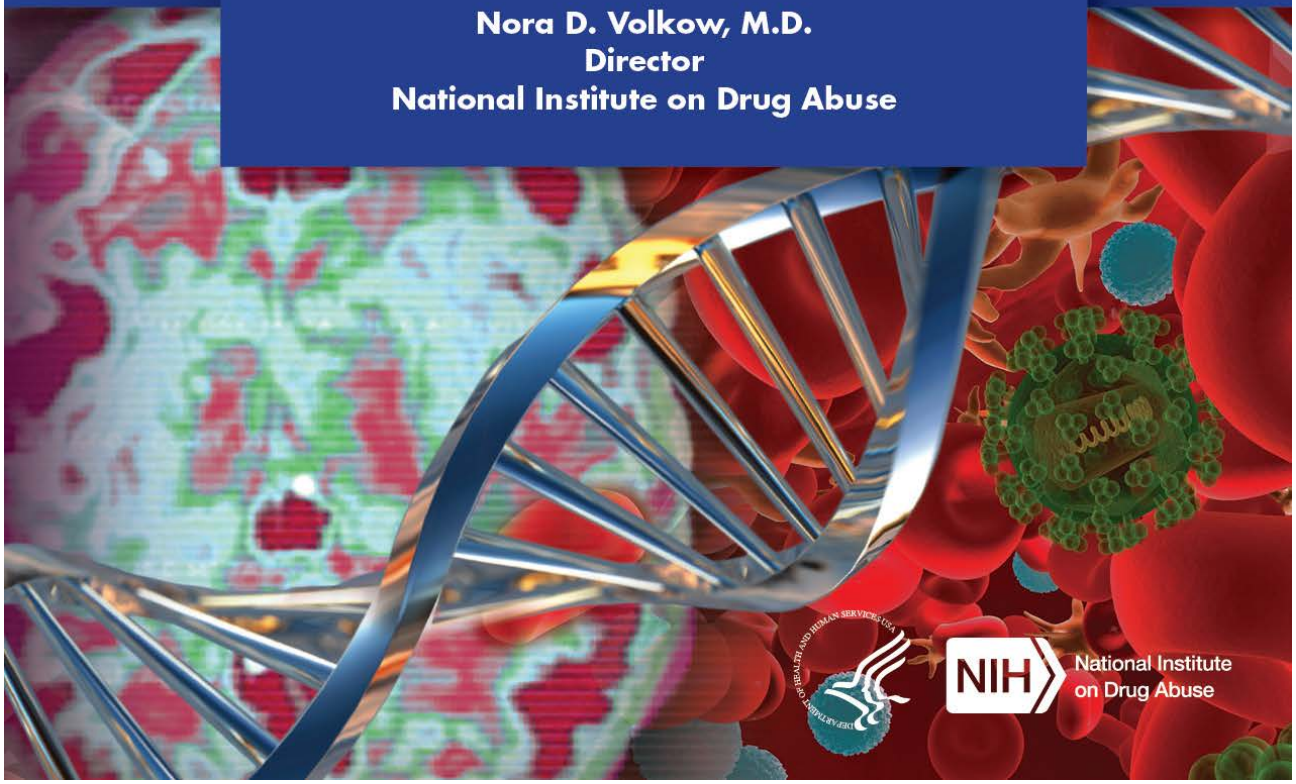
DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

September 2017

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



NIH National Institute on Drug Abuse

TABLE OF CONTENTS

RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Genetic and Pharmacological Antagonism Of NK_1 Receptor Prevents Opiate Abuse Potential
A J Sandweiss, M I McIntosh, A Moutal, R Davidson-Knapp, J Hu, A K Giri, T Yamamoto, V J Hruby R Khanna, T M Largent-Milnes, T W Vanderah. Molecular Psychiatry advance online publication 9 May 2017; doi: 10.1038/mp.2017.102.
Development of an efficacious, non-addicting analgesic has been challenging. Discovery of novel mechanisms underlying addiction may present a solution. Here the authors target the neurokinin system, which is involved in both pain and addiction. Morphine exerts its rewarding actions, at least in part, by inhibiting GABAergic input onto substance P (SP) neurons in the ventral tegmental area (VTA), subsequently increasing SP release onto dopaminergic neurons. Genome editing of the neurokinin 1 receptor (NK_1R) in the VTA renders morphine non-rewarding. Complementing the authors' genetic approach, they demonstrate utility of a bivalent pharmacophore with dual activity as a μ/δ opioid agonist and NK_1R antagonist in inhibiting nociception in an animal model of acute pain while lacking any positive reinforcement. These data indicate that dual targeting of the dopaminergic reward circuitry and pain pathways with a multifunctional opioid agonist–NK_1R antagonist may be an efficacious strategy in developing future analgesics that lack abuse potential.

Crystal Structures Of Agonist-Bound Human Cannabinoid Receptor CB1 Hua T, Vemuri K, Nikas SP, Laprairie RB, Wu Y, Qu L, Pu M, Korde A, Jiang S, Ho JH, Han GW, Ding K, Li X, Liu H, Hanson MA, Zhao S, Bohn LM, Makriyannis A, Stevens RC, Liu ZJ. Nature. 2017 Jul 7;547(7664):468-471. doi: 10.1038/nature23272. Epub 2017 Jul 5.
The cannabinoid receptor 1 (CB1) is the principal target of the psychoactive constituent of marijuana, the partial agonist Δ9-tetrahydrocannabinol (Δ9-THC). Here the authors report two agonist-bound crystal structures of human CB1 in complex with a tetrahydrocannabinol (AM11542) and a hexahydrocannabinol (AM841) at 2.80 Å and 2.95 Å resolution, respectively. The two CB1-agonist complexes reveal important conformational changes in the overall structure, relative to the antagonist-bound state, including a 53% reduction in the volume of the ligand-binding pocket and an increase in the surface area of the G-protein-binding region. In addition, a 'twin toggle switch' of Phe2003.36 and Trp3566.48 (superscripts denote Ballesteros-Weinstein numbering) is experimentally observed and appears to be essential for receptor activation. The structures reveal important insights into the activation mechanism of CB1 and provide a molecular basis for predicting the binding modes of Δ9-THC, and endogenous and synthetic cannabinoids. The plasticity of the binding pocket of CB1 seems to be a common feature among certain class A G-protein-coupled receptors. These findings should inspire the design of chemically diverse ligands with distinct pharmacological properties.

Cytoplasmic FMR1-Interacting Protein 2 Is A Major Genetic Factor Underlying Binge Eating
Kirkpatrick, Stacey L; Goldberg, Lisa R; Yazdani, Neema; Babbs, R Keith; Wu, Jiayi; Reed, Eric R; Jenkins, David F; Bolgioni, Amanda F; Landaverde, Kelsey I; Luttik, Kimberly P; Mitchell, Karen S; Kumar, Vivek; Johnson, W Evan; Mulligan, Megan K; Cottone, Pietro; Bryant, Camron D. Biol Psychiatry. 2017; 81(9): 757-769.
Eating disorders are lethal and heritable; however, the underlying genetic factors are unknown. Binge eating is a highly heritable trait associated with eating disorders that is comorbid with mood and substance use disorders. Therefore, understanding its genetic basis will inform therapeutic development that could improve several comorbid neuropsychiatric conditions. The authors

assessed binge eating in closely related C57BL/6 mouse substrains and in an F2 cross to identify quantitative trait loci associated with binge eating. They used gene targeting to validate candidate genetic factors. Finally, they used transcriptome analysis of the striatum via messenger RNA sequencing to identify the premorbid transcriptome and the binge-induced transcriptome to inform molecular mechanisms mediating binge eating susceptibility and establishment. C57BL/6NJ but not C57BL/6J mice showed rapid and robust escalation in palatable food consumption. The authors mapped a single genome-wide significant quantitative trait locus on chromosome 11 (logarithm of the odds = 7.4) to a missense mutation in cytoplasmic FMR1-interacting protein 2 (Cyfip2). They validated Cyfip2 as a major genetic factor underlying binge eating in heterozygous knockout mice on a C57BL/6N background that showed reduced binge eating toward a wild-type C57BL/6J-like level. Transcriptome analysis of premorbid genetic risk identified the enrichment terms morphine addiction and retrograde endocannabinoid signaling, whereas binge eating resulted in the downregulation of a gene set enriched for decreased myelination, oligodendrocyte differentiation, and expression. The authors identified Cyfip2 as a major significant genetic factor underlying binge eating and provide a behavioral paradigm for future genome-wide association studies in populations with increased genetic complexity.

