017; 25(4): 249-254.

Because electronic cigarettes (e-cigs) containing nicotine may relieve smoking abstinence symptoms similar to nicotine replacement therapy medication, the authors used within-subjects designs to test these effects with a first-generation e-cig in nonquitting and quitting smokers. In Study 1, 28 nontreatment-seeking smokers abstained overnight prior to each of 3 sessions. Minnesota Nicotine Withdrawal Scale (MNWS) withdrawal (and craving item) relief was assessed following 4 exposures (each 10 puffs) over 2 hr. to e-cigs that either did (36 mg/ml) or did not (i.e., placebo, 0 mg/ml) contain nicotine or after no e-cig. Relief was greater after nicotine versus placebo e-cig ($p < .05$) but not after placebo versus no e-cig, showing relief was due to nicotine per se and not simple e-cig use behavior. Using a crossover design in Study 2, smokers preparing to quit soon engaged in 2 experimental 4-day quit periods on separate weeks. In weeks 1 and 3, all received a nicotine or placebo e-cig on Monday to use ad libitum while trying to abstain from smoking on Tuesday through Friday. (Week 2 involved resumption of ad libitum smoking.) MNWS and Questionnaire of Smoking Urges (QSU) craving were assessed at daily visits following 24-hr abstinence. Of 17 enrolled, 12 quit for ≥ 24 hr. at least once, allowing test of relief because of e-cig use on quit days. Withdrawal and craving were reduced because of nicotine versus placebo e-cig use (both $p < .05$). In sum, compared with placebo e-cigs, nicotine e-cigs can relieve smoking abstinence symptoms, perhaps in a manner similar to Food and Drug Administration-approved nicotine replacement therapy products, although much more research with larger samples is needed.

Reductions In Cannabis Use Are Associated With Improvements In Anxiety, Depression, and Sleep Quality, But Not Quality Of Life

Hser, Yih-Ing; Mooney, Larissa J; Huang, David; Zhu, Yuhui; Tomko, Rachel L; McClure, Erin; Chou, Chih-Ping; Gray, Kevin M. *J Subst Abuse Treat.* 2017; 81: 53-58.

This study examined the longitudinal association between reductions in cannabis use and changes in anxiety, depression, sleep quality, and quality of life. Secondary analyses were conducted based on data from a cannabis use disorder medication trial in 302 adults (ages 18-50). Changes in symptoms of anxiety and depression, sleep quality, and quality of life were assessed in relation to changes in cannabis use during the 12-week trial of treatment. Based on the slope of individual cannabis use trajectory, the sample was classified into two groups (Cannabis Use Reduction, $n=152$ vs. Cannabis Use Increase, $n=150$) which was included as a binary covariate in subsequent modeling. Controlling for demographics (age, gender, race/ethnicity), treatment condition, and time-varying tobacco and alcohol use, separate latent growth curve models showed a significant association between the Cannabis Use Reduction group and improvement (i.e., lower values in slope) in anxiety ($\beta=-0.09$, $SE=0.04$; $p<0.05$), depression ($\beta=-0.11$, $SE=0.04$; $p<0.01$), and sleep quality ($\beta=-0.07$, $SE=0.03$; $p<0.05$) over the observation period, but not in quality of life. These results indicate a longitudinal relationship between reductions in cannabis use and improvements in anxiety, depression, and sleep quality. Clinicians treating patients with co-occurring cannabis use and problems with anxiety, depression, or sleep quality should attend to cannabis use reduction as a component of treatment.

Efficacy Of Tramadol Extended-Release For Opioid Withdrawal: A Randomized Clinical Trial Dunn, Kelly E; Tompkins, D Andrew; Bigelow, George E; Strain, Eric C. *JAMA Psychiatry*. 2017; 74(9): 885-893.

Opioid use disorder (OUD) is a significant public health problem. Supervised withdrawal (i.e., detoxification) from opioids using clonidine or buprenorphine hydrochloride is a widely used treatment. The objective of this study was to evaluate whether tramadol hydrochloride extended-release (ER), an approved analgesic with opioid and nonopioid mechanisms of action and low abuse potential, is effective for use in supervised withdrawal settings. A randomized clinical trial was conducted in a residential research setting with 103 participants with OUD. Participants' treatment was stabilized with morphine, 30 mg, administered subcutaneously 4 times daily. A 7-day taper using clonidine (n = 36), tramadol ER (n = 36), or buprenorphine (n = 31) was then instituted, and patients were crossed-over to double-blind placebo during a post-taper period. The study was conducted from October 25, 2010, to June 23, 2015. Retention, withdrawal symptom management, concomitant medication utilization, and naltrexone induction. Results were analyzed over time and using area under the curve for the intention-to-treat and completer groups. Of the 103 participants, 88 (85.4%) were men and 43 (41.7%) were white; mean (SD) age was 28.9 (10.4) years. Buprenorphine participants (28 [90.3%]) were significantly more likely to be retained at the end of the taper compared with clonidine participants (22 [61.1%]); tramadol ER retention was intermediate and did not differ significantly from that of the other groups (26 [72.2%]; $\chi^2 = 8.5$, $P = .01$). Time-course analyses of withdrawal revealed significant effects of phase (taper, post taper) for the Clinical Opiate Withdrawal Scale (COWS) score (taper mean, 5.19 [SE, .26]; post-taper mean, 3.97 [SE, .23]; $F_{2,170} = 3.6$, $P = .03$) and Subjective Opiate Withdrawal Scale (SOWS) score (taper mean, 8.81 [SE, .40]; post-taper mean, 4.14 [SE, .30]; $F_{2,170} = 15.7$, $P < .001$), but no group effects or group \times phase interactions. Analyses of area under the curve of SOWS total scores showed significant reductions ($F_{2,159} = 17.7$, $P < .001$) in withdrawal severity between the taper and post-taper periods for clonidine (taper mean, 13.1; post-taper mean, 3.2; $P < .001$) and tramadol ER (taper mean, 7.4; post-taper mean, 2.8; $P = .03$), but not buprenorphine (taper mean, 6.4; post-taper mean, 7.4). Use of concomitant medication increased significantly ($F_{2,159} = 30.7$, $P < .001$) from stabilization to taper in the clonidine (stabilization mean, 0.64 [SE, .05]; taper mean, 1.54 [SE, .10]; $P < .001$) and tramadol ER (stabilization mean, 0.53 [SE, .05]; taper mean, 1.19 [SE, .09]; $P = .003$) groups and from stabilization to post taper in the buprenorphine group (stabilization mean, 0.46 [SE, .05] post-taper mean, 1.17 [SE, .09]; $P = .006$), suggesting higher withdrawal for those groups during those periods. Naltrexone initiation was voluntary and the percentage of participants choosing naltrexone therapy within the clonidine (8 [22.2%]), tramadol ER (7 [19.4%]), or buprenorphine (3 [9.7%]) groups did not differ significantly ($\chi^2 = 2.5$, $P = .29$). The results of this trial suggest that tramadol ER is more effective than clonidine and comparable to buprenorphine in reducing opioid withdrawal symptoms during a residential tapering program. Data support further examination of tramadol ER as a method to manage opioid withdrawal symptoms. Clinicaltrials.gov Identifier: NCT01188421.

Extended Treatment For Cigarette Smoking Cessation: A Randomized Control Trial

Laude, Jennifer R; Bailey, Steffani R; Crew, Erin; Varady, Ann; Lembke, Anna; McFall, Danielle; Jeon, Anna; Killen, Diana; Killen, Joel D; David, Sean P. *Addiction*. 2017; 112(8): 1451-1459. The aim of this study was to test the potential benefit of extending cognitive-behavioral therapy (CBT) relative to not extending CBT on long-term abstinence from smoking. This was a two-group parallel randomized controlled trial. Patients were randomized to receive non-extended CBT (n = 111) or extended CBT (n = 112) following a 26-week open-label treatment. The study was conducted in a community clinic in the United States. Participants comprised a total of 219 smokers

(mean age: 43 years; mean cigarettes/day: 18). All participants received 10 weeks of combined CBT + bupropion sustained release (bupropion SR) + nicotine patch and were continued on CBT and either no medications if abstinent, continued bupropion + nicotine replacement therapy (NRT) if increased craving or depression scores, or varenicline if still smoking at 10 weeks. Half the participants were randomized at 26 weeks to extended CBT (E-CBT) to week 48 and half to non-extended CBT (no additional CBT sessions). The primary outcome was expired CO-confirmed, 7-day point-prevalence (PP) at 52- and 104-week follow-up. Analyses were based on intention-to-treat. PP abstinence rates at the 52-week follow-up were comparable across non-extended CBT (40%) and E-CBT (39%) groups [odds ratio (OR) = 0.99; 95% confidence interval (CI) = 0.55, 1.78]. A similar pattern was observed across non-extended CBT (39%) and E-CBT (33%) groups at the 104-week follow-up (OR = 0.79; 95% CI= 0.44, 1.40). Prolonging cognitive-behavioral therapy from 26 to 48 weeks does not appear to improve long-term abstinence from smoking.

Feasibility and Preliminary Effectiveness Of Varenicline For Treating Co-Occurring Cannabis and Tobacco Use Adams, Tangeria R; Arnsten, Julia H; Ning, Yuming; Nahvi, Shadi. J Psychoactive Drugs. 2017; 1-7.

Few studies have evaluated treatment for co-occurring cannabis and tobacco use. The objective of this pilot study was to evaluate the feasibility and preliminary effectiveness of varenicline for co-occurring cannabis and tobacco use. Participants who reported cannabis use on ≥ 5 days per week were recruited from an urban, outpatient opioid treatment program (OTP). Participants were randomized to either four weeks of standard OTP clinical care (SCC; medication-assisted treatment for opioid use disorder and individual behavioral counseling), followed by four weeks of SCC plus varenicline (SCC+VT), or to four weeks of SCC+VT followed by four weeks of SCC. All participants contributed feasibility and outcome data during both study phases. Of 193 persons screened, seven were enrolled. Retention at eight weeks was 100%. No adverse effects prompted varenicline discontinuation. Participants reported lower cannabis craving during the SCC+VT phase compared to baseline, and lower frequencies and quantities of cannabis use compared to both baseline and the SCC alone phase. In the SCC+VT phase, participants also reported fewer cigarettes per day. Among persons with co-occurring cannabis and tobacco use, varenicline is well-tolerated and may reduce cannabis craving, cannabis use, and tobacco use.

Maintenance On Naltrexone+Amphetamine Decreases Cocaine-vs.-food Choice In Male Rhesus Monkeys Moerke, Megan J; Banks, Matthew L; Cheng, Kejun; Rice, Kenner C; Negus, S Stevens. Drug Alcohol Depend. 2017; 181: 85-93.