Alternatively Spliced Mu Opioid Receptor C Termini Impact The Diverse Actions Of Morphine Xu, Jin; Lu, Zhigang; Narayan, Ankita; Le Rouzic, Valerie P; Xu, Mingming; Hunkele, Amanda; Brown, Taylor G; Hoefer, William F; Rossi, Grace C; Rice, Richard C; Martínez-Rivera, Arlene; Rajadhyaksha, Anjali M; Cartegni, Luca; Bassoni, Daniel L; Pasternak, Gavril W; Pan, Ying-Xian. J Clin Invest. 2017; 127(4): 1561-1573.
Extensive alternative splicing of the mu opioid receptor gene OPRM1 creates multiple C-terminal splice variants. However, their behavioral relevance remains unknown. The present study generated 3 mutant mouse models with truncated C termini in 2 different mouse strains, C57BL/6J (B6) and 129/SvEv (129). One mouse truncated all C termini downstream of Oprm1 exon 3 (mE3M mice), while the other two selectively truncated C-terminal tails encoded by either exon 4 (mE4M mice) or exon 7 (mE7M mice). Studies of these mice revealed divergent roles for the C termini in morphine-induced behaviors, highlighting the importance of C-terminal variants in complex morphine actions. In mE7M-B6 mice, the exon 7-associated truncation diminished morphine tolerance and reward without altering physical dependence, whereas the exon 4-associated truncation in mE4M-B6 mice facilitated morphine tolerance and reduced morphine dependence without affecting morphine reward. mE7M-B6 mutant mice lost morphine-induced receptor desensitization in the brain stem and hypothalamus, consistent with exon 7 involvement in morphine tolerance. In cell-based studies, exon 7-associated variants shifted the bias of several mu opioids toward β-arrestin 2 over G protein activation compared with the exon 4-associated variant, suggesting an interaction of exon 7-associated C-terminal tails with β-arrestin 2 in morphine-induced desensitization and tolerance. Together, the differential effects of C-terminal truncation illustrate the pharmacological importance of OPRM1' alternative splicing.

GLP-1 Acts On Habenular Avoidance Circuits To Control Nicotine Intake Tuesta, Luis M; Chen, Zuxin; Duncan, Alexander; Fowler, Christie D; Ishikawa, Masago; Lee, Brian R; Liu, Xin-An; Lu, Qun; Cameron, Michael; Hayes, Matthew R; Kamenecka, Theodore M; Pletcher, Matthew; Kenny, Paul J. Nat Neurosci. 2017; 20(5): 708-716.
Tobacco smokers titrate their nicotine intake to avoid its noxious effects, sensitivity to which may influence vulnerability to tobacco dependence, yet mechanisms of nicotine avoidance are poorly understood. Here the authors show that nicotine activates glucagon-like peptide-1 (GLP-1) neurons in the nucleus tractus solitarius (NTS). The antidiabetic drugs sitagliptin and exenatide, which

inhibit GLP-1 breakdown and stimulate GLP-1 receptors, respectively, decreased nicotine intake in mice. Chemogenetic activation of GLP-1 neurons in NTS similarly decreased nicotine intake. Conversely, Glp1r knockout mice consumed greater quantities of nicotine than wild-type mice. Using optogenetic stimulation, we show that GLP-1 excites medial habenular (MHb) projections to the interpeduncular nucleus (IPN). Activation of GLP-1 receptors in the MHb-IPN circuit abolished nicotine reward and decreased nicotine intake, whereas their knockdown or pharmacological blockade increased intake. GLP-1 neurons may therefore serve as satiety sensors for nicotine that stimulate habenular systems to promote nicotine avoidance before its aversive effects are encountered.

EPIDEMIOLOGY RESEARCH

Neural Correlates Of Graphic Cigarette Warning Labels Predict Smoking Cessation Relapse
Owens, Max M; MacKillop, James; Gray, Joshua C; Hawkshead, Brittany E; Murphy, Cara M; Sweet, Lawrence H. Psychiatry Res. 2017 April 30; 262: 63-70.
Exposure to graphic warning labels (GWLs) on cigarette packaging has been found to produce heightened activity in brain regions central to emotional processing and higher-order cognitive processes. The current study extends this literature by using functional magnetic resonance imaging (fMRI) to investigate neural activation in response to GWLs and use it to predict relapse in an evidence-based smoking cessation treatment program. Participants were 48 treatment-seeking nicotine-dependent smokers who completed an fMRI paradigm in which they were exposed to GWLs, text-only warning labels (TOLs), and matched control stimuli. Subsequently, they enrolled in smoking cessation treatment and their smoking behavior was monitored. Activation in bilateral amygdala, right dorsolateral prefrontal cortex, right inferior frontal gyrus, left medial temporal gyrus, bilateral occipital lobe, and bilateral fusiform gyrus was greater during GWLs than TOLs. Neural response in the ventromedial prefrontal cortex (vmPFC) during exposure to GWLs (relative to a visual control image) predicted relapse during treatment beyond baseline demographic and dependence severity, but response in the amygdala to GWLs did not. These findings suggest that neurocognitive processes in the vmPFC may be critical to understanding how GWL's induce behavior change and may be useful as a predictor of smoking cessation treatment prognosis.

Medical Marijuana Policies and Hospitalizations Related To Marijuana and Opioid Pain Relievers Shi, Yuyan. Drug Alcohol Depend. 2017 April 1; 173: 144-150.
Twenty-eight states in the U.S have legalized medical marijuana, yet its impact on severe health consequences such as hospitalizations remain unknown. Meanwhile, the prevalence of opioid pain reliever (OPR) use and outcomes has increased dramatically. Recent studies suggested unintended impacts of legalizing medical marijuana on OPR, but the evidence is still limited. This study examined the associations between state medical marijuana policies and hospitalizations related to marijuana and OPR. State-level annual administrative records of hospital discharges during 1997-2014 were obtained from the State Inpatient Databases (SID). The outcome variables were rates of hospitalizations involving marijuana dependence or abuse, opioid dependence or abuse, and OPR overdose in 1000 discharges. Linear time-series regressions were used to assess the associations of implementing medical marijuana policies to hospitalizations, controlling for other marijuana- and OPR-related policies, socioeconomic factors, and state and year fixed effects. Hospitalizations related to marijuana and OPR increased sharply by 300% on average in all states. Medical marijuana legalization was associated with 23% (p=0.008) and 13% (p=0.025) reductions in hospitalizations related to opioid dependence or abuse and OPR overdose, respectively; lagged

effects were observed after policy implementation. The operation of medical marijuana dispensaries had no independent impacts on OPR-related hospitalizations. Medical marijuana polices had no associations with marijuana-related hospitalizations. Medical marijuana policies were significantly associated with reduced OPR-related hospitalizations but had no associations with marijuana-related hospitalizations. Given the epidemic of problematic use of OPR, future investigation is needed to explore the causal pathways of these findings.

"It Takes Longer, But When It Hits You It Hits You!": Videos About Marijuana Edibles On YouTube Krauss, Melissa J; Sowles, Shaina J; Stelzer-Monahan, Haley E; Bierut, Tatiana; Cavazos-Rehg, Patricia A. Subst Use Misuse. 2017; 52(6): 709-716.
Interest in marijuana edibles has increased as perceptions of harm from marijuana have decreased. Media and peer influences impact youth substance use, and YouTube is the most popular video-sharing website. No studies have examined the content and accessibility of YouTube videos related to marijuana edibles. To describe the messages conveyed to viewers in YouTube videos about edibles and determine their accessibility to youth. On June 12, 2015, the authors searched YouTube for videos about marijuana/cannabis/weed edibles. A total of 51 videos were coded for presence of an age restriction, purpose(s) of the videos, consumption of edibles during the video, effects, and safety concerns. Total views across all 51 videos were >9 million. Only 14% (7/51) were restricted to viewers over the age of 18 years. Over half (27/51, 53%) were informative videos, most (20/27, 74%) teaching how to make edibles, and 37% (19/51) were entertaining videos. Someone consumed an edible in 31% (16/51) of the videos, and the type of high was mentioned in 51% (26/51) of the videos, including delayed (18/26, 69%) or intense high (13/26, 50%). Fifty-five percent (28/51) mentioned delta-9-tetrahydrocannabinol potency or dosage. Only 10 of these (36%) presented this information specifically as a warning to prevent adverse effects. Edibles-related videos are easily found on YouTube, often instructing how to bake your own edibles and lacking information needed for safe consumption, and most are not age-restricted. Videos showing how to make edibles or presenting edibles use in an entertaining way that could influence youth to initiate use.

Parent and Peer Pathways Linking Childhood Experiences Of Abuse With Marijuana Use In Adolescence and Adulthood Alex Mason, W; Jean Russo, M; Chmelka, Mary B; Herrenkohl, Roy C; Herrenkohl, Todd I. Addict Behav. 2017 Mar; 66: 70-75.
The social developmental processes by which child maltreatment increases risk for marijuana use are understudied. This study examined hypothesized parent and peer pathways linking preschool abuse and sexual abuse with adolescent and adult marijuana use. Analyses used data from the Lehigh Longitudinal Study. Measures included child abuse (physical abuse, emotional abuse, domestic violence, and neglect) in preschool, sexual abuse up to age 18, adolescent (average age=18years) parental attachment and peer marijuana approval/use, as well as adolescent and adult (average age=36years) marijuana use. Confirming elevated risk due to child maltreatment, path analysis showed that sexual abuse was positively related to adolescent marijuana use, whereas preschool abuse was positively related to adult marijuana use. In support of mediation, it was found that both forms of maltreatment were negatively related to parental attachment, which was negatively related, in turn, to having peers who use and approve of marijuana use. Peer marijuana approval/use was a strong positive predictor of adolescent marijuana use, which was a strong positive predictor, in turn, of adult marijuana use. Results support social developmental theories that hypothesize a sequence of events leading from child maltreatment experiences to lower levels of parental attachment and, in turn, higher levels of involvement with pro-marijuana peers and, ultimately, to both adolescent and adult marijuana use. This sequence of events suggests

developmentally-timed intervention activities designed to prevent maltreatment as well as the initiation and progression of marijuana use among vulnerable individuals.

Overdose Education and Naloxone Distribution Program Attendees: Who Attends, What Do They Know, and How Do They Feel? Heavey, Sarah Cercone; Burstein, Gale; Moore, Cheryll; Homish, Gregory G. J Public Health Manag Pract. 2017 Mar. 1.
The United States is in the midst of an opioid overdose epidemic. Opioids killed more than 28,000 people in 2014, more than any year on record. One approach to addressing this growing epidemic is Opioid Overdose Education and Naloxone Distribution (OEND) training. Little is known about these programs' participants and their effectiveness across different demographic groups. The aims of this study were to examine (1) whether knowledge and attitudes improved over the course of the training programs; (2) whether training outcomes differ by demographics; and (3) what overdose experiences do attendees have, and whether those experiences influence their knowledge and attitudes. A pre- and posttest survey was used to collect data on participants' demographics, overdose experiences, and opioid overdose knowledge and attitudes. Surveys that took place at community-wide OEND programs were offered throughout Erie County, New York, during October and November 2015.Community members who elected to attend the training programs, were at least 18 years of age, spoke English, and were willing and able to participate were included in the sample (N = 198). The Opioid Overdose Knowledge and Attitudes Scale was used. Knowledge and attitude scores significantly improved from pre- to posttest assessments, increasing by 23.1% and 15.4%, respectively (Ps < .001). There were significant demographic differences in knowledge and attitudes at the pretest assessment, but these differences were ameliorated by the OEND program and did not persist at posttest assessment. In addition, 62.9% of participants had never experienced, witnessed, or known someone who had overdosed. Results indicate that OEND programs are effective at improving knowledge and attitudes toward opioid overdose. These results indicate that OEND programs are not reaching the highest risk individuals but are instead attracting concerned family and significant others. Future programs should focus on reaching current opioid users, overdose victims, and their families to ensure OEND programs are reaching the target audiences.

The 3-Year Course Of Multiple Substance Use Disorders In The United States: A National Longitudinal Study McCabe, Sean Esteban; West, Brady T. J Clin Psychiatry. 2017; 78(5): e537-e544.
The aim of this study was to examine the 3-year course of multiple co-occurring substance use disorders (SUDs) based on longitudinal survey data from a large, nationally representative sample. National estimates of the prevalence of DSM-IV SUDs were derived by analyzing data from structured, face-to-face diagnostic interviews as part of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which collected data from a large, nationally representative sample of noninstitutionalized US adults at 2 waves (2001-2002 and 2004-2005; N = 34,653).US adults with multiple past-year SUDs at Wave 1 were substantially more likely than those with an individual past-year SUD or no SUD at Wave 1 to report at least 1 past-year SUD at Wave 2 (66.3% vs 46.0% vs 6.9%, respectively). There were several sociodemographic characteristics and psychiatric disorders (i.e., male, younger age, never married, sexual minority identity, nicotine dependence, mood disorder, and personality disorder) associated with increased odds of developing multiple SUDs and having 3-year persistence of multiple SUDs. The majority of adults with multiple past-year SUDs had a lifetime personality disorder and did not utilize substance abuse treatment or other help-seeking. Multiple SUDs are associated with a more persistent 3-year course of disease over time relative to individual SUDs. Despite a more severe 3-year course and

higher rates of comorbidity with other psychiatric disorders, the majority of US adults with multiple SUDs do not utilize substance abuse treatment or other help-seeking. Clinical assessments and the substance abuse literature tend to focus on drug-specific individual SUDs rather than considering the more complex multiple SUDs, which can be more challenging to treat.

Adolescents' Prescription Stimulant Use and Adult Functional Outcomes: A National Prospective Study McCabe, Sean Esteban; Veliz, Philip; Wilens, Timothy E; Schulenberg, John E. J Am Acad Child Adolesc Psychiatry. 2017; 56(3): 226-233.e4.
The aim of this study was to assess the prospective 17-year relationship between the medical and nonmedical use of prescription stimulants during adolescence (age 18 years) and educational attainment and substance use disorder (SUD) symptoms in adulthood (age 35 years). A survey was self-administered by nationally representative probability samples of US high school seniors from the Monitoring the Future study; 8,362 of these individuals were followed longitudinally from adolescence (age 18, high school senior years 1976-1996) to adulthood (age 35, 1993-2013). An estimated 8.1% reported medical use of prescription stimulants, and 16.7% reported nonmedical use of prescription stimulants by age 18 years. Approximately 43% of adolescent medical users of prescription stimulants had also engaged in nonmedical use of prescription stimulants during adolescence. Among past-year adolescent nonmedical users of prescription stimulants, 97.3% had used at least one other substance during the past year. Medical users of prescription stimulants without any history of nonmedical use during adolescence did not differ significantly from population controls (i.e., non-attention-deficit/hyperactivity disorder [ADHD] and non-stimulant-medicated ADHD during adolescence) in educational attainment and SUD symptoms in adulthood. In contrast, adolescent nonmedical users of prescription stimulants (with or without medical use) had lower educational attainment and more SUD symptoms in adulthood, compared to population controls and medical users of prescription stimulants without nonmedical use during adolescence. Nonmedical use of prescription stimulants is common among adolescents prescribed these medications. The findings indicate youth should be carefully monitored for nonmedical use because this behavior is associated with lower educational attainment and more SUD symptoms in adulthood.

The Association Between Personality Disorders With Alcohol Use and Misuse: A Population-based Twin Study Long, E C; Aggen, S H; Neale, M C; Knudsen, G P; Krueger, R F; South, S C; Czajkowski, N; Nesvåg, R; Ystrom, E; Torvik, F A; Kendler, K S; Gillespie, N A; Reichborn-Kjennerud, T. Drug Alcohol Depend. 2017 May 1; 174: 171-180.
A clearer understanding of the etiological overlap between DSM-IV personality disorders (PDs) and alcohol use (AU) and alcohol use disorder (AUD) is needed. To the authors' knowledge, no study has modeled the association between all 10 DSM-IV PDs and lifetime AU and AUD. The aim of the present study is to identify which PDs are most strongly associated with the phenotypic, genetic, and environmental risks of lifetime AU and AUD, and to determine if these associations are stable across time. Participants were Norwegian twins assessed at two waves. At Wave 1, 2801 twins were assessed for all 10 DSM-IV PD criteria, lifetime AU, and DSM-IV AUD criteria. At Wave 2, six of the 10 PDs were again assessed along with AU and AUD among 2393 twins. Univariate and multiple logistic regressions were run. Significant predictors were further analyzed using bivariate twin Cholesky decompositions. Borderline and antisocial PD criteria were the strongest predictors of AU and AUD across the two waves. Despite moderate phenotypic and genetic correlations, genetic variation in these PD criteria explained only 4% and 3% of the risks in AU, and 5% to 10% of the risks in AUD criteria, respectively. At Wave 2, these estimates increased to 8% and 23% for AU, and 17% and 33% for AUD. Among a large Norwegian twin sample, borderline and antisocial

PD criteria were the strongest predictors of the phenotypic and genotypic liability to AU and AUD. This effect remained consistent across time.

PREVENTION RESEARCH

Peer Network Counseling As Brief Treatment For Urban Adolescent Heavy Cannabis Users
Mason, Michael J; Sabo, Roy; Zaharakis, Nikola M. J Stud Alcohol Drugs. 2017; 78(1): 152-157.
A small body of evidence supports targeting adolescents who are heavy users of cannabis with brief interventions, yet more research is needed to confirm the effectiveness of these studies. The authors conducted a secondary analysis of our Peer Network Counseling (PNC) study (Mason et al., 2015), focusing on 46 adolescents of the sample of 119 who reported heavy cannabis use at baseline. Urban adolescents (91% African American) presenting for primary health care were randomized to intervention or control conditions and followed for 6 months. The authors selected cases (n = 46) to analyze based on heavy cannabis use reported at baseline (≥10 times in past month). The ordinal response data (cannabis use) were modeled using a mixed-effects proportional odds model, including fixed effects for treatment, time, and their interaction, and a subject-level random effect. In the subsample of adolescents with heavy cannabis use, those assigned to PNC had a 35.9% probability of being abstinent at 6 months, compared with a 13.2% probability in the control condition. Adolescents in the PNC condition had a 16.6% probability of using cannabis 10 or more times per month, compared with a 38.1% probability in the control condition. This differs from results of the full sample (N = 119), where no significant effects on cannabis use were found. PNC increased the probability of abstinence and reduced heavy cannabis use. These results provide initial support for PNC as a model for brief treatment with non-treatment seeking adolescents who are heavy users of cannabis

Prenatal Tobacco Exposure, Birthweight, and Offspring Psychopathology Talati, Ardesheer; Wickramaratne, Priya J; Wesselhoeft, Rikke; Weissman, Myrna M. Psychiatry Res. 2017; 252: 346-352.
Although prenatal tobacco exposure (PTE) is associated with several adverse offspring mental health outcomes, mechanisms remain unclear. The authors test whether associations between PTE and offspring psychopathology are explained by birthweight, one of the earliest-occurring outcomes of PTE. The analysis focuses on 238 offspring from a family study of depression with (1) collected prenatal histories and (2) at least one clinical interview in adulthood to assess psychiatric problems. Exposure was categorized by maternal smoking of ≥10 cigarettes daily/nearly daily; diagnostic outcomes were confirmed by clinicians using the best-estimate procedure, blind to exposure. After adjusting for potential confounders, PTE was associated with 0.7lb (9%) lower birthweight (p=0.0002), increased rates of disruptive behavior disorders [males: OR=2.66(1.15,6.16), and (trend) substance use disorders [females: OR=2.23(0.98,5.09)], and decreased rates of mood disorders (males: OR=0.42(0.17,0.98)]. Birthweight was not independently associated with diagnoses and did not mediate the association between exposure and psychopathology. Maternal smoking has long-term adverse consequences for offspring. Although birthweight cannot be manipulated, smoking is a modifiable risk factor. Thus, cessation efforts focused on pregnant women may not only improve maternal wellbeing, but also mitigate adverse proximal (e.g., birthweight) and long-term (psychopathology) outcomes in offspring.