Cocaine use disorder remains a significant public health issue for which there are no FDA-approved pharmacotherapies. Amphetamine maintenance reduces cocaine use in preclinical and clinical studies, but the mechanism of this effect is unknown. Previous studies indicate a role for endogenous opioid release and subsequent opioid receptor activation in some amphetamine effects; therefore, the current study examined the role of mu-opioid receptor activation in d-amphetamine treatment effects in an assay of cocaine-vs.-food choice. Adult male rhesus monkeys with double-lumen intravenous catheters responded for concurrently available food pellets and cocaine injections (0-0.1mg/kg/injection) during daily sessions. Cocaine choice and overall reinforcement rates were evaluated during 7-day treatments with saline or test drugs. During saline treatment, cocaine maintained a dose-dependent increase in cocaine-vs.-food choice. The mu-opioid receptor agonist morphine (0.032-0.32mg/kg/h) dose-dependently increased cocaine choice and decreased rates of reinforcement. A dose of the mu-selective opioid receptor antagonist naltrexone (0.0032mg/kg/h) that completely blocked morphine effects had no effect on cocaine choice when it was administered alone, but it enhanced the effectiveness of a threshold dose of 0.032mg/kg/h

amphetamine to decrease cocaine choice without also enhancing nonselective behavioral disruption by this dose of amphetamine. Conversely, the kappa-selective opioid antagonist norbinalorphimine did not enhance amphetamine effects on cocaine choice. These results suggest that amphetamine maintenance produces mu opioid-receptor mediated effects that oppose its anti-cocaine effects. Co-administration of naltrexone may selectively enhance amphetamine potency to decrease cocaine choice without increasing amphetamine potency to produce general behavioral disruption.

[Trace Amine-associated Receptor 1 Agonists RO5263397 and RO5166017 Attenuate Quinpirole-induced Yawning But Not Hypothermia In Rats](#) Siemian, Justin N; Zhang, Yanan; Li, Jun-Xu. *Behav Pharmacol.* 2017; 28(7): 590-593.

Increasing evidence suggests that trace amine-associated receptor 1 (TAAR1) is an important modulator of the dopaminergic system. Existing molecular evidence indicates that TAAR1 regulates dopamine levels through interactions with dopamine transporters and D2 receptors. However, investigations to date have not been exhaustive and other pathways may be involved. In this study, the authors used a well-described set of behaviors, quinpirole-induced yawning and hypothermia, to explore the potential interaction of TAAR1 and D3 receptors, which are members of the D2-like dopamine receptor subfamily. Previous studies have shown that for D2/D3 receptor agonists, the induction of yawning is a D3 receptor-mediated effect, whereas the inhibition of yawning and induction of hypothermia are D2 receptor-mediated effects. Quinpirole produced an inverted U-shaped dose-effect curve for yawning, which was shifted downward dose-dependently by each of the TAAR1 agonists RO5263397 and RO5166017. Quinpirole also produced dose-dependent hypothermia, which was not affected by either TAAR1 agonist. These results suggest that TAAR1 agonists may interact with D3 receptors and/or its downstream pathways, as opposed to D2 receptors. These findings may shed light on a previously unexplored possibility for the mechanism of TAAR1-mediated effects.

[Cocaine-like Discriminative Stimulus Effects Of Alpha-pyrrolidinovalerophenone, Methcathinone and Their 3,4-methylenedioxy Or 4-methyl Analogs In Rhesus Monkeys](#) Smith, Douglas A; Negus, S Stevens; Poklis, Justin L; Blough, Bruce E; Banks, Matthew L. *Addict Biol.* 2017; 22(5): 1169-1178.

Synthetic cathinones are beta-ketone amphetamine analogs that have emerged as a heterogeneous class of abused compounds that function as either monoamine transporter substrates or inhibitors. Pre-clinical drug discrimination procedures are useful for interrogating structure-activity relationships of abuse-related drug effects; however, *in vivo* structure-activity relationship comparisons between synthetic cathinones with different mechanisms of action are lacking. The aim of the present study was to determine whether the cocaine-like discriminative stimulus effects of the monoamine transporter inhibitor alpha-pyrrolidinovalerophenone (alpha-PVP) and the monoamine transporter substrate methcathinone were differentially sensitive to 3,4-methylenedioxy and 4-methyl substitutions. Male rhesus monkeys ($n = 4$) were trained to discriminate intramuscular cocaine (0.32 mg/kg) from saline in a two-key food-reinforced discrimination procedure. Potency and timecourse of cocaine-like discriminative stimulus effects were determined for (\pm)-alpha-PVP, (\pm)-methcathinone and their 3,4-methylenedioxy or 4-methyl analogs. Alpha-PVP and methcathinone produced dose- and time-dependent cocaine-like effects. A 3,4-methylenedioxy addition to either alpha-PVP or methcathinone (methylo) did not alter the potency or efficacy to produce cocaine-like effects, but did prolong the time course. A 4-methyl addition to alpha-PVP (pyrovalerone) did not alter the potency or efficacy to produce cocaine-like effects, but did prolong the time course. In contrast, addition of a 4-methyl moiety to methcathinone (4MMC; mephedrone) significantly attenuated efficacy to produce cocaine-like effects. Overall, these results suggest

different structural requirements for cocaine-like discriminative stimulus effects of monoamine transporter inhibitor and substrate synthetic cathinone analogs. Given that 4MMC is more hydrophobic than MDMC, these results suggest that hydrophobicity may be an important determinant for limiting monoamine transporter substrate abuse-related behavioral effects.

Cost-effectiveness Of Extended Release Naltrexone To Prevent Relapse Among Criminal Justice-involved Individuals With A History Of Opioid Use Disorder

Murphy, Sean M; Polsky, Daniel; Lee, Joshua D; Friedmann, Peter D; Kinlock, Timothy W; Nunes, Edward V; Bonnie, Richard J; Gordon, Michael; Chen, Donna T; Boney, Tamara Y; O'Brien, Charles P. *Addiction*. 2017; 112(8): 1440-1450.

Criminal justice-involved individuals are highly susceptible to opioid relapse and overdose-related deaths. In a recent randomized trial, the authors demonstrated the effectiveness of extended-release naltrexone (XR-NTX; Vivitrol®) in preventing opioid relapse among criminal justice-involved US adults with a history of opioid use disorder. The cost of XR-NTX may be a significant barrier to adoption. Thus, it is important to account for improved quality of life and downstream cost-offsets. The authors' aims were to (1) estimate the incremental cost per quality-adjusted life-year (QALY) gained for XR-NTX versus treatment as usual (TAU) and evaluate it relative to generally accepted value thresholds; and (2) estimate the incremental cost per additional year of opioid abstinence. Economic evaluation of the aforementioned trial from the taxpayer perspective. Participants were randomized to 25 weeks of XR-NTX injections or TAU; follow-up occurred at 52 and 78 weeks. The study was conducted at five study sites in the US Northeast corridor. A total of 308 participants were randomized to XR-NTX (n = 153) or TAU (n = 155). Incremental costs relative to incremental economic and clinical effectiveness measures, QALYs and abstinent years, were measured. The 25-week cost per QALY and abstinent-year figures were \$162,150 and \$46,329, respectively. The 78-week figures were \$76,400/QALY and \$16,371/abstinent year. At 25 weeks, we can be 10% certain that XR-NTX is cost-effective at a value threshold of \$100,000/QALY and 62% certain at \$200,000/QALY. At 78 weeks, the cost-effectiveness probabilities are 59% at \$100,000/QALY and 76% at \$200,000/QALY. We can be 95% confident that the intervention would be considered a good value at \$90,000/abstinent year at 25 weeks and \$500/abstinent year at 78 weeks. While extended-release naltrexone appears to be effective in increasing both quality-adjusted life-years (QALYs) and abstinence, it does not appear to be cost-effective using generally accepted value thresholds for QALYs, due to the high price of the injection.

Acceptability and Effectiveness Of A Web-based Psychosocial Intervention Among Criminal Justice Involved Adults

Lee, J D; Tofighi, B; McDonald, R; Campbell, A; Hu, M C; Nunes, E. *Health Justice*. 2017; 5(1): 3.

The acceptability, feasibility and effectiveness of web-based interventions among criminal justice involved populations are understudied. This study is a secondary analysis of baseline characteristics associated with criminal justice system (CJS) status as treatment outcome moderators among participants enrolling in a large randomized trial of a web-based psychosocial intervention (Therapeutic Education System [TES]) as part of outpatient addiction treatment. The authors compared demographic and clinical characteristics, TES participation rates, and the trials' two co-primary outcomes, end of treatment abstinence and treatment retention, by self-reported CJS status at baseline: 1) CJS-mandated to community treatment (CJS-mandated), 2) CJS-recommended to treatment (CJS-recommended), 3) no CJS treatment mandate (CJS-none). CJS-mandated (n = 107) and CJS-recommended (n = 69) participants differed from CJS-none (n = 331) at baseline: CJS-mandated were significantly more likely to be male, uninsured, report cannabis as the primary drug problem, report fewer days of drug use at baseline, screen negative for depression, and score lower

for psychological distress and higher on physical health status; CJS-recommended were younger, more likely single, less likely to report no regular Internet use, and to report cannabis as the primary drug problem. Both CJS-involved (CJS -recommended and -mandated) groups were more likely to have been recently incarcerated. Among participants randomized to the TES arm, module completion was similar across the CJS subgroups. A three-way interaction of treatment, baseline abstinence and CJS status showed no associations with the study's primary abstinence outcome. Overall, CJS-involved participants in this study tended to be young, male, and in treatment for a primary cannabis problem. The feasibility and effectiveness of the web-based psychosocial intervention, TES, did not vary by CJS-mandated or CJS-recommended participants compared to CJS-none. Web-based counseling interventions may be effective interventions as US public safety policies begin to emphasize supervised community drug treatment over incarceration.

Exposure To Fentanyl-contaminated Heroin and Overdose Risk Among Illicit Opioid Users In Rhode Island: A Mixed Methods Study Carroll, Jennifer J; Marshall, Brandon D L; Rich, Josiah D; Green, Traci C. *Int J Drug Policy*. 2017; 46: 136-145.

Illicit fentanyl use has become wide spread in the US, causing high rates of overdose deaths among people who use drugs. This study describes patterns and perceptions of fentanyl exposure among opioid users in Rhode Island. A mixed methods study was conducted via questionnaire with a convenience sample of 149 individuals using illicit opioids or misusing prescription opioids in Rhode Island between January and November 2016. Of these, 121 knew of fentanyl and reported known or suspected exposure to fentanyl in the past year. Semi-structured interviews were conducted with the first 47 participants. Study participants were predominantly male (64%) and white (61%). Demographic variables were similar across sample strata. Heroin was the most frequently reported drug of choice (72%). Self-reported exposure to illicit fentanyl in the past year was common (50.4%, n=61). In multivariate models, regular (at least weekly) heroin use was independently associated with known or suspected fentanyl exposure in the past year (adjusted prevalence ratio (APR)=4.07, 95% CI: 1.24-13.3, p=0.020). In interviews, users described fentanyl as unpleasant, potentially deadly, and to be avoided. Participants reporting fentanyl exposure routinely experienced or encountered non-fatal overdose. Heroin users reported limited ability to identify fentanyl in their drugs. Harm reduction strategies used to protect themselves from fentanyl exposure and overdose, included test hits, seeking prescription opioids in lieu of heroin, and seeking treatment with combination buprenorphine/naloxone. Participants were often unsuccessful in accessing structured treatment programs. Among illicit opioid users in Rhode Island, known or suspected fentanyl exposure is common, yet demand for fentanyl is low. Fentanyl-contaminated drugs are generating user interest in effective risk mitigation strategies, including treatment. Responses to the fentanyl epidemic should be informed by the perceptions and experiences of local users. The rapid scale-up of buprenorphine/naloxone provision may slow the rate of fentanyl-involved overdose deaths.