Eveningness and Later Sleep Timing Are Associated With Greater Risk For Alcohol and Marijuana Use In Adolescence: Initial Findings From The NCANDA Study Hasler, Brant P; Franzen, Peter L; de Zambotti, Massimiliano; Prouty, Devin; Brown, Sandra A; Tapert, Susan F; Pfefferbaum, Adolf; Pohl, Kilian M; Sullivan, Edith V; De Bellis, Michael D; Nagel, Bonnie J; Baker, Fiona C; Colrain, Ian M; Clark, Duncan B. Alcohol Clin Exp Res. 2017; 6.
Abundant cross-sectional evidence links eveningness (a preference for later sleep-wake timing) and increased alcohol and drug use among adolescents and young adults. However, longitudinal studies are needed to examine whether eveningness is a risk factor for subsequent alcohol and drug use, particularly during adolescence, which is marked by parallel peaks in eveningness and risk for the onset of alcohol use disorders. The present study examined whether eveningness and other sleep characteristics were associated with concurrent or subsequent substance involvement in a longitudinal study of adolescents. Participants were 729 adolescents (368 females; age 12-21 years) in the National Consortium on Adolescent Neurodevelopment and Alcohol [NCANDA] study. Associations between the sleep variables (circadian preference, sleep quality, daytime sleepiness, sleep timing, and sleep duration) and three categorical substance variables (at-risk alcohol use, alcohol bingeing, and past year marijuana use (y/n)) were examined using ordinal and logistic regression with baseline age, sex, race, ethnicity, socioeconomic status, and psychiatric problems as covariates. At baseline, greater eveningness was associated with greater at-risk alcohol use, greater bingeing, and past-year use of marijuana. Later weekday and weekend bedtimes, but not weekday or weekend sleep duration, showed similar associations across the three substance outcomes at baseline. Greater baseline eveningness was also prospectively associated with greater bingeing and past-year use of marijuana at the 1-year follow-up, after covarying for baseline bingeing and marijuana use. Later baseline weekday and weekend bedtimes, and shorter baseline weekday sleep duration, were similarly associated with greater bingeing and past-year use of marijuana at the 1-year follow-up after covarying for baseline values.

Parent-Centered Prevention Of Risky Behaviors Among Hispanic Youths In Florida Estrada, Yannine; Lee, Tae Kyoung; Huang, Shi; Tapia, Maria I; Velázquez, Maria-Rosa; Martinez, Marcos J; Pantin, Hilda; Ocasio, Manuel A; Vidot, Denise C; Molleda, Lourdes; Villamar, Juan; Stepanenko, Bryan A; Brown, C Hendricks; Prado, Guillermo. Am J Public Health. 2017; 107(4): 607-613.
The aim of this study was to evaluate the effectiveness of an evidence-based, parent-centered intervention, Familias Unidas, delivered by nonresearch personnel, in preventing substance use (alcohol, illicit drugs) and sex without a condom among Hispanic adolescents. A randomized controlled trial (n = 746) evaluated the effectiveness of Familias Unidas among Hispanic eighth graders (age range = 12-16 years), relative to prevention as usual, within a public school system. School personnel, including social workers and mental health counselors, were trained to deliver the evidence-based intervention. Participant recruitment, intervention delivery, and follow-up ran from September 2010 through June 2014 in Miami-Dade County, Florida. Familias Unidas was effective in preventing drug use from increasing and prevented greater increases in sex without a condom 30 months after baseline, relative to prevention as usual. Familias Unidas also had a positive impact on family functioning and parental monitoring of peers at 6 months after baseline. This study demonstrated the effectiveness of a parent-centered preventive intervention program in preventing risky behaviors among Hispanic youths. Findings highlight the feasibility of training non-research personnel on effectively delivering a manualized intervention in a real-world setting.

Male Sex Associated With Increased Risk Of Neonatal Abstinence Syndrome Charles, M Katherine; Cooper, William O; Jansson, Lauren M; Dudley, Judith; Slaughter, James C; Patrick, Stephen W. Hosp Pediatr. 2017; 6.
Neonatal abstinence syndrome (NAS) is a postnatal opioid withdrawal syndrome. Factors associated with development of the syndrome are poorly understood; however, infant sex may influence the risk of NAS. The authors' objective was to determine if infant sex was associated with the development or severity of the syndrome in a large population-based cohort. This retrospective cohort study used vital statistics and prescription, outpatient, and inpatient administrative data for mothers and infants enrolled in the Tennessee Medicaid program between 2009 and 2011. Multivariable logistic regression models were used to evaluate the association between male sex and diagnosis of NAS, accounting for potential demographic and clinical confounders. NAS severity, as evidenced by hospital length of stay, was modeled by using negative binomial regression. Of 102 695 infants, 927 infants were diagnosed with NAS (484 male subjects and 443 female subjects). Adjustments were made for the following: maternal age, race, and education; maternal hepatitis C infection, anxiety, or depression; in utero exposure to selective serotonin reuptake inhibitors and cigarettes; infant birth weight, small for gestational age, and year; and the interaction between opioid type and opioid amount. Male infants were more likely than female infants to be diagnosed with NAS (adjusted odds ratio, 1.18 [95% confidence interval, 1.05-1.33]) and NAS requiring treatment (adjusted odds ratio, 1.24 [95% confidence interval, 1.04-1.47]). However, there was no sex-based difference in severity for those diagnosed with NAS.

HIV Incidence Among People Who Inject Drugs (PWID) In Ukraine: Results From A Clustered Randomized Trial Robert E Booth; Jonathan M Davis; Sergey Dvoryak; John T Brewster; Oksana Lisovska; Steffanie A Strathdee; Carl A Latkin The Lancet HIV. 2016 3(10) 482-489

HIV prevalence among people who inject drugs (PWID) in Ukraine is among the highest in the world. In this study, the authors aimed to assess whether a social network intervention was superior to HIV testing and counselling in affecting HIV incidence among PWID. Although this was not the primary aim of the study, it is associated with reducing drug and sex risk behaviors, which were primary aims. In this clustered randomized trial, PWID who were 16 years of age or older, had used self-reported drug injection in the past 30 days, were willing to be interviewed for about 1 hour and tested for HIV, were not too impaired to comprehend and provide informed consent, and, for this paper, who tested HIV negative at baseline were recruited from the streets by project outreach workers in three cities in southern and eastern Ukraine: Odessa, Donetsk, and Nikolayev. Index or peer leaders, along with two of their network members, were randomly assigned (1:1) by the study statistician to the testing and counselling block (control group) or the testing and counselling plus a social network intervention block (intervention group). No stratification or minimalization was done. Participants in the network intervention received five sessions to train their network members in risk reduction. Those participants assigned to the control group received no further intervention after counselling. The main outcome of this study was HIV seroconversion in the intent-to-treat population as estimated with Cox regression and incorporating a γ frailty term to account for clustering. Between July 12, 2010, and Nov 23, 2012, 2304 PWIDs were recruited, 1200 of whom were HIV negative and are included in the present study. 589 index or peer leaders were randomly assigned to the control group and 611 were assigned to the intervention group. Of the 1200 HIV-negative participants, 1085 (90%) were retained at 12 months. In 553.0 person-years in the intervention group, 102 participants had seroconversion (incidence density 18.45 per 100 person-years; 95% CI 14·87–22·03); in 497.1 person-years in the control group 158 participants

seroconverted (31.78 per 100 person-years; 26.83–36.74). This corresponded to a reduced hazard in the intervention group (hazard ratio 0.53, 95% CI 0.38–0.76, p=0.0003). No study-related adverse events were reported. These data provide strong support for integrating peer education into comprehensive HIV prevention programs for PWID and suggest the value in developing and testing peer-led interventions to improve access and adherence to pre-exposure prophylaxis and antiretroviral therapy.

TREATMENT RESEARCH

Development of a Clinically Viable Heroin Vaccine Bremer PT, Schlosburg JE, Banks ML, Steele FF, Zhou B, Poklis JL, Janda KD. Heroin is a highly-abused opioid and incurs a significant detriment to society worldwide. In an effort to expand the limited pharmacotherapy options for opioid use disorders, a heroin conjugate vaccine was developed through comprehensive evaluation of hapten structure, carrier protein, adjuvant and dosing. Immunization of mice with an optimized heroin-tetanus toxoid (TT) conjugate formulated with adjuvants alum and CpG oligodeoxynucleotide (ODN) generated heroin "immunoantagonism", reducing heroin potency by >15-fold. Moreover, the vaccine effects proved to be durable, persisting for over eight months. The lead vaccine was effective in rhesus monkeys, generating significant and sustained antidrug IgG titers in each subject. Characterization of both mouse and monkey antiheroin antibodies by surface plasmon resonance (SPR) revealed low nanomolar antiserum affinity for the key heroin metabolite, 6-acetylmorphine (6AM), with minimal cross reactivity to clinically used opioids. Following a series of heroin challenges over six months in vaccinated monkeys, drug-sequestering antibodies caused marked attenuation of heroin potency (>4-fold) in a schedule-controlled responding (SCR) behavioral assay. Overall, these preclinical results provide an empirical foundation supporting the further evaluation and potential clinical utility of an effective heroin vaccine in treating opioid use disorders.

Effects Of Nalfurafine On the Reinforcing, Thermal Antinociceptive, and Respiratory-depressant Effects Of Oxycodone: Modeling An Abuse-deterrent Opioid Analgesic In Rats Townsend, E Andrew; Naylor, Jennifer E; Negus, S Stevens; Edwards, Shelley R; Qureshi, Hina N; McLendon, Hunter W; McCurdy, Christopher R; Kapanda, Coco N; do Carmo, Jussara M; da Silva, Fernanda S; Hall, John E; Sufka, Kenneth J; Freeman, Kevin B. Psychopharmacology (Berl). 2017. Strategies to reduce the misuse of mu opioid agonists are critically needed. Previous work has shown that kappa opioid agonists can diminish the abuse-related effects and augment the antinociceptive effects of mu agonists. However, use of traditional kappa agonists is limited by their dysphoric side effects. The current study examined the effects of nalfurafine, a clinically available atypical kappa agonist, on the reinforcing, thermal antinociceptive, and respiratory-depressant effects of oxycodone in male rats. To determine oxycodone/nalfurafine mixture proportions to be examined intravenously across procedures, a progressive ratio (PR) self-administration procedure compared the reinforcing effects of oxycodone (56 μg/kg/inj) available alone or as a mixture with co-administered nalfurafine (0.32, 1, or 3.2 μg/kg/inj), corresponding to oxycodone/nalfurafine proportions of 175:1, 56:1, and 18:1, respectively. Next, PR and thermal antinociception dose-effect functions were each determined for oxycodone, nalfurafine, and the same oxycodone/nalfurafine mixture proportions. Finally, the respiratory-depressant effects of equi-antinociceptive doses of oxycodone, nalfurafine, and the mixtures were compared. Nalfurafine decreased the reinforcing effects of oxycodone, and the 18:1 mixture did not function as a reinforcer. Oxycodone and nalfurafine each produced dose-dependent antinociception, and the mixtures produced additive

antinociception. In addition, antinociceptive doses of the 56:1 and 18:1 mixtures did not produce respiratory depression. These results suggest that nalfurafine may augment the thermal antinociceptive effects while reducing the reinforcing and respiratory-depressant effects of oxycodone.

Mothering From the Inside Out: Results Of A Second Randomized Clinical Trial Testing A Mentalization-based Intervention For Mothers In Addiction Treatment Suchman, Nancy E; DeCoste, Cindy L; McMahon, Thomas J; Dalton, Rachel; Mayes, Linda C; Borelli, Jessica. Dev Psychopathol. 2017; 29(2): 617-636.
Mothers with histories of alcohol and drug addiction have shown greater difficulty parenting young children than mothers with no history of substance misuse. This study was the second randomized clinical trial testing the efficacy of Mothering From the Inside Out (MIO), a 12-week mentalization-based individual therapy designed to address psychological deficits commonly associated with chronic substance use that also interfere with the capacity to parent young children. Eighty-seven mothers caring for a child between 11 and 60 months of age were randomly assigned to receive 12 sessions of MIO versus 12 sessions of parent education (PE), a psychoeducation active control comparison. Maternal reflective functioning, representations of caregiving, mother-child interaction quality, and child attachment were evaluated at baseline and posttreatment and 3-month follow-up. Mother-child interaction quality was assessed again at 12-month follow-up. In comparison with PE mothers, MIO mothers demonstrated a higher capacity for reflective functioning and representational coherence at posttreatment and 3-month follow-up. At 12-month follow-up, compared to PE cohorts, MIO mothers demonstrated greater sensitivity, their children showed greater involvement, and MIO dyads showed greater reciprocity. As addiction severity increased, MIO also appeared to serve as a protective factor for maternal reflective functioning, quality of mother-child interactions, and child attachment status. Results demonstrate the promise of mentalization-based interventions provided concomitant with addiction treatment for mothers and their young children.

Cardiovascular Toxicity of Anabolic-Androgenic Steroid Use Baggish AL, Weiner RB, Kanayama G, Hudson JI, Lu MT, Hoffmann U, Pope HG Jr. Circulation. 2017 May 23;135(21):1991-2002.
Millions of individuals have used illicit anabolic-androgenic steroids (AAS), but the long-term cardiovascular associations of these drugs. remain incompletely understood. Using a cross-sectional cohort design, the authors recruited 140 experienced male weightlifters 34 to 54 years of age, comprising 86 men reporting ≥2 years of cumulative lifetime AAS use and 54 non-using men. Using transthoracic echocardiography and coronary computed tomography angiography, we assessed 3 primary outcome measures: left ventricular (LV) systolic function (left ventricular ejection fraction), LV diastolic function (early relaxation velocity), and coronary atherosclerosis (coronary artery plaque volume). Compared with nonusers, AAS users demonstrated relatively reduced LV systolic function (mean±SD left ventricular ejection fraction = 52±11% versus 63±8%; P<0.001) and diastolic function (early relaxation velocity = 9.3±2.4 cm/second versus 11.1±2.0 cm/second; P<0.001). Users currently taking AAS at the time of evaluation (N=58) showed significantly reduced LV systolic (left ventricular ejection fraction = 49±10% versus 58±10%; P<0.001) and diastolic function (early relaxation velocity = 8.9±2.4 cm/second versus 10.1±2.4 cm/second; P=0.035) compared with users currently off-drug (N=28). In addition, AAS users demonstrated higher coronary artery plaque volume than nonusers (median [interquartile range] 3 [0, 174] mL(3) versus 0 [0, 69] mL(3); P=0.012). Lifetime AAS dose was strongly associated with coronary atherosclerotic burden (increase [95% confidence interval] in rank of plaque volume for

each 10-year increase in cumulative duration of AAS use: 0.60 SD units [0.16-1.03 SD units]; P=0.008). The authors conclude that long-term AAS use appears to be associated with myocardial dysfunction and accelerated coronary atherosclerosis. These forms of AAS-associated adverse cardiovascular phenotypes may represent a previously underrecognized public-health problem.

Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome Kraft WK, Adeniyi-Jones SC, Chervoneva I, Greenspan JS, Abatemarco D, Kaltenbach K, Ehrlich ME. N Engl J Med. 2017 Jun 15;376(24):2341-2348.

Current pharmacologic treatment of the neonatal abstinence syndrome with morphine is associated with a lengthy duration of therapy and hospitalization. Buprenorphine may be more effective than morphine for this indication. In this single-site, double-blind, double-dummy clinical trial, the authors randomly assigned 63 term infants (≥37 weeks of gestation) who had been exposed to opioids in utero and who had signs of the neonatal abstinence syndrome to receive either sublingual buprenorphine or oral morphine. Infants with symptoms that were not controlled with the maximum dose of opioid were treated with adjunctive phenobarbital. The primary end point was the duration of treatment for symptoms of neonatal opioid withdrawal. Secondary clinical end points were the length of hospital stay, the percentage of infants who required supplemental treatment with phenobarbital, and safety. The median duration of treatment was significantly shorter with buprenorphine than with morphine (15 days vs. 28 days), as was the median length of hospital stay (21 days vs. 33 days) (P<0.001 for both comparisons). Adjunctive phenobarbital was administered in 5 of 33 infants (15%) in the buprenorphine group and in 7 of 30 infants (23%) in the morphine group (P=0.36). Rates of adverse events were similar in the two groups. Among infants with the neonatal abstinence syndrome, treatment with sublingual buprenorphine resulted in a shorter duration of treatment and shorter length of hospital stay than treatment with oral morphine, with similar rates of adverse events. Funded by the National Institute on Drug Abuse; BBORN ClinicalTrials.gov number, NCT01452789.

Effect Of Oxytocin Pretreatment On Cannabis Outcomes In A Brief Motivational Intervention Sherman, Brian J; Baker, Nathaniel L; McRae-Clark, Aimee L. Psychiatry Res. 2017; 249: 318-320.