Emotion Regulation and Coping Motives Serially Affect Cannabis Cessation Problems Among Dually Diagnosed Outpatients Buckner, Julia D; Walukevich, Katherine A; Zvolensky, Michael J; Gallagher, Matthew W. *Psychol Addict Behav*. 2017; 31(7): 839-845.

Little empirical work has evaluated why anxious cannabis users are especially vulnerable to poorer cannabis cessation outcomes. Presumably, these individuals rely on cannabis because they have difficulties with emotion regulation and they therefore use cannabis to manage their negative emotions. The current study examined the direct and indirect effects of anxiety severity on a range of cannabis cessation variables among 79 (63.3% non-Hispanic White; 43.0% female) adults with anxiety disorders seeking outpatient treatment for cannabis use disorder. The independent and serial

indirect effects of difficulties with emotion regulation and coping motives were examined in relation to the anxiety-cannabis variables. Anxiety severity was directly and robustly related to greater cannabis withdrawal symptom severity, less self-efficacy to refrain from using cannabis in emotionally distressing situations, and more reasons for quitting. Anxiety was indirectly related to cannabis outcomes via the serial effects of emotion regulation and coping motives. These findings document the important role of emotion regulation and coping motives in the relations of anxiety with cannabis cessation variables among dually diagnosed outpatients.

Effect Of Computerized Cognitive Behavioral Therapy On Acquisition Of Coping Skills Among Cocaine-dependent Individuals Enrolled In Methadone Maintenance

Kiluk, Brian D; DeVito, Elise E; Buck, Matthew B; Hunkele, Karen; Nich, Charla; Carroll, Kathleen M. *J Subst Abuse Treat.* 2017; 82: 87-92.

The acquisition of coping skills has long been considered one of the putative mechanisms of cognitive behavioral therapy (CBT) for substance use disorders, yet consistent statistical support is lacking. This study sought to replicate and extend prior findings regarding the quality of coping skills as a mediator of abstinence outcomes from a computerized CBT program for substance users. Participants were methadone-maintained, cocaine dependent individuals enrolled in a clinical trial evaluating the efficacy of computer-based training for CBT (CBT4CBT) as an add-on to treatment as usual (TAU+CBT4CBT) compared to TAU only. A subsample (N=71) completed a role play assessment to measure coping skills, the Drug Risk Response Test (DRRT), which was administered before, during (week 4), and after the 8-week treatment period. Participants' verbal responses to various high-risk situations for cocaine use were recorded and independent evaluators rated the quality of the coping responses. Results of repeated measures analyses revealed a main effect of time for the quality of overall responses [$F(1, 141.26)=4.29, p<0.01$], indicating improvement in the quality of coping skills across groups, yet no differential effect of treatment. Despite the significant association between coping responses and abstinence outcomes, analyses did not support the quality of coping skills as a mediator of treatment effects. However, among the high-risk situations wherein individuals provided lower quality responses at baseline, those assigned to TAU+CBT4CBT showed greater improvement compared to those assigned to TAU only [$F(1, 697.65)=6.47, p=0.01$]. This study failed to replicate the quality of coping skills as a mediator of CBT4CBT's effect on reducing drug use previously shown in a mixed outpatient substance use sample. However, in this methadone maintained sample, those with poorer quality skills in response to certain high-risk situations at baseline appeared to improve their coping strategies following CBT4CBT compared to standard methadone treatment alone.

Simple Tetrahydroisoquinolines Are Potent and Selective Kappa Opioid Receptor Antagonists

Kormos, Chad M; Ondachi, Pauline W; Runyon, Scott P; Thomas, James B; Mascarella, S Wayne; Decker, Ann M; Navarro, Hernán A; Carroll, F Ivy. *ACS Med Chem Lett.* 2017; 8(7): 742-745.

Potent and selective κ opioid receptor antagonists have been derived from the N-substituted trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of pure opioid receptor antagonists. In order to determine if the 3-hydroxyphenyl and/or the piperidine amino groups are required for obtaining the pure opioid antagonists, (3R)-7-hydroxy-N-[(1S)-2-methyl-1-(piperidine-1-ylmethyl)propyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (1), which does not have a 4-(3-hydroxyphenyl) group, and (3R)-N-(1R)-1-(cyclohexylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (2), which does not have a 4-hydroxyphenyl or a piperidine amino group, were synthesized and evaluated for their [(35S)]GTP γ S binding properties at the μ , δ , and κ opioid receptors. Surprisingly compound 1 remained a pure opioid antagonist with a $K_e = 6.80$ nM at the κ opioid receptor and is 21- and 441-fold selective for the κ receptor relative to the μ

and δ opioid receptors, respectively. Even more unexpected and novel is the finding that 2 has a $K_e = 0.14$ nM at κ and is 1730- and 4570-fold selective for κ relative to the μ and δ opioid receptors, respectively.

Extended-Release Naltrexone For Methamphetamine Dependence Among Men Who Have Sex With Men: A Randomized Placebo-Controlled Trial Coffin, Phillip O; Santos, Glenn-Milo; Hern, Jaclyn; Vittinghoff, Eric; Santos, Deirdre; Matheson, Tim; Colfax, Grant; Batki, Steven L. *Addiction*. 2017.

Methamphetamine use is increasingly prevalent and associated with HIV transmission. Early phase human studies suggested naltrexone reduced amphetamine use among dependent individuals. The authors tested if extended-release naltrexone (XRNTX) reduces methamphetamine use and associated sexual risk behaviors among high-risk methamphetamine-dependent men who have sex with men (MSM). This was a double-blind, placebo-controlled, randomized trial of XRNTX versus placebo over 12 weeks from 2012-2015. San Francisco Department of Public Health, California, USA. Participants comprised 100 community-recruited, sexually-active, actively-using methamphetamine-dependent MSM. Mean age was 43 years, 98% were born male, 55% white, 19% African-American, and 18% Latino. XRNTX 380mg (N=50) or matched placebo (N=50) administered in 3 gluteal injections at 4-week intervals. Regression estimated average level and change in level of positive urines over the period 2-12 weeks (primary outcomes) and sexual risk behaviors (secondary outcome). Ninety percent of visits were completed. By intent-to-treat, participants assigned to XRNTX had similar differences over 2-12 weeks in methamphetamine-positive urines as participants assigned to placebo [IRR 0.95, 95% CI = 0.76 - 1.20; Bayes Factor < 0.3]. Observed urine positivity declined from 78% to 70% in the XRNTX arm and 74% to 64% in the placebo arm. Adherence to injections was 96.7% in the XRNTX arm and 91.3% in the placebo arm. Sexual risk behaviors declined similarly among participants in both arms (all $P > 0.05$). There were no serious adverse events related to study drug, and no differences in frequency of adverse events by treatment arm. Notwithstanding very high medication adherence for this study, extended-release naltrexone does not appear to reduce methamphetamine use or sexual risk behaviors among methamphetamine-dependent men who have sex with men compared with placebo.

Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination Of Initial Prescription Characteristics and Pain Etiologies Shah, Anuj; Hayes, Corey J; Martin, Bradley C. *J Pain*. 2017; 18(11): 1374-1383.

The relationships between the initial opioid prescription characteristics and pain etiology with the probability of opioid discontinuation were explored in this retrospective cohort study using health insurance claims data from a nationally representative database of commercially insured patients in the United States. The authors identified 1,353,902 persons aged 14 years and older with no history of cancer or substance abuse, with new opioid use episodes and categorized them into 11 mutually exclusive pain etiologies. Cox proportional hazards models were estimated to identify factors associated with time to opioid discontinuation. After accounting for losses to follow-up, the probability of continued opioid use at 1 year was 5.3% across all subjects. Patients with chronic pain had the highest probability for continued opioid use followed by patients with inpatient admissions. Patients prescribed doses ≥ 90 morphine milligram equivalents (hazard ratio [HR] = .91; 95% confidence interval [CI], .91-.92), initiated with tramadol (HR = .89; 95% CI, .89-.90) or long-acting opioids (HR = .79; 95% CI, .77-.82) were less likely to discontinue opioids. Increasing days' supply of the first prescription was consistently associated with a lower likelihood of opioid discontinuation (HRs, CIs: 3-4 days' supply = .70, .70-.71; 5-7 days' supply = .48, .47-.48; 8-10 days' supply = .37, .37-.38; 11-14 days' supply = .32, .31-.33; 15-21 days' supply = .29, .28-.29;

≥ 22 days supplied = .20, .19-.20). The direction of this relationship was consistent across all pain etiologies. Clinicians should initiate patients with the lowest supply of opioids to mitigate unintentional long-term opioid use. This study shows that characteristics of the first opioid prescription, particularly duration of the prescription, are significant predictors of continued opioid use irrespective of the indication for an opioid prescription. These data should encourage prescribers to initiate patients using the minimum effective opioid dose and duration to reduce unintended long-term use and could motivate policies that restrict the initial supply of opioids.

Buspirone Maintenance Does Not Alter the Reinforcing, Subjective, and Cardiovascular Effects Of Intranasal Methamphetamine

Reynolds, Anna R; Strickland, Justin C; Stoops, William W; Lile, Joshua A; Rush, Craig R. Drug Alcohol Depend. 2017; 181: 25-29.

Medications development efforts for methamphetamine-use disorder have targeted central monoamines because these systems are directly involved in the effects of methamphetamine. Buspirone is a dopamine autoreceptor and D3 receptor antagonist and partial agonist at serotonin 1A receptors, making it a logical candidate medication for methamphetamine-use disorder. Buspirone effects on abuse-related behaviors of methamphetamine have been mixed in clinical and preclinical studies. Experimental research using maintenance dosing, which models therapeutic use, is limited. This study evaluated the influence of buspirone maintenance on the reinforcing effects of methamphetamine using a self-administration procedure, which has predictive validity for clinical efficacy. The impact of buspirone maintenance on the subjective and cardiovascular response to methamphetamine was also determined. Eight research participants (1 female) reporting recent illicit stimulant use completed a placebo-controlled, crossover, double-blind protocol in which the pharmacodynamic effects of intranasal methamphetamine (0, 15, and 30mg) were assessed after at least 6days of buspirone (0 and 45mg/day) maintenance. Intranasal methamphetamine functioned as a reinforcer and produced prototypical stimulant-like subjective (e.g., increased ratings of Good Effects and Like Drug) and cardiovascular (e.g., elevated blood pressure) effects. These effects of methamphetamine were similar under buspirone and placebo maintenance conditions. Maintenance on buspirone was well tolerated and devoid of effects when administered alone. These data suggest that buspirone is unlikely to be an effective pharmacotherapy for methamphetamine-use disorder. Given the central role of monoamines in methamphetamine-use disorder, it is reasonable for future studies to continue to target these systems.

Cocaine Use Is Associated With A Higher Prevalence Of Elevated ST2 Concentrations.

van Wijk, Xander M R; Vittinghoff, Eric; Wu, Alan H B; Lynch, Kara L; Riley, Elise D. Clin Biochem. 2017; 50(13-14): 791-793.

Cocaine is a well-known risk factor for acute cardiac events, but the effects in users outside of acute events are less clear. The authors investigated a possible association between cocaine use and the concentration of a novel biomarker for cardiac stress and heart failure, ST2. A case-control study was conducted to compare ST2 concentrations by the presence of cocaine in patients presenting for care, but not cardiac care, at an urban safety net hospital. In samples taken from 100 cocaine-positive and 100 cocaine-negative patients, the presence of cocaine was associated with ST2 concentrations > 35 ng/mL. Serum concentrations of benzoylecgonine, a major cocaine metabolite, were significantly correlated with ST2 concentrations. Cocaine use is associated with subclinical cardiac stress and damage outside of acute cardiac events. This information could add to better stratification of cocaine users with elevated ST2 concentrations who may be at higher risk for developing heart failure and other cardiac complications.

Daily Marijuana Use Is Associated With Missed Clinic Appointments Among HIV-Infected Persons Engaged In HIV Care Kipp, Aaron M; Rebeiro, Peter F; Shepherd, Bryan E; Brinkley-Rubinstein, Lauren; Turner, Megan; Bebawy, Sally; Sterling, Timothy R; Hulgian, Todd. AIDS Behav. 2017; 21(7): 1996-2004.

The authors assessed the association between marijuana use and retention in HIV care through a retrospective cohort study of patients engaged in care at a large HIV clinic in 2011 and 2012. Two different retention outcomes were assessed: not meeting the Institute of Medicine's (IOM) retention definition (≥ 2 provider visits ≥ 90 days apart in a calendar year) and no-show visits. Any marijuana use and frequency of marijuana use were obtained from a substance use screening questionnaire administered at each clinic visit. Modified Poisson regression was used to estimate risk ratios and 95% confidence intervals for the association between marijuana use and retention outcomes. Marijuana use was reported by 17% of 1791 patients and 21% were not retained (IOM definition). Marijuana use was not associated with the IOM retention outcome, but was associated with missing the next scheduled appointment. A non-linear dose-response was observed for frequency of marijuana use and missed visits, with daily users having the highest risk compared to non-users. Daily marijuana use had a negative impact on HIV clinic attendance. Further research is needed to elucidate the mechanisms by which marijuana use affects this outcome to inform targeted interventions.

Statistical Considerations In The Choice Of Endpoint For Drug Use Disorder Trials

Fitzmaurice, Garrett M; Lipsitz, Stuart R; Weiss, Roger D. Drug Alcohol Depend. 2017; 181: 219-222.

To date, the US Food and Drug Administration (FDA) requires drug use disorder trials developing new medications to use abstinence, a clinically meaningful endpoint, as the primary outcome. Although abstinence is the gold standard, only a relatively small percentage of participants in drug use disorder trials ever achieve this endpoint. This has prompted clinical trialists to consider quantitative measures of frequency of use, recognizing that some reductions in drug use that fall short of complete abstinence may potentially represent clinically important improvements. While much of the discussion concerning alternative outcomes to abstinence has focused on their clinical relevance, there are important statistical considerations that should also be taken into account. In this paper, the authors demonstrate and highlight the degree to which use of a quantitative measure of frequency of use, relative to a binary measure of abstinence, yields a very discernible increase in statistical power for assessing efficacy or effectiveness of treatments for drug use disorders. While it is well established that dichotomizing a quantitative measure invariably results in loss of statistical power, what is less well recognized is the degree of loss in the context of drug use disorder trials. In some cases, the required sample size must be almost doubled to achieve the same level of power.

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

Public Health Benefit of Peer-Referral Strategies For Detecting Undiagnosed HIV Infection among High-Risk Heterosexuals In New York City Gwadz, Marya; Cleland, Charles M; Perlman, David C; Hagan, Holly; Jenness, Samuel M; Leonard, Noelle R; Ritchie, Amanda S; Kutnick, Alexandra. J Acquir Immune Defic Syndr. 2017; 74(5): 499-507.

Identifying undiagnosed HIV infection is necessary for the elimination of HIV transmission in the United States. The present study evaluated the efficacy of 3 community-based approaches for uncovering undiagnosed HIV among heterosexuals at high-risk (HHR), who are mainly African

American/Black and Hispanic. Heterosexuals comprise 24% of newly reported HIV infections in the United States, but experience complex multilevel barriers to HIV testing. The authors recruited African American/Black and Hispanic HHR in a discrete urban area with both elevated HIV prevalence and poverty rates. Approaches tested were (1) respondent-driven sampling (RDS) and confidential HIV testing in 2 sessions (n = 3116); (2) RDS and anonymous HIV testing in one session (n = 498); and (3) venue-based sampling (VBS) and HIV testing in a single session (n = 403). The main outcome was newly diagnosed HIV infection. RDS with anonymous testing and one session reached HHR with less HIV testing experience and more risk factors than the other approaches. Furthermore, RDS with anonymous (4.0%) and confidential (1.0%) testing yielded significantly higher rates of newly diagnosed HIV than VBS (0.3%). Thus peer-referral approaches were more efficacious than VBS for uncovering HHR with undiagnosed HIV, particularly a single-session/anonymous strategy, and have a vital role to play in efforts to eliminate HIV transmission.

[Novel Nanoformulation To Mitigate Co-effects Of Drugs Of Abuse and HIV-1 Infection: Towards The Treatment Of NeuroAIDS](#) Jayant, Rahul Dev; Atluri, Venkata S R; Tiwari, Sneham; Pilakka-Kanthikeel, Sudheesh; Kaushik, Ajeet; Yndart, Adriana; Nair, Madhavan. J Neurovirol. 2017; 23(4): 603-614.

Drug abuse (e.g., methamphetamine-Meth or cocaine-Coc) is one of the major risk factors for becoming infected with HIV-1, and studies show that in combination, drug abuse and HIV-1 lead to significantly greater damage to CNS. To overcome these issues, the authors have developed a novel nanoformulation (NF) for drug-abusing population infected with HIV-1. In this work, a novel approach was developed for the co-encapsulation of Nelfinavir (Nel) and Rimcazole (Rico) using layer-by-layer (LbL) assembled magnetic nanoformulation for the cure of neuroAIDS. Developed NF was evaluated for blood-brain barrier (BBB) transmigration, cell uptake, cytotoxicity and efficacy (p24 assay) in HIV-1 infected primary astrocyte (HA) in presence or absence of Coc and Meth. Developed magnetic nanoformulation (NF) fabricated using the LbL approach exhibited higher amounts of drug loading (Nel and Rico) with 100% release of both the therapeutic agents in a sustained manner for 8 days. NF efficacy studies indicated a dose-dependent decrease in p24 levels in HIV-1-infected HA (~55%) compared to Coc + Meth treated (~50%). The results showed that Rico significantly subdued the effect of drugs of abuse on HIV infectivity. NF successfully transmigrated ($38.8 \pm 6.5\%$) across in vitro BBB model on the application of an external magnetic field and showed >90% of cell viability with efficient cell uptake. In conclusion, the authors' proof of concept study revealed that sustained and concurrent release of sigma σ_1 antagonist and anti-HIV drug from the developed novel sustained release NF can overcome the exacerbated effects of drugs of abuse in HIV infection and may solve the issue of medication adherence in the drug-abusing HIV-1 infected population.

[Hepatitis C Cascade Of Care Among Pregnant Women On Opioid Agonist Pharmacotherapy Attending A Comprehensive Prenatal Program](#) Page, Kimberly; Leeman, Lawrence; Bishop, Steven; Cano, Sandra; Bakhireva, Ludmila N. Matern Child Health J. 2017; 21(9): 1778-1783.

Given the large increases in opioid use among pregnant women and associations with hepatitis C virus (HCV) infection, screening pregnant women who are on (opioid agonist) pharmacotherapy for HCV infection has potential to inform medical care for these mothers as well as their newborns. The authors investigated the HCV testing cascade among pregnant women on pharmacotherapy in order to describe exposure and infection rates and to identify opportunities that would improve care. Secondary analyses of laboratory results were performed for HCV testing, including anti-HCV, viremia (RNA) and genotype. Information was abstracted from the medical records of women who were followed at a comprehensive prenatal care clinic for women with substance use disorders at

the University of New Mexico. The sample included 190 pregnant women, of whom 188 were on pharmacotherapy (43.7% on buprenorphine and 55.3% on methadone); the remaining two had tested positive for heroin or prescription opioids. A total of 178 (93.7%) were tested for anti-HCV, 94 (98.9%) of whom were tested for RNA, and 41 (57.7%) were genotyped. Prevalence of exposure to HCV by anti-HCV results was 53.3%, and 37.3% were positive for HCV RNA indicating chronic infection. The high prevalence of exposure and infection with HCV in pregnant women involved in pharmacotherapy for a substance use disorder indicate a need for ongoing surveillance and testing for HCV. Identifying HCV during pregnancy is crucial because this identification would serve to enhance medical care and potentially prevent vertical transmission. Identifying HCV would also facilitate referrals to newly available curative HCV treatments following delivery.

Testing and Linkage to HIV Care in China: A Cluster-Randomised Trial Wu Z, Tang Z, Mao Y, Van Veldhuisen P, Ling W, Liu D, Shen Z, Detels R, Lan G, Erinoff L, Lindblad R, Gu D, Tang H, Hu L, Zhu Q, Lu L, Oden N, Hasson AL, Zhao Y, McGoogan JM, Ge X, Zhang N, Rou K, Zhu J, Wei H, Shi CX, Jin X, Li J, Montaner JSG. *Lancet HIV*. 2017 Aug 31. pii: S2352-3018(17)30131-5. doi: 10.1016/S2352-3018(17)30131-5. [Epub ahead of print].