Motivational enhancement therapy (MET) is efficacious in reducing cannabis use, yet benefits are generally short-lived. Oxytocin is a hypothalamic neuropeptide that promotes prosocial behaviors and plays a role in drug-related neuroadaptations; as such, oxytocin may enhance the effect of MET on cannabis outcomes. Cannabis dependent adults were randomized to receive MET plus oxytocin (n =8) or placebo (n =8). Participants receiving oxytocin showed reductions in amount of cannabis used daily and number of sessions per day. Participants receiving placebo did not evidence significant reductions. Powered clinical trials of oxytocin-enhanced MET for cannabis use disorder are warranted.

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.

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>35ng/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.

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

Comparison of Three Popular Methods for Recruiting Young Persons Who Inject Drugs for Interventional Studies Collier MG, Garfein RS, Cuevas-Mota J, Teshale EH. J Urban Health. 2017 Aug;94(4):587-591. doi: 10.1007/s11524-017-0158-x.
Persons who inject drugs (PWID) are at risk for adverse health outcomes as a result of their drug use, and the resulting social stigma makes this a difficult population to reach for interventions aimed at reducing morbidity and mortality. During this study of adult PWID aged ≤40 years living in San Diego during 2009 and 2010, the authors compared three different sampling methods: respondent-driven sampling (RDS), venue-based sampling at one syringe exchange program (SEP), and street-based outreach. They compared demographic, socioeconomic, health, and behavioral factors and tested participants for HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) and compared across the three methods. Overall, 561 (74.8%) of the targeted 750 PWID were enrolled. Venue-based convenience sampling enrolled 96% (242/250) of the targeted participants, followed closely by street-based outreach with 92% (232/250) recruited. While RDS yielded the fewest recruits, producing only 35% (87/250) of the expected participants, those recruited through RDS were more likely to be female, more racially diverse, and younger.

Everyday Functional Ability In HIV and Methamphetamine Dependence Minassian A, Henry BL, Iudicello JE, Morgan EE, Letendre SL, Heaton RK, Perry W; Translational Methamphetamine AIDS Research Center. Drug Alcohol Depend. 2017 Jun 1;175:60-66. doi: 10.1016/j.drugalcdep. 2017.01.035. Epub 2017 Mar 28.
Methamphetamine (METH) use is a risk factor for the transmission of HIV. Each is associated with neurocognitive impairment and subsequent problems in everyday functioning, yet additive effects of HIV and METH are not consistently observed. This study used the UCSD Performance-Based Skills Assessment (UPSA-2) to assess whether METH use disorder and HIV together resulted in poorer functional outcome than either condition alone. Participants in the Translational Methamphetamine AIDS Research Center (TMARC) cohort were stratified based upon HIV infection and METH use disorder: HIV-/METH- (n=49), HIV-/METH+ (n=48), HIV+/METH- (n=37), and HIV+/METH+ (n=38). They were administered the UPSA-2 which measures abilities in six domains of everyday functioning. Main effects and interactions of HIV and METH were examined, as were relationships between UPSA-2 scores and disease characteristics. Significant HIV-by-METH interactions were observed for the UPSA-2 total score and comprehension/Planning and Financial subscales such that METH was associated with lower scores in HIV- participants but not HIV+ participants. METH was associated with lower scores on the Communications subscale. All three risk groups had lower scores than HIV-/METH- participants. Recency and frequency of METH use were associated with lower scores. Lower Medication Management scores were related to lower nadir CD4 counts. The authors conclude that METH use disorder and HIV each impair functional performance, but there is no additive effect when the two conditions occur together. The

neurocognitive sequelae of combined HIV infection and METH use are complex and warrant further study, as do the potential effects of compensatory strategies and other factors.

HIV/HCV Co-infection, Liver Disease Progression, and Age-Related IGF-1 Decline Quinn J, Astemborski J, Mehta SH, Kirk GD, Thomas DL, Balagopal A. Pathog Immun. 2017;2(1):50-59. doi: 10.20411/pai. v2i1.183. Epub 2017 Mar 3.
The authors have previously reported that persons co-infected with HIV and hepatitis C virus (HCV) had liver disease stages similar to HIV-uninfected individuals who were approximately 10 years older. Insulin-like growth factor 1(IGF-1) levels have long been known to decline with advancing age in humans and non-humans alike. The authors examined whether HIV infection affects the expected decline in IGF-1 in persons with chronic hepatitis C virus (HCV) infection and if that alteration in IGF-1 decline contributes to the link between HIV, aging, and liver disease progression. A total of 553 individuals with HCV infection were studied from the AIDS Linked to the Intravenous Experience (ALIVE) cohort for whom more than 10 years of follow-up was available. Serum IGF-1 levels were determined by ELISA and evaluated according to baseline characteristics and over time by HIV status and liver disease progression. Linear regression with generalized estimating equations was used to determine whether IGF-1 decline over time was independently associated with liver disease progression. Baseline IGF-1 levels were strongly associated with age ($P < 0.0001$) but not with gender or HIV infection. Levels of IGF-1 declined at a rate of -1.75 ng/mL each year in HCV mono-infected individuals and at a rate of -1.23 ng/mL each year in HIV/HCV co-infected individuals ($P < 0.05$). In a multivariable linear regression model, progression of liver fibrosis was associated with HIV infection and age, as well as with a slower rate of IGF-1 decline ($P = 0.001$); however, the rate of IGF-1 decline did not alter the strength of the associations between HIV, liver disease, and age. The normal decline in IGF-1 levels with age was attenuated in HIV/HCV co-infected individuals compared to those with HCV mono-infection, and slower IGF-1 decline was independently associated with liver disease progression.

Genetic Basis For Variation In Plasma IL-18 Levels In Persons With Chronic Hepatitis C Virus and Human Immunodeficiency Virus-1 Infections Vergara C, Thio C, Latanich R, Cox AL, Kirk GD, Mehta SH, Busch M, Murphy EL, Villacres MC, Peters MG, French AL, Golub E, Eron J, Lahiri CD, Shrestha S, Gustafson D, Young M, Anastos K, Aouizerat B, Kim AY, Lauer G, Thomas DL, Duggal P. Genes Immun. 2017 Mar;18(2):82-87. doi: 10.1038/gene.2017.2. Epub 2017 Mar 16.
Inflammasomes are multi-protein complexes integrating pathogen-triggered signaling leading to the generation of pro-inflammatory cytokines including interleukin-18 (IL-18). Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections are associated with elevated IL-18, suggesting inflammasome activation. However, there is marked person-to-person variation in the inflammasome response to HCV and HIV. The authors hypothesized that host genetics may explain this variation. To test this, they analyzed the associations of plasma IL-18 levels and polymorphisms in 10 genes in the inflammasome cascade. About 1538 participants with active HIV and/or HCV infection in three ancestry groups are included. Samples were genotyped using the Illumina Omni 1-quad and Omni 2.5 arrays. Linear regression analyses were performed to test the association of variants with log IL-18 including HCV and HIV infection status, and HIV RNA in each ancestry group and then meta-analyzed. Eleven highly correlated single-nucleotide polymorphisms (r^2=0.98-1) in the IL-18-BCO2 region were significantly associated with log IL-18; each T allele of rs80011693 confers a decrease of 0.06 log pg ml^{-1} of IL-18 after adjusting for covariates (rs80011693; rs111311302 β=-0.06, P-value=2.7×10^{-4}). In conclusion, genetic variation

in IL-18 is associated with IL-18 production in response to HIV and HCV infection, and may explain variability in the inflammatory outcomes of chronic viral infections.

Marijuana Use Impacts Midlife Cardiovascular Events In HIV-Infected Men Lorenz DR, Dutta A, Mukerji SS, Holman A, Uno H, Gabuzda D. Clin Infect Dis. 2017 Apr 25. doi: 10.1093/cid/cix391. [Epub ahead of print].
Marijuana use is prevalent among persons infected with HIV, but its long-term effects on HIV disease progression and comorbidities are unknown. This was a prospective study of 558 HIV-infected men enrolled in the Multicenter AIDS Cohort Study between 1990-2010: 182 HIV seroconverters and 376 with viral suppression on combination antiretroviral therapy (ART). Associations between heavy marijuana use and HIV disease markers or white blood cell (WBC) count were examined using mixed-effects and linear regression models. Effects of marijuana use on cardiovascular (CV) events and other endpoints were estimated by Kaplan-Meier and logistic regression analyses. The median baseline age of participants was 41, 66% were white, 79% had education > 12 years, and 20% reported heavy marijuana use at ≥ 50% of biannual visits during follow-up. Long-term heavy marijuana use showed no significant associations with viral load, CD4 counts, AIDS, cancer, or mortality in both cohorts, but was independently associated with increased CV events between ages 40-60 after adjusting for age, tobacco smoking, viral load, and traditional risk factors (odds ratio [OR], 2.5; 95% confidence interval [CI] 1.3, 5.1). Marijuana and tobacco use were each independently associated with higher WBC counts in adjusted models ($P<0.01$); in turn, the highest quartile of WBC counts (≥ 6500 cells/μL) was associated with increased CV events (OR 4.3; 95% CI, 1.5, 12.9). The authors conclude that heavy marijuana use is a risk factor for CV disease in HIV-infected men ages 40-60, independent of tobacco smoking and traditional risk factors.

SERVICES RESEARCH

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; 26 (2).
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. 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, respectively. 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. The authors 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.