Multistage, stepwise HIV testing and treatment procedures can result in lost opportunities to provide timely antiretroviral therapy (ART). Incomplete engagement of patients along the care cascade translates into high preventable mortality. The authors aimed to identify whether a structural intervention to streamline testing and linkage to HIV health care would improve testing completeness, ART initiation, and viral suppression and reduce mortality. They did a cluster-randomised, controlled trial in 12 hospitals in Guangxi, China. All hospitals were required to be level 2A county general hospitals and ART delivery sites. The authors selected the 12 most similar hospitals in terms of structural characteristics, past patient caseloads, and testing procedures. Hospitals were randomly assigned (1:1) to either the One4All intervention or standard of care. Hospitals were randomised in a block design and stratified by the historical rate of testing completeness of the individual hospital during the first 6 months of 2013. The authors enrolled patients aged 18 years or older who were identified as HIV-reactive during screening in study hospitals, who sought inpatient or outpatient care in a study hospital, and who resided in the study catchment area. The One4All strategy incorporated rapid, point-of-care HIV screening and CD4 counts, and in-parallel viral load testing, to promote fast and complete diagnosis and staging and provide immediate ART to eligible patients. Participants in control hospitals received standard care services. All enrolled patients were assessed for the primary outcome, which was testing completeness within 30 days, defined as completion of three required tests and their post-test counselling. Safety assessments were hospital admissions for the first 90 days and deaths up to 12 months after enrolment. This trial is registered with ClinicalTrials.gov, number [NCT02084316](https://clinicaltrials.gov/ct2/show/study/NCT02084316). Between February 24 and November 25, 2014, the authors enrolled 478 patients (232 in One4All, 246 in standard of care). In the One4All group, 177 (76%) of 232 achieved testing completeness within 30 days versus 63 (26%) of 246 in the standard-of-care group (odds ratio 19.94, 95% CI 3.86-103.04, $p=0.0004$). Although no difference was observed between study groups in the number of hospital admissions at 90 days, by 12 months there were 65 deaths (28%) in the in the One4All group compared with 115 (47%) in the standard-of-care group (Cox proportional hazard ratio 0.44, 0.19-1.01, $p=0.0531$). This study provides strong evidence for the benefits of a patient-centred approach to streamlined HIV testing and treatment that could help China change the trajectory of its HIV epidemic, and help to achieve the goal of an end to AIDS.

Increased Risk Of Myocardial Infarction In HIV-Infected Individuals In North America Compared With The General Population

Drozd, Daniel R; Kitahata, Mari M; Althoff, Keri N; Zhang, Jinbing; Gange, Stephen J; Napravnik, Sonia; Burkholder, Greer A; Mathews, William C; Silverberg, Michael J; Sterling, Timothy R; Heckbert, Susan R; Budoff, Matthew J; Van Rompaey, Stephen; Delaney, Joseph A C; Wong, Cherise; Tong, Weiqun; Palella, Frank J; Elion, Richard A; Martin, Jeffrey N; Brooks, John T; Jacobson, Lisa P; Eron, Joseph J; Justice, Amy C; Freiberg, Matthew S; Klein, Daniel B; Post, Wendy S; Saag, Michael S; Moore, Richard D; Crane, Heidi M. *J Acquir Immune Defic Syndr.* 2017; 75(5): 568-576.

Previous studies of cardiovascular disease (CVD) among HIV-infected individuals have been limited by the inability to validate and differentiate atherosclerotic type 1 myocardial infarctions (T1MIs) from other events. The authors sought to define the incidence of T1MIs and risk attributable to traditional and HIV-specific factors among participants in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) and compare adjusted incidence rates (IRs) to the general population Atherosclerosis Risk in Communities (ARIC) cohort. The authors ascertained and adjudicated incident MIs among individuals enrolled in 7 NA-ACCORD cohorts between 1995 and 2014. They calculated IRs, adjusted incidence rate ratios (aIRRs), and 95% confidence intervals of risk factors for T1MI using Poisson regression. They compared aIRRs of T1MIs in NA-ACCORD with those from ARIC. Among 29,169 HIV-infected individuals, the IR for T1MIs was 2.57 (2.30 to 2.86) per 1000 person-years, and the aIRR was significantly higher compared with participants in ARIC [1.30 (1.09 to 1.56)]. In multivariable analysis restricted to HIV-infected individuals and including traditional CVD risk factors, the rate of T1MI increased with decreasing CD4 count [≥ 500 cells/ μL : ref; 350-499 cells/ μL : aIRR = 1.32 (0.98 to 1.77); 200-349 cells/ μL : aIRR = 1.37 (1.01 to 1.86); 100-199 cells/ μL : aIRR = 1.60 (1.09 to 2.34); < 100 cells/ μL : aIRR = 2.19 (1.44 to 3.33)]. Risk associated with detectable HIV RNA [< 400 copies/mL: ref; ≥ 400 copies/mL: aIRR = 1.36 (1.06 to 1.75)] was significantly increased only when CD4 was excluded. The higher incidence of T1MI in HIV-infected individuals and increased risk associated with lower CD4 count and detectable HIV RNA suggest that early suppressive antiretroviral treatment and aggressive management of traditional CVD risk factors are necessary to maximally reduce MI risk.

CLINICAL TRIALS NETWORK-RELATED RESEARCH

Frequency of Cannabis Use Among Primary Care Patients in Washington State

Lapham GT, Lee AK, Caldeiro RM, McCarty D, Browne KC, Walker DD, Kivlahan DR, Bradley KA. *J Am Board Fam Med.* 2017 Nov-Dec;30(6):795-805. doi: 10.3122/jabfm.2017.06.170062. Over 12% of US adults report past-year cannabis use, and among those who use daily, 25% or more have a cannabis use disorder. Use is increasing as legal access expands. Yet, cannabis use is not routinely assessed in primary care, and little is known about use among primary care patients and relevant demographic and behavioral health subgroups. This study describes the prevalence and frequency of past-year cannabis use among primary care patients assessed for use during a primary care visit. This observational cohort study included adults who made a visit to primary care clinics with annual behavioral health screening, including a single-item question about frequency past-year cannabis use (March 2015 to February 2016; n = 29,857). Depression, alcohol and other drug use were also assessed by behavioral health screening. Screening results, tobacco use, and diagnoses for past-year behavioral health conditions (e.g., mental health and substance use disorders) were obtained from EHRs. Among patients who completed the cannabis use question (n = 22,095; 74% of eligible patients), 15.3% (14.8% to 15.8%) reported any past-year use: 12.2% (11.8% to 12.6%)

less than daily, and 3.1% (2.9%-3.3%) daily. Among 2228 patients age 18 to 29 years, 36.0% (34.0% to 38.0%) reported any cannabis use and 8.1% (7.0% to 9.3%) daily use. Daily cannabis use was common among men age 18 to 29 years who used tobacco or screened positive for depression or used tobacco: 25.5% (18.8% to 32.1%) and 31.7% (23.3% to 40.0%), respectively. Cannabis use was common in adult primary care patients, especially among younger patients and those with behavioral health conditions. Results highlight the need for primary care approaches to address cannabis use.

Comparative Effectiveness Of Extended-Release Naltrexone Versus Buprenorphine-Naloxone For Opioid Relapse Prevention (X:BOT): A Multicentre, Open-Label, Randomised Controlled Trial

Lee JD, Nunes EV Jr, Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins CC, King J, Lindblad R, Liu D, Matthews AG, May J, Peavy KM, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J. *Lancet*. 2017 Nov 14. pii: S0140-6736(17)32812-X. doi: 10.1016/S0140-6736(17)32812-X. [Epub ahead of print].

Extended-release naltrexone (XR-NTX), an opioid antagonist, and sublingual buprenorphine-naloxone (BUP-NX), a partial opioid agonist, are pharmacologically and conceptually distinct interventions to prevent opioid relapse. The authors aimed to estimate the difference in opioid relapse-free survival between XR-NTX and BUP-NX. They initiated this 24-week, open-label, randomised controlled, comparative effectiveness trial at eight US community-based inpatient services and followed up participants as outpatients. Participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder, and had used non-prescribed opioids in the past 30 days. The authors stratified participants by treatment site and opioid use severity and used a web-based permuted block design with random equally weighted block sizes of four and six for randomisation (1:1) to receive XR-NTX or BUP-NX. XR-NTX was monthly intramuscular injections (Vivitrol; Alkermes) and BUP-NX was daily self-administered buprenorphine-naloxone sublingual film (Suboxone; Indivior). The primary outcome was opioid relapse-free survival during 24 weeks of outpatient treatment. Relapse was 4 consecutive weeks of any non-study opioid use by urine toxicology or self-report, or 7 consecutive days of self-reported use. This trial is registered with ClinicalTrials.gov, [NCT02032433](https://clinicaltrials.gov/ct2/show/study/NCT02032433). Between Jan 30, 2014, and May 25, 2016, the authors randomly assigned 570 participants to receive XR-NTX (n=283) or BUP-NX (n=287). The last follow-up visit was Jan 31, 2017. As expected, XR-NTX had a substantial induction hurdle: fewer participants successfully initiated XR-NTX (204 [72%] of 283) than BUP-NX (270 [94%] of 287; $p < 0.0001$). Among all participants who were randomly assigned (intention-to-treat population, n=570) 24-week relapse events were greater for XR-NTX (185 [65%] of 283) than for BUP-NX (163 [57%] of 287; hazard ratio [HR] 1.36, 95% CI 1.10-1.68), most or all of this difference accounted for by early relapse in nearly all (70 [89%] of 79) XR-NTX induction failures. Among participants successfully inducted (per-protocol population, n=474), 24-week relapse events were similar across study groups ($p = 0.44$). Opioid-negative urine samples ($p < 0.0001$) and opioid-abstinent days ($p < 0.0001$) favoured BUP-NX compared with XR-NTX among the intention-to-treat population, but were similar across study groups among the per-protocol population. Self-reported opioid craving was initially less with XR-NTX than with BUP-NX ($p = 0.0012$), then converged by week 24 ($p = 0.20$). With the exception of mild-to-moderate XR-NTX injection site reactions, treatment-emergent adverse events including overdose did not differ between treatment groups. Five fatal overdoses occurred (two in the XR-NTX group and three in the BUP-NX group). In this population it is more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective.

Future work should focus on facilitating induction to XR-NTX and on improving treatment retention for both medications.

Validation of the TAPS-1: A Four-Item Screening Tool to Identify Unhealthy Substance Use in Primary Care

Gryczynski J, McNeely J, Wu LT, Subramaniam GA, Svikis DS, Cathers LA, Sharma G, King J, Jelstrom E, Nordeck CD, Sharma A, Mitchell SG, O'Grady KE, Schwartz RP. *J Gen Intern Med.* 2017 Sep;32(9):990-996. doi: 10.1007/s11606-017-4079-x. Epub 2017 May 26. The Tobacco, Alcohol, Prescription Medication, and Other Substance use (TAPS) tool is a combined two-part screening and brief assessment developed for adult primary care patients. The tool's first-stage screening component (TAPS-1) consists of four items asking about past 12-month use for four substance categories, with response options of never, less than monthly, monthly, weekly, and daily or almost daily. The objective of this study was to validate the TAPS-1 in primary care patients. Participants completed the TAPS tool in self- and interviewer-administered formats, in random order. In this secondary analysis, the TAPS-1 was evaluated against DSM-5 substance use disorder (SUD) criteria to determine optimal cut-points for identifying unhealthy substance use at three severity levels (problem use, mild SUD, and moderate-to-severe SUD). Participants were two thousand adult patients at five primary care sites. DSM-5 SUD criteria were determined via the modified Composite International Diagnostic Interview. Oral fluid was used as a biomarker of recent drug use. Key results included optimal frequency-of-use cut-points on the self-administered TAPS-1 for identifying SUDs were \geq monthly use for tobacco and alcohol (sensitivity = 0.92 and 0.71, specificity = 0.80 and 0.85, AUC = 0.86 and 0.78, respectively) and any reported use for illicit drugs and prescription medication misuse (sensitivity = 0.93 and 0.89, specificity = 0.85 and 0.91, AUC = 0.89 and 0.90, respectively). The performance of the interviewer-administered format was similar. When administered first, the self-administered format yielded higher disclosure rates for past 12-month alcohol use, illicit drug use, and prescription medication misuse. Frequency of use alone did not provide sufficient information to discriminate between gradations of substance use problem severity. Among those who denied drug use on the TAPS-1, less than 4% had a drug-positive biomarker. The authors conclude that the TAPS-1 can identify unhealthy substance use in primary care patients with a high level of accuracy, and may have utility in primary care for rapid triage.