Shared Microstructural Features Of Behavioral and Substance Addictions Revealed In Areas Of Crossing Fibers Yip, Sarah W; Morie, Kristen P; Xu, Jiansong; Constable, R Todd; Malison, Robert T; Carroll, Kathleen M; Potenza, Marc N. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017; 2(2): 188-195.
Similarities between behavioral and substance addictions exist. However, direct neurobiological comparison between addictive disorders is rare. Determination of disorder-specificity (or lack thereof) of alterations within white-matter microstructures will advance understanding of the pathophysiology of addictions. The authors compared white-matter microstructural features between individuals with gambling disorder (GD; n=38), cocaine-use disorder (CUD; n=38) and healthy comparison (HC; n=38) participants, as assessed using diffusion-weighted magnetic resonance imaging (dMRI). To provide a more precise estimate of diffusion within regions of complex architecture (e.g., cortico-limbic tracts), analyses were conducted using a crossing-fiber model incorporating local-orientation modeling (tbss_x). Anisotropy estimates for primary and secondary fiber orientations were compared using ANOVAs corrected for multiple comparisons across space using threshold-free cluster enhancement (pFWE<.05). A main effect of group on anisotropy of secondary fiber orientations within the left internal capsule, corona radiata, forceps major and posterior thalamic radiation, involving reduced anisotropy among GD and CUD participants in comparison to HC participants. No differences in anisotropy measures were found between GD and CUD individuals. This is the first study to compare diffusion indices directly between behavioral and substance addictions and the largest dMRI study of GD. These findings indicate similar white-matter microstructural alterations across addictions that cannot be attributed solely to exposure to drugs or alcohol and thus may be a vulnerability mechanism for addictive disorders.

Gray-matter Relationships To Diagnostic and Transdiagnostic Features Of Drug and Behavioral Addictions Yip, Sarah W; Worhunsky, Patrick D; Xu, Jiansong; Morie, Kristen P; Constable, R Todd; Malison, Robert T; Carroll, Kathleen M; Potenza, Marc N. Addict Biol. 2017; Feb. 1.
Alterations in neural structure have been reported in both cocaine-use disorder and gambling disorder, separately, suggesting similarities across addiction diagnoses. Individual variation in neural structure has also been associated with impulsivity, a dimensional construct implicated in addictions. This study combines categorical (diagnosis-based) and dimensional (transdiagnostic) approaches to identify neural structural alterations linked to addiction subtypes and trait impulsivity, respectively, across individuals with gambling disorder (n = 35), individuals with cocaine-use disorder (n = 37) and healthy comparison individuals (n = 37). High-resolution T1-weighted data were analyzed using modulated voxel-based morphometry (VBM). Statistical analyses were conducted using whole-brain general-linear models, corrected for family-wise error (pFWE < .05). Categorical analyses indicated a main effect of diagnostic group on prefrontal (dorsal anterior cingulate and ventromedial prefrontal cortex) gray matter volumes (GMVs), involving decreased GMVs among cocaine-use disorder participants only. Dimensional analyses indicated a negative

association between trait impulsivity and cortical (insula) and subcortical (amygdala and hippocampus) GMVs across all participants. Conjunction analysis indicated little anatomical overlap between regions identified as differentiating diagnostic groups and regions covarying with impulsivity. These data provide first evidence of neural structural differences between gambling disorder and an illicit substance-use disorder. They further indicate dissociable effects of diagnostic groupings and trait impulsivity on neural structure among individuals with behavioral and drug addictions. Study findings highlight the importance of considering both categorical and dimensional (e.g. Research Domain Criteria; RDoC) analysis approaches within the context of addictions research.

Higher Prescription Opioid Dose Is Associated With Worse Patient-Reported Pain Outcomes and More Health Care Utilization Morasco, Benjamin J; Yarborough, Bobbi Jo; Smith, Ning X; Dobscha, Steven K; Deyo, Richard A; Perrin, Nancy A; Green, Carla A. J Pain. 2017; 18(4): 437-445.
Some previous research has examined pain-related variables on the basis of prescription opioid dose, but data from studies involving patient-reported outcomes have been limited. This study examined the relationships between prescription opioid dose and self-reported pain intensity, function, quality of life, and mental health. Participants were recruited from 2 large integrated health systems, Kaiser Permanente Northwest (n = 331) and VA Portland Health Care System (n = 186). To be included, participants had to have musculoskeletal pain diagnoses and be receiving stable doses of long-term opioid therapy. The authors divided participants into 3 groups on the basis of current prescription opioid dose in daily morphine equivalent dose (MED): low dose (5-20 mg MED), moderate dose (20.1-50 mg MED), and higher dose (50.1-120 mg MED) groups. A statistically significant trend emerged where higher prescription opioid dose was associated with moderately sized effects including greater pain intensity, more impairments in functioning and quality of life, poorer self-efficacy for managing pain, greater fear avoidance, and more health care utilization. Rates of potential alcohol and substance use disorders also differed among groups. Findings from this evaluation reveal significant differences in pain-related and substance-related factors on the basis of prescription opioid dose. This study included 517 patients who were prescribed long-term opioid therapy and compared differences on pain- and mental health-related variables on the basis of prescription opioid dose. Findings reveal small- to medium-sized differences on pain-related variables, alcohol and substance use, and health care utilization on the basis of the dose of opioid prescribed.

What Happened To The HIV Epidemic Among Non-injecting Drug Users In New York City? Des Jarlais, Don C; Arasteh, Kamyar; McKnight, Courtney; Feelemyer, Jonathan; Campbell, Aimee N C; Tross, Susan; Cooper, Hannah L F; Hagan, Holly; Perlman, David C. Addiction. 2017; 112(2): 290-298.
HIV has reached high prevalence in many non-injecting drug user (NIDU) populations. The aims of this study were to (1) examine the trend in HIV prevalence among non-injecting cocaine and heroin NIDUs in New York City, (2) identify factors potentially associated with the trend and (3) estimate HIV incidence among NIDUs. Serial-cross sectional surveys of people entering drug treatment programs. People were permitted to participate only once per year, but could participate in multiple years. Mount Sinai Beth Israel drug treatment programs in New York City, USA. The authors recruited 3298 non-injecting cocaine and heroin users from 2005 to 2014. Participants were 78.7% male, 6.1% white, 25.7% Hispanic and 65.8% African American. Smoking crack cocaine was the most common non-injecting drug practice. Trend tests were used to examine HIV prevalence, demographics, drug use, sexual behavior and use of antiretroviral treatment (ART) by calendar

year; $\chi(2)$ and multivariable logistic regression were used to compare 2005-10 versus 2011-14.HIV prevalence declined approximately 1% per year ($P < 0.001$), with a decline from 16% in 2005-10 to 8% in 2011-14 ($P < 0.001$). The percentages of participants smoking crack and having multiple sexual partners declined and the percentage of HIV-positive people on ART increased. HIV incidence among repeat participants was 1.2 per 1000 person-years (95% confidence interval = 0.03/1000-7/1000). HIV prevalence has declined and a high percentage of HIV-positive non-injecting drug users (NIDUs) are receiving antiretroviral treatment, suggesting an end to the HIV epidemic among NIDUs in New York City. These results can be considered a proof of concept that it is possible to control non-injecting drug use related sexual transmission HIV epidemics.

Beliefs About The Consequences Of Using Benzodiazepines Among Persons with Opioid Use Disorder Stein, Michael D; Anderson, Bradley J; Kenney, Shannon R; Bailey, Genie L. J Subst Abuse Treat. 2017 June; 77: 67-71.
Patients admitted to addiction treatment programs report high rates of concurrent opioid and benzodiazepine (BZD) use. This combination places individuals at high risk for accidental overdose and other serious consequences. However, little is known about the beliefs opioid users have about the consequences of BZD use. The authors surveyed consecutive persons initiating inpatient opioid detoxification (N=476; 95.0% enrollment) and identified 245 who reported BZD use in the past 30 days and/or had a positive toxicology. They compared those who did and did not report BZD use on demographic and substance use variables, and specific beliefs about the potential effects of BZDs. Participants averaged 32.2 years of age, 71.2% were male, 86.6% used heroin, and 68.7% reported injection drug use in the past 30 days. Over half (51.5%) used a BZD in the month prior to admission; of these, 26.2% (n=64) reported being prescribed a BZD. Alprazolam (Xanax) was the most commonly used BZD (54%). Benzodiazepine users (versus non-users) were significantly more likely to be female and non-Hispanic White, use concurrent substances, and report past year overdose. Overall, nearly all BZD users endorsed accurate beliefs that BZDs can increase the risk of overdose and can be addictive. However, BZD users, relative to non-users, were significantly less likely to endorse some known adverse consequences of BZDs, such as risk of worsening depression and poor medication-assisted opioid treatment retention. Delineating the full array of risks from combining BZDs and opioids should be a high priority in detoxification settings, given the increased risks associated with BZD misuse in this population.