Racial/Ethnic Subgroup Differences in Outcomes and Acceptability of an Internet-delivered Intervention for Substance Use Disorders

Campbell ANC, Montgomery L, Sanchez K, Pavlicova M, Hu M, Newville H, Weaver L, Nunes EV. *J Ethn Subst Abuse.* 2017 Apr 3:1-19. doi: 10.1080/15332640.2017.1300550. [Epub ahead of print].

The Therapeutic Education System (TES), an Internet version of the Community Reinforcement Approach plus prize-based motivational incentives, is one of few empirically supported technology-based interventions. To date, however, there has not been a study exploring differences in substance use outcomes or acceptability of TES among racial/ethnic subgroups. This study uses data from a multisite (N = 10) effectiveness study of TES to explore whether race/ethnicity subgroups (White [n = 267], Black/African American [n = 112], and Hispanic/Latino [n = 55]) moderate the effect of TES. Generalized linear mixed models were used to test whether abstinence, retention, social functioning, coping, craving, or acceptability differed by racial/ethnic subgroup. Findings demonstrated that race/ethnicity did not moderate the effect of TES versus TAU on abstinence, retention, social functioning, or craving. A three-way interaction (treatment, race/ethnicity, and abstinence status at study entry) showed that TES was associated with greater coping scores among non-abstinent White participants (p = .008) and among abstinent Black participants (p < .001). Acceptability of the TES intervention, although high overall, was significantly different by

race/ethnicity subgroup with White participants reporting lower acceptability of TES compared to Black ($p = .006$) and Hispanic/Latino ($p = .008$) participants. TES appears to be a good candidate treatment among a diverse population of treatment-seeking individuals with substance use disorders.

INTRAMURAL RESEARCH

Chemogenetics Revealed: DREADD Occupancy and Activation via Converted Clozapine

Gomez JL, Bonaventura J, Lesniak W, Mathews WB, Sysa-Shah P, Rodriguez LA, Ellis RJ, Richie CT, Harvey BK, Dannals RF, Pomper MG, Bonci A, Michaelides M. *Science*. 2017 Aug 4;357(6350):503-507.

The chemogenetic technology DREADD (designer receptors exclusively activated by designer drugs) is widely used for remote manipulation of neuronal activity in freely moving animals. DREADD technology posits the use of "designer receptors," which are exclusively activated by the "designer drug" clozapine N-oxide (CNO). Nevertheless, the in vivo mechanism of action of CNO at DREADDs has never been confirmed. CNO does not enter the brain after systemic drug injections and shows low affinity for DREADDs. Clozapine, to which CNO rapidly converts in vivo, shows high DREADD affinity and potency. Upon systemic CNO injections, converted clozapine readily enters the brain and occupies central nervous system-expressed DREADDs, whereas systemic subthreshold clozapine injections induce preferential DREADD-mediated behaviors.

The Anterior Insular Cortex→Central Amygdala Glutamatergic Pathway Is Critical to Relapse after Contingency Management

Venniro M, Caprioli D, Zhang M, Whitaker LR, Zhang S, Warren BL, Cifani C, Marchant NJ, Yizhar O, Bossert JM, Chiamulera C, Morales M, Shaham Y. *Neuron*. 2017 Oct 11;96(2):414-427.

Despite decades of research on neurobiological mechanisms of psychostimulant addiction, the only effective treatment for many addicts is contingency management, a behavioral treatment that uses alternative non-drug reward to maintain abstinence. However, when contingency management is discontinued, most addicts relapse to drug use. The brain mechanisms underlying relapse after cessation of contingency management are largely unknown, and, until recently, an animal model of this human condition did not exist. Here the authors used a novel rat model, in which the availability of a mutually exclusive palatable food maintains prolonged voluntary abstinence from intravenous methamphetamine self-administration, to demonstrate that the activation of monosynaptic glutamatergic projections from anterior insular cortex to central amygdala is critical to relapse after the cessation of contingency management. The authors identified the anterior insular cortex-to-central amygdala projection as a new addiction- and motivation-related projection and a potential target for relapse prevention.

Neural Signatures of Cognitive Flexibility and Reward Sensitivity Following Nicotinic Receptor Stimulation in Dependent Smokers: A Randomized Trial

Lesage E, Aronson SE, Sutherland MT, Ross TJ, Salmeron BJ, Stein EA. *JAMA Psychiatry*. 2017 Jun 1;74(6):632-640.

Withdrawal from nicotine is an important contributor to smoking relapse. Understanding how reward-based decision making is affected by abstinence and by pharmacotherapies such as nicotine replacement therapy and varenicline tartrate may aid cessation treatment. The objective of this study was to independently assess the effects of nicotine dependence and stimulation of the nicotinic acetylcholine receptor on the ability to interpret valence information (reward sensitivity) and

subsequently alter behavior as reward contingencies change (cognitive flexibility) in a probabilistic reversal learning task. Nicotine-dependent smokers and nonsmokers completed a probabilistic reversal learning task during acquisition of functional magnetic resonance imaging (fMRI) in a 2-drug, double-blind placebo-controlled crossover design conducted from January 21, 2009, to September 29, 2011. Smokers were abstinent from cigarette smoking for 12 hours for all sessions. In a fully Latin square fashion, participants in both groups underwent MRI twice while receiving varenicline and twice while receiving a placebo pill, wearing either a nicotine or a placebo patch. Imaging analysis was performed from June 15, 2015, to August 10, 2016. A well-established computational model captured effects of smoking status and administration of nicotine and varenicline on probabilistic reversal learning choice behavior. Neural effects of smoking status, nicotine, and varenicline were tested for on MRI contrasts that captured reward sensitivity and cognitive flexibility. The study included 24 nicotine-dependent smokers (12 women and 12 men; mean [SD] age, 35.8 [9.9] years) and 20 nonsmokers (10 women and 10 men; mean [SD] age, 30.4 [7.2] years). Computational modeling indicated that abstinent smokers were biased toward response shifting and that their decisions were less sensitive to the available evidence, suggesting increased impulsivity during withdrawal. These behavioral impairments were mitigated with nicotine and varenicline. Similarly, decreased mesocorticolimbic activity associated with cognitive flexibility in abstinent smokers was restored to the level of nonsmokers following stimulation of nicotinic acetylcholine receptors (familywise error-corrected $P < .05$). Conversely, neural signatures of decreased reward sensitivity in smokers (vs nonsmokers; familywise error-corrected $P < .05$) in the dorsal striatum and anterior cingulate cortex were not mitigated by nicotine or varenicline. There was a double dissociation between the effects of chronic nicotine dependence on neural representations of reward sensitivity and acute effects of stimulation of nicotinic acetylcholine receptors on behavioral and neural signatures of cognitive flexibility in smokers. These chronic and acute pharmacologic effects were observed in overlapping mesocorticolimbic regions, suggesting that available pharmacotherapies may alleviate deficits in the same circuitry for certain mental computations but not for others. **Trial Registration:** clinicaltrials.gov Identifier: [NCT00830739](https://clinicaltrials.gov/ct2/show/study/NCT00830739).

Dopamine Neurons Respond to Errors in the Prediction of Sensory Features of Expected Rewards

Takahashi YK, Batchelor HM, Liu B, Khanna A, Morales M, Schoenbaum G. *Neuron*. 2017 Sep 13;95(6):1395-1405.

Midbrain dopamine neurons have been proposed to signal prediction errors as defined in model-free reinforcement learning algorithms. While these algorithms have been extremely powerful in interpreting dopamine activity, these models do not register any error unless there is a difference between the value of what is predicted and what is received. Yet learning often occurs in response to changes in the unique features that characterize what is received, sometimes with no change in its value at all. Here, the authors show that classic error-signaling dopamine neurons also respond to changes in value-neutral sensory features of an expected reward. This suggests that dopamine neurons have access to a wider variety of information than contemplated by the models currently used to interpret their activity and that, while their firing may conform to predictions of these models in some cases, they are not restricted to signaling errors in the prediction of value.

Exogenous Ghrelin Administration Increases Alcohol Self-Administration and Modulates Brain Functional Activity In Heavy-Drinking Alcohol-Dependent Individuals

Farokhnia M, Grodin EN, Lee MR, Oot EN, Blackburn AN, Stangl BL, Schwandt ML, Farinelli LA, Momenan R, Ramchandani VA, Leggio L. *Mol Psychiatry*. 2017 Nov 14. doi: 10.1038/mp.2017.

Preclinical evidence suggests that ghrelin, a peptide synthesized by endocrine cells of the stomach and a key component of the gut-brain axis, is involved in alcohol seeking as it modulates both

central reward and stress pathways. However, whether and how ghrelin administration may impact alcohol intake in humans is not clear. For, the authors believe, the first time, this was investigated in the present randomized, crossover, double-blind, placebo-controlled, human laboratory study. Participants were non-treatment-seeking alcohol-dependent heavy-drinking individuals. A 10-min loading dose of intravenous ghrelin/placebo (3 mcg kg^{-1}) followed by a continuous ghrelin/placebo infusion (16.9 ng/kg/min) was administered. During a progressive-ratio alcohol self-administration experiment, participants could press a button to receive intravenous alcohol using the Computerized Alcohol Infusion System. In another experiment, brain functional magnetic resonance imaging was conducted while participants performed a task to gain points for alcohol, food or no reward. Results showed that intravenous ghrelin, compared to placebo, significantly increased the number of alcohol infusions self-administered (percent change: 24.97 ± 10.65 , $P=0.04$, Cohen's $d=0.74$). Participants were also significantly faster to initiate alcohol self-administration when they received ghrelin, compared to placebo ($P=0.03$). The relationships between breath alcohol concentration and subjective effects of alcohol were also moderated by ghrelin administration. Neuroimaging data showed that ghrelin increased the alcohol-related signal in the amygdala ($P=0.01$) and modulated the food-related signal in the medial orbitofrontal cortex ($P=0.01$) and nucleus accumbens ($P=0.08$). These data indicate that ghrelin signaling affects alcohol seeking in humans and should be further investigated as a promising target for developing novel medications for alcohol use disorder.

GRANTEE HONORS AND AWARDS

NIDA DNB Grantee, **Dr. Michael Rosbash**, Peter Gruber Endowed Chair in Neuroscience, Professor of Biology, and Howard Hughes Medical Institute Investigator at Brandeis University, shared the Nobel Prize with Drs. Michael Hall and Jeffrey Young for seminal discoveries of the molecular regulation of circadian rhythm.

Two DNB grantees, **Dr. Ben Cravatt** of Scripps Institute and **Dr. Yasmin Hurd** of Mt. Sinai, were recently elected to the National Academy of Medicine.

Dr. Garrett Stuber of the University of North Carolina was the recipient of the Efron award for outstanding basic research contributions to neuropsychopharmacology.

Dr. Lara Ray from UCLA was the recipient of the Killam Award for outstanding translational research contributions to neuropsychopharmacology.

Dr. Eric Nestler was the recipient of the Hoch Award which recognizes outstanding contributions to the American College of Neuropsychopharmacology.

Dr. Robert Malenka from Stanford won the Goldman-Rakic prize for Outstanding Achievements in Cognitive Neuroscience.

Dr. Sharon Walsh of the University of Kentucky, received the 2017 Marian W. Fischman Award from the College on Problems of Drug Dependence. This award recognizes the contributions of an outstanding woman scientist in drug abuse research.

Dr. Adam Leventhal, University of Southern California, received 3 national awards in 2017: Distinguished Scientific Award from the American Psychological Association for Early Career Contribution to Psychology in Applied Research in 2017, a Mentorship Award from the American Academy of Health Behavior and the Theodore Millon Award for Outstanding Mid-Career Scientific Contributions to Personality Psychology from the American Psychological Foundation.

K99 awardee **Karsten Lunze, M.D., Dr.P.H., M.P.H.**, assistant professor at Boston Medical Center, was honored along with his wife Dr. Fatima Lunze with the American Public Health Association's Victor Sidel and Barry Levy Award for Peace for service to victims of war and terrorism. See: <https://www.apha.org/news-and-media/news-releases/apha-news-releases/2017/2017-awards>

STAFF HONORS AND AWARDS

2017 NIH DIRECTOR'S AWARDS – Presented October 2017

Dr. Chung-Yui B. Tai, *Scientific/Medical Award* for extraordinary vision, efforts and successes in bridging the research-to-practice gap for addictive disorders.

Joellen M. Austin, *Administrative Award* for exceptional executive leadership to critical NIH and HHS initiatives and for promoting transparency, communication, and inclusion at NIDA.

Dr. Albert H. Avila, *Ruth L. Kirschstein Mentoring Award* -- given to individuals who have demonstrated significant leadership, skill, and ability in serving as a mentor to one or more individuals.

Kirkland L. Davis, *NIH Work/Live and Well-Being Champion Award* -- recognizes one supervisor's exceptional performance or special efforts in supporting employees' work/life and well-being while maintaining or improving productivity in support of the agency's mission.

2017 NIDA DIRECTOR'S AWARDS -- Presented October 2017

CENTER FOR THE CLINICAL TRIALS NETWORK

Petra Jacobs

In recognition of outstanding contributions in support of the NIDA mission.

DIVISION OF EXTRAMURAL RESEARCH

Grants Management Team

Yinka Abu
Debra Battle-Dudley
Nadia Brown
Amy Bucheimer
Maryellen Connell
Amy Connolly
Edith Davis
Christine Kidd
Cheryl Nathaniel
Jennifer Schermerhorn
Aida Vasquez
Ericka Wells

In recognition of effective and seamless stewardship of NIDA's extramural grant awards in a year of delayed obligations and increasing budget.

DIVISION OF EPIDEMIOLOGY, SERVICES AND PREVENTION RESEARCH

The HIV, HCV, and Rural Opioid Team

Amy Connolly
Aria Crump
Sarah Duffy

Peter Hartsock
Richard Jenkins
Shoshana Kahana
Jag Khalsa
Hiromi Ono
Tisha Wiley

In recognition of addressing the opioid crisis in rural America by building systems for prevention, treatment, control, and support.

DIVISION OF NEUROSCIENCE AND BEHAVIOR

Roger Little

In recognition of outstanding contributions in support of the NIDA mission.

Susan Volman

In recognition of work shaping the NIDA portfolio in basic science, shepherding new investigators in their careers, and developing NIDA and NIH programs that are transforming science.

DIVISION OF THERAPEUTICS AND MEDICAL CONSEQUENCES

Liza Zeinert

In recognition of supporting clinical trial stewardship by implementing the Final Rule requirements for clinical trials registration and data submission in ClinicalTrials.gov

NIDA Addiction Treatment Discovery Program

Naresh Chand
Hirsch Davis
Carol Hubner
Richard Kline
Ming Shih
David White

In recognition of sustained excellence in collaborative team efforts using preclinical models to evaluate the potential efficacy of new medications for substance use disorder treatments.

NIDA Marijuana Supply and Research Support Team

Steve Gust
Richard Kline
Robert Walsh

In recognition of excellence in supporting NIDA researchers in obtaining marijuana and cannabinoids and rapidly responding to requests for information and guidance.

INTRAMURAL RESEARCH PROGRAM

Francois Vautier

In recognition of selection by the HHS Ignite Accelerator team to advance the use of state of the art centralized transgenic rodent breeding programs.

OFFICE OF THE DIRECTOR

NIDA's Workgroup on the NIH Opioid Research Initiative

Josie Anderson
Maureen Boyle
Usha Charya
Michelle Corbin
Jessica Cotto
Kim DiFonzo
Emily Einstein
Mark Fleming
Tara Garwood
Emily Jones
Carol Krause
Jinhee Lee
Janet Linton
David McCann
Ivan Montoya
Lanette Palmquist
Shirley Simson
Jack Stein
David Thomas
Eric Wargo

In recognition of outstanding activities in support of the NIH 2017 response in addressing the opioid crisis.

NIDA PATH Study Team

Cathy Backinger
Nicolette Borek
Kevin Conway
Victoria Green
Nahla Hilmi
Andrew Hotaling
Donna Jones
Heather Kimmel
Elizabeth Lambert
Josh Lazarus
Linda Moore
Ndiri Okeagu
Brian O'Laughlin
Marushka Silveira
Christopher Squiers
Andrew Varley

In recognition of success in launching the second phase of this landmark tobacco epidemiology study.

OFFICE OF MANAGEMENT

Christopher Belt

In recognition of exceptional leadership and vision as Acting Director of the Office of Acquisitions.

The NIDA NEPS Redesign Team

Rushan Ahmed
Stacey Berry
Michael Cole
Gregg Friedman
Stacy Gardner
Donna Jones
Jagdeep Kathuria
Yvonne Moskal
Shyam Namavaram
Emine Oymak
Xiao-Yan Su

In recognition of work on the development and implementation of an enhanced program coding and portfolio analysis module in NEPS.

The NIDA Animal Care Contract Team

Kenneth Goodling
Thomas Haines
Megan Nathan
Brian O'Laughlin
Kyle Stump

In recognition of the team's tireless pursuit of the critical NIDA animal care replacement contract.

OFFICE OF SCIENCE POLICY AND COMMUNICATIONS

Jessica Cotto

In recognition of boundless energy and consistently high performance in taking on new initiative following staff changes in Science Policy Branch.

Facebook Live Q&A on Pain & Opioid Management for Veterans

Josie Anderson
Kim DiFonzo
Tara Garwood
Alexa Lopez
Shirley Simson
David Thomas

In recognition of the NIDA team that partnered with NCCIH to provide answers to veteran's questions about opioids during a Facebook Live event.

NIDA Director's Award for Collaboration

The NIDA Clinical Trials Stewardship (CTS) Team

Carol Alderson
Kristopher Bough
Bethany Deeds
Ronald Dobbins

Pamela Fleming
Steve Grant
Katia Howlett
Petra Jacobs
Dionne Jones
Aida Klun
Ivan Montoya
Ivan Navarro
Brian O’Laughlin
Vani Pariyadath
Karran Phillips
Michele Rankin
Carmen Rosa
Mark Swieter
Yvonne Walker
Robert Walsh
Kevin Walton
Susan Weiss
Lisa Zeinert

In recognition of collaboration to ensure the successful NIDA implementation of the rapidly changing NIH Clinical Trials Stewardship policies.

The DNB/IRP Workshop on Models of Compulsive Drug Use

Antonello Bonci
Jean Lud Cadet
David Epstein
Carl Lupica
Vani Pariyadath
Yavin Shaham
Yihong Yang

In recognition of cross-NIDA collaboration on a workshop to advance new models with which to study the neuroscience of addiction and substance use disorders.

NIDA Standardized Research E-cigarette Team

Julia Berzhanskaya
Jeffrey Brown
Philip Decastro
Marta De Santis
Lyle Furr
Kenneth Goodling
Aidan Hampson
Mark McNally
Jurij Mojsiak
Brian O’Laughlin
Robert Walsh
Kevin Walton

NIDA Director's Award for Diversity

Christie Brannock

In recognition of contributions to promote diversity in science by providing training opportunities to young scientists.

NIDA Director's Award for Quality Worklife

Aida Klun

In recognition of outstanding efforts in positively impacting NIDA's Quality of Worklife.

NIDA Director's Award Rising Star

Emily Jones

In recognition of accomplishments, creativity, energy, and ability to inspire others at NIDA.

Michael Michaelides

In recognition of accomplishments, creativity, energy, and ability to inspire others at NIDA.

Jeffrey Schmidt

In recognition of accomplishments, creativity, energy, and ability to inspire others at NIDA.

NIDA Director's Innovator Award

Bethany Deeds

In recognition of your leadership and innovation in proactively managing the Adolescent Brain Cognitive Development Study using a results-based accountability framework.

The IRP Mobile Device Group

Jia-Ling Lin

Mustapha Mezghanni

Massoud Vahabzadeh

In recognition of innovations in providing real-time collection of clinical data and the provision of complex educational information.

PHS NIH Commissioned Corps Achievement Medal Award

CAPT Michelle Leff

For outstanding service as NIDA Technology Development Coordinator and facilitating NIDA scientific discoveries from patents to commercial potential.

LT Stacy Yung

For outstanding leadership and impeccable work dedication during a period of extended nursing staff shortage from April 1 to August 21, 2016.

30 Years of Government Service Recognition

Edith Davis

Stacey Gardner

Kathleen Giuliano

Moira O'Brien

Robert Walsh

Cora Lee Wetherington

40 Years of Government Service Award

Joyce Williams

Other Staff Awards

Drs. Kris Bough and **Jonathan Pollock**, DNB, served as editors for a special issue of Trends in Molecular Medicine on Peripheral Biomarkers for Substance Use Disorders that will appear in March 2018.

Andrew Kesner, IRP, received the NIH FARE Award in July 2017 (\$1000.00 towards travel); the Outstanding Poster Award; at the NIDA Mentoring Awards and Poster Day; and the NIH Summer Research Mentor Award.

Dr. Lorenzo Leggio, IRP, was invited to join the Scientific Committee of the Zardi-Gori Foundation (Milan, Italy), a non-profit organization focused on promoting research and education on addictions. The Foundation recently organized a two-day scientific meeting entitled “Alcohol Use Disorder: From Bench to Bedside.” Drs. Leggio and Bonci served in the Scientific Committee for this scientific meeting and they also served as speakers and chairs in symposia during this scientific meeting.

Dr. Da-Ting Lin, IRP, was elected the President of SfN Greater Baltimore Chapter for 2017 and will host the GBSfN annual meeting at the BRC Atrium to foster interaction between NIDA IRP and Greater Baltimore area neuroscience colleagues.

Dr. Kenner Rice, IRP, was named a Fellow into the National Academy of Inventors and will be inducted in April 2018.

Drs. Tyburski, Preston, and Epstein, IRP, are coinventors on a patent (PCT/US2016/029553) for our mHealth platform that uses predictive analytics to deliver just-in-time treatment for addictive disorders.

Dr. Massoud Vahabzadeh, Biomedical Informatics Section, IRP, was listed as the lead inventor for a PHS Employee Invention entitled “Mobile Interconnected Evaluation & Learning (MIEL),” filed in August 2017. Co-inventors include **Dr. Jia-Ling Lin** and **Mustapha Mezghanni**. MIEL is a mobile health application for real-time communication of patient-reported assessment data associated with automatically collected geolocation data on one side, and the user’s enterprise-scale patient record system on the other.

Dr. Francois Vautier, IRP, was selected to join an HHS program called “Ignite Accelerator,” an internal innovation startup program for staff within the HHS who want to improve the way their agency works. His idea should open the possibility for other NIH institutes to breed their research animals with the same tremendous success and benefits as NIDA’s centralized breeding facility. After three months of intense inquiries, Dr. Vautier presented his findings and solutions to a large panel of HHS representatives on December 13 to check the feasibility of extending his ideas across NIH facilities.

STAFF CHANGES

New Appointments/Employees

Redonna Chandler, Ph.D. has been named Director of the AIDS Research Program at the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH). In this role, she will be responsible for the development, planning, and coordination of high priority research on HIV and AIDS and drug use within NIDA and across other NIH Institutes. She will also oversee NIDA's annual Avant-Garde Award competition, which stimulates high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of HIV/AIDS in drug users. Dr. Chandler's new position marks a return to NIDA, where she previously served as the Acting Director for the Division of Epidemiology, Services and Prevention Research, as well as the Chief of the Services Research Branch. Most recently, Dr. Chandler was Deputy Director for the Division of Clinical Innovation (DCI) at the National Center for Advancing Translational Sciences, providing executive leadership for the Division's scientific, financial, managerial, and administrative components. She also served as Senior Advisor at DCI where she led the formation and coordination of scientific initiatives and special projects within the Division designed to fulfill its translational science research mission. Dr. Chandler worked for the Department of Justice from 1996-2002, directing large drug treatment programs. Her areas of expertise include research with criminal justice system populations, clinical trials, improving adherence to drug use treatment and HIV care, and implementing evidence based treatments into routine practice settings. Dr. Chandler earned her Ph.D. in psychology from the University of Kentucky and is a licensed psychologist. As a clinician, she has treated those struggling with addiction use disorder and serious mental health issues. Dr. Chandler will begin at NIDA on January 8, 2018. She fills the position left by Dr. Jacques Normand, who recently retired from NIDA after 12 years.

Eugene Gutman, Ph.D. joined the section on Drug Design and Synthesis as an IRTA Postdoctoral Fellow after receiving his degree from the University of California-Irvine.

Chloe Jordan, Ph.D. joined the IRP Addiction Biology Unit as a new post-doctoral research fellow.

Sung Kim, Ph.D. joined the DTMC as Health Scientist Administrator in the Chemistry & Pharmaceuticals Branch. Dr. Kim graduated from OSU with a Ph.D. in medicinal chemistry. He served as Contract Officer for 11 years at the Division of Cancer Treatment and Diagnosis of NCI, managing drug substance and formulation contracts dedicated to new cancer drug development. Then, he worked at the FDA, reviewing CMC sections for INDs, DMFs, NDAs, and ANDAs for regulatory decision about clinical trials or marketing of drug products. He now serves as Program Officer for the development and production of new and improved medications for the treatment of Substance Use Disorders (SUDs) and assists in the management of the medicinal chemistry program in support of the Addiction Treatment Discovery and Development program.

Kimberly LeBlanc, Ph.D. began a detail in November 2017 with the Division of Neuroscience and Behavior's (DNB) Behavioral & Cognitive Neuroscience Branch. She is completing a postdoctoral fellow at the NIDDK IRP where she has been studying the relationship between striatal activity, reinforcement, and compulsive food seeking. In addition to her behavioral neuroscience background she brings her interest in computational neuroscience and data mining.

Ying Liang, Ph.D. joined the IRP Addiction Biology Unit as a new guest research fellow.

Raul N. Mandler, M.D. joined the DTMC as Senior Medical Officer in the Medical Consequences Branch. Prior to joining DTMC, Dr. Mandler served as Senior Medical Officer in the CCTN, where he was instrumental in developing clinical trials for the diagnosis and prevention of HIV and Hep-C in drug abuse populations. He will be serving as Project Officer and will support the Division's work on medical safety and human subjects' protection issues in grants and contracts.

Shang-Yi (Anne) Tsai, Ph.D., joined NIDA's Review Branch in January 2017 after a productive career with NIDA intramural, and has transitioned this January 8, 2018 to be a Program Officer within NIDA's Division of Neuroscience and Behavior. As an SRO, Anne quickly understood and adopted best practices regarding NIH and NIDA reviews, and was attentive to implementing these. She learned from everyone, and Anne's relationships with applicants, reviewers and program staff were both cordial and compliant with NIH review policies and practices. Anne also took active roles with the NIAID/NIDA Neurosciences Consortium, notably co-arranging and co-chairing a Frontiers symposium in November 2017 and with the NIDA Developmental Neuroscience workgroup, she is developing a review chapter on stress and neurobiology.

Departures

Maureen Boyle, Ph.D., left the Science Policy Branch, Office of Science Policy and Communications on December 1, 2017, to assume a new position as Chief, Scientific Officer at the Addiction Policy Forum.

Zenab Chowdhry, A Contract Specialist in NIDA's Office of Acquisitions' Station Support Branch left on November 17, 2017 for a position in the private sector.

Anne Pierce, IRP, left NIDA to join the Neuroscience PhD program at The University of Colorado, Boulder.

Dong Wang, Ph.D. IRP, left NIDA for a tenure-track assistant professor position at Drexel University.

Hai-Ying Zhang, Ph.D. left the NIDA-IRP to accept a position as a Research Associate in the Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine.

Retirements

Nora Chiang, Ph.D., Chief of the Chemistry and Pharmaceutics Branch of DTMC, retired on January 20, 2018. She joined NIDA in 1980 and served as Program Officer overseeing research projects in the areas of pharmaceutics and pharmacokinetics. Since 1999, she has served as the Chief for the Chemistry and Pharmaceutics Branch, DTMC and manages Branch activities involving medicinal and analytical chemistry, dosage form development and production, and pharmacokinetics. She directs the medications development program in biopharmaceutics and pharmacokinetics. She made significant contributions to the FDA approval of LAAM and Buprenorphine for opioid use disorders, the approval of intranasal naloxone for treating opioid

overdose, and Lofexidine for opioid withdrawal. She has received numerous distinguished awards for her outstanding services from the NIDA Director, the NIH Director and the Secretary of the Department of Health and Human Services.

Maryellen Connell retired from DER/GMB after working 15 years as a Grants Management Specialist and over 40 years of Federal Service.

Katherine Davenny, Ph.D. retired from Federal service on December 31, 2017 after 26 years of a very productive career at NIDA. As Associate Director of the AIDS Research Program, she has also played a central role in developing NIDA's substance use-HIV research agenda. Her exceptional multidisciplinary knowledge in HIV research have been crucial in shaping NIDA's engagement in new areas of HIV research and in forming partnerships across NIH, other government entities, and domestic and international researchers. She has been instrumental in enhancing the visibility and in integrating substance use into the broader HIV arena.

Debra Hawkins a Supervisory Contract Specialist in the Office of Administration OD retired from Federal service on January 3, 2018.

Jag Khalsa Ph.D., retired from NIDA after almost 40 years of dedicated federal service. Dr. Khalsa began his career as a pharmacologist/toxicologist/clinical evaluator on several aspects of drug safety (Food Additives, INDs, NDAs, Adverse Drug Reactions), and joined NIDA in 1987 and developed highly significant programs of research (maternal drug abuse and fetal complications, adolescent drug abuse, medical consequences of drug abuse, and co-occurring infections such as HIV, HCV, TB, and STIs). Jag has been integral part of the Division of Therapeutics and Medical Consequences, overseeing the Medical Consequences Branch, where he led the multidisciplinary program of clinical research on medical consequences of drug abuse both in domestic and international settings.

Marguerite Lewis, an IT Specialist in NIDA's IRMB retired from Federal service on January 3, 2018.

Jacques Normand Ph.D. retired from a distinguished Federal service career on December 31, 2017. Over the last 12 years Jacques has served as a very effective Director of the AIDS Research Program (ARP), and NIDA has been very fortunate to have him. His remarkable leadership helped expand NIDA's HIV research program and attracted prominent HIV researchers as NIDA grantees. He has had many accomplishments including his ability to build innovative research programs, to help investigators from the most junior to the most senior succeed, and to form strong partnership with research programs across NIH. Jacques leaves NIDA and the field with an incredible scientific legacy.

Ming Shih, Ph.D. retired from NIDA on January 3, 2018. Ming has 20 years of R & D experience in medication and diagnostic device development in the Department of Defense prior to joining the National Institute on Drug Abuse in 2000. She worked for the Center for Clinical Trials Network for 5 years and then she joined the Chemistry and Pharmaceutics Branch in the Division of Therapeutics and Medical Consequences (DTMC) in 2005. She served as the Program Director of research grants in medicinal chemistry and managed a grant portfolio for the synthesis and pre-clinical evaluation of novel chemical compounds for the treatment of drug dependence. She also supervised contracts involving analytical

Mark Swieter Ph.D., after over 26 years of dedicated federal service, retired from NIDA January 26, 2018. Trained as an anatomist, his research focused on mast cell biology. Dr. Swieter was an invaluable member of the NIDA family and most recently, the Division of Extramural Research. His extensive knowledge of NIDA and NIH extramural policy made him a tremendous resource for all NIDA staff and his colleagues at NIH. His commitment to excellence and his deep understanding of NIH's history, especially in policy and review, will be missed by his many colleagues and friends.

Susan Volman, Ph.D., a Program officer in the Division of Neuroscience and Behavior's Behavioral Cognitive Neuroscience Branch, retired on December 31, 2017 after 20 years of government service, with 19 of them serving as a NIDA Program Director in BCN. She will serve as a special volunteer to help us when Shelley Su, another program officer in BCN goes out on maternity leave.



National Institute
on Drug Abuse