Imaging Decision About Whether To Benefit Self By Harming Others: Adolescents With Conduct And Substance Problems, With Or Without Callous-unemotionality, Or Developing Typically Sakai, Joseph T; Dalwani, Manish S; Mikulich-Gilbertson, Susan K; Raymond, Kristen; McWilliams, Shannon; Tanabe, Jody; Rojas, Don; Regner, Michael; Banich, Marie T; Crowley, Thomas J. Psychiatry Res. 2017 May 30; 263103-112.
He authors sought to identify brain activation differences in conduct-problem youth with limited prosocial emotions (LPE) compared to conduct-problem youth without LPE and community adolescents, and to test associations between brain activation and severity of callous-unemotional traits. They utilized a novel task, which asks subjects to repeatedly decide whether to accept offers where they will benefit but a beneficent other will be harmed. Behavior on this task has been previously associated with levels of prosocial emotions and severity of callous-unemotional traits, and is related to empathic concern. During fMRI acquisition, 66 male adolescents (21 conduct-problem patients with LPE, 21 without, and 24 typically-developing controls) played this novel game. Within typically-developing controls, the authors identified a network engaged during decision involving bilateral insula, and inferior parietal and medial frontal cortices, among other regions. Group comparisons using non-parametric (distribution-free) permutation tests

demonstrated LPE patients had lower activation estimates than typically-developing adolescents in right anterior insula. Additional significant group differences emerged with our a priori parametric cluster-wise inference threshold. These results suggest measurable functional brain activation differences in conduct-problem adolescents with LPE compared to typically-developing adolescents. Such differences may underscore differential treatment needs for conduct-problem males with and without LPE.

CTN-RELATED RESEARCH

A Randomized Placebo-Controlled Trial Of N-Acetylcysteine For Cannabis Use Disorder In Adults Gray KM, Sonne SC, McClure EA, Ghitza UE, Matthews AG, McRae-Clark AL, Carroll KM, Potter JS, Wiest K, Mooney LJ, Hasson A, Walsh SL, Lofwall MR, Babalonis S, Lindblad RW, Sparenborg S, Wahle A, King JS, Baker NL, Tomko RL, Haynes LF, Vandrey RG, Levin FR. Drug Alcohol Depend. 2017 Aug 1; 177:249-257. doi: 10.1016/j.drugalcdep. 2017. 04.020. Epub 2017 Jun 10.

Cannabis use disorder (CUD) is a prevalent and impairing condition, and established psychosocial treatments convey limited efficacy. In light of recent findings supporting the efficacy of N-acetylcysteine (NAC) for CUD in adolescents, the objective of this trial was to evaluate its efficacy in adults. In a 12-week double-blind randomized placebo-controlled trial, treatment-seeking adults ages 18-50 with CUD (N=302), enrolled across six National Drug Abuse Treatment Clinical Trials Network-affiliated clinical sites, were randomized in a 1:1 ratio to a 12-week course of NAC 1200mg (n=153) or placebo (n=149) twice daily. All participants received contingency management (CM) and medical management. The primary efficacy measure was the odds of negative urine cannabinoid tests during treatment, compared between NAC and placebo participants. There was not statistically significant evidence that the NAC and placebo groups differed in cannabis abstinence (odds ratio=1.00, 95% confidence interval 0.63-1.59, p=0.984). Overall, 22.3% of urine cannabinoid tests in the NAC group were negative, compared with 22.4% in the placebo group. Many participants were medication non-adherent; exploratory analysis within medication-adherent subgroups revealed no significant differential abstinence outcomes by treatment group. In contrast with prior findings in adolescents, there is no evidence that NAC 1200mg twice daily plus CM is differentially efficacious for CUD in adults when compared to placebo plus CM. This discrepant finding between adolescents and adults with CUD may have been influenced by differences in development, cannabis use profiles, responses to embedded behavioral treatment, medication adherence, and other factors.

DSM-5 Substance Use Disorders Among Adult Primary Care Patients: Results From A Multisite Study Wu LT, McNeely J, Subramaniam GA, Brady KT, Sharma G, VanVeldhuisen P, Zhu H, Schwartz RP. Drug Alcohol Depend. 2017 Jul 13;179: 42-46. doi: 10.1016/j.drugalcdep 2017.05.048. [Epub ahead of print].

There are limited data about the extent of DSM-5 substance use disorders (SUDs) among primary care patients. This study analyzed data from a multisite validation study of a substance use screening instrument conducted in a diverse sample of 2000 adults aged ≥18 years recruited from five primary care practices in four states. Prevalence and correlates of 12-month DSM-5 SUDs were examined. Overall, 75.5% of the sample used any substance, including alcohol (62.0%), tobacco (44.1%), or illicit drugs/nonmedical medications (27.9%) in the past 12 months (marijuana 20.8%, cocaine 7.3%, opioids 4.8%, sedatives 4.1%, heroin 3.9%). The prevalence of any 12-month SUD was 36.0% (mild disorder 14.2%, moderate/severe disorder 21.8%): tobacco 25.3% (mild 11.5%,

moderate/severe 13.8%); alcohol 13.9% (mild 6.9%, moderate/severe 7.0%); and any illicit/ nonmedical drug 14.0% (mild 4.0%, moderate/severe 10.0%). Among past 12-month users, a high proportion of tobacco or drug users met criteria for a disorder: tobacco use disorder 57.4% (26.1% mild, 31.3% moderate/severe) and any drug use disorder 50.2% (14.3% mild, 35.8% moderate/ severe); a lower proportion of alcohol users (22.4%) met criteria for alcohol use disorder (11.1% mild, 11.3% moderate/severe). Over 80% of adults with opioid/heroin use disorder met criteria for a moderate/severe disorder. Younger ages, male sex, and low education were associated with increased odds of having SUD. These findings reveal the high prevalence of SUDs in primary care and underscore the need to identify and address them.

Racial and Ethnic Differences In Treatment Outcomes Among Adults With Stimulant Use Disorders After A Dosed Exercise Intervention Sanchez K, Greer TL, Walker R, Carmody T, Rethorst CD, Trivedi MH. J Ethn Subst Abuse. 2017 May 19:1-16. doi: 10.1080/15332640. 2017.1317310. [Epub ahead of print].
The current study examined differences in substance abuse treatment outcomes among racial and ethnic groups enrolled in the Stimulant Reduction Intervention using Dosed Exercise (STRIDE) trial, a multisite randomized clinical trial implemented through the National Institute on Drug Abuse's (NIDA's) Clinical Trials Network (CTN). STRIDE aimed to test vigorous exercise as a novel approach to the treatment of stimulant abuse compared to a health education intervention. A hurdle model with a complier average causal effects (CACE) adjustment was used to provide an unbiased estimate of the exercise effect had all participants been adherent to exercise. Among 214 exercise-adherent participants, the authors found significantly lower probability of use for Blacks ($z = -2.45$, $p = .014$) and significantly lower number of days of use for Whites compared to Hispanics ($z = -54.87$, $p = <.001$) and for Whites compared to Blacks ($z = -28.54$, $p = <.001$), which suggests that vigorous, regular exercise might improve treatment outcomes given adequate levels of adherence.

High Mortality Among Patients With Opioid Use Disorder in a Large Healthcare System Hser YI, Mooney LJ, Saxon AJ, Miotto K, Bell DS, Zhu Y, Liang D, Huang D. J Addict Med. 2017 Apr 20. doi: 10.1097/ADM.0000000000000312. [Epub ahead of print].
Elevated mortality has been observed among individuals with opioid use disorder (OUD) treated in addiction specialty clinics or programs. Information about OUD patients in general healthcare settings is needed in light of the current effort to integrate addiction services into primary healthcare systems. This study examined mortality rates, causes of death, and associated risk factors among patients with OUD in a large general healthcare system. Mortality data were linked with electronic health records of 2576 OUD patients cared for in a large university health system from 2006 to 2014. There were 465 deaths confirmed (18.1% of the study participants), corresponding to a crude mortality rate of 48.6 per 1000 person-years and standardized mortality ratio of 10.3 (95% confidence interval [CI] 9.4-11.3). Drug overdose and disorder (19.8%), cardiovascular diseases (17.4%), cancer (16.8%), and infectious diseases (13.5%, including 12% hepatitis C virus [HCV]) were the leading causes of death. HCV (hazard ratio [HR] 1.99, 95% CI 1.62-2.46) and alcohol use disorder (HR 1.27, 95% CI 1.05-1.55) were 2 clinically important indicators of overall mortality risk. Tobacco use disorder (adjusted HR [AHR] 2.58, 95% CI 1.60-4.17) was associated with increased risk of cardiovascular death, HCV infection (AHR 2.55, 95% CI 1.52-4.26) with cancer mortality risk, and HCV (AHR 1.92, 95% CI 1.03-3.60) and alcohol use disorder (AHR 5.44, 95% CI 2.95-10.05) with liver-related mortality risk. Patients with OUD in a general healthcare system demonstrated alarmingly high morbidity and mortality, which challenges healthcare systems to find innovative ways to identify and treat patients with substance use disorder.

Prescription Opioid Registry Protocol in an Integrated Health System Ray GT, Bahorik AL, VanVeldhuisen PC, Weisner CM, Rubinstein AL, Campbell CI. Am J Manag Care. 2017;23(5): e146-e155.
The objectives of this study were to establish a prescription opioid registry protocol in a large health system and to describe algorithms to characterize individuals using prescription opioids, opioid use episodes, and concurrent use of sedative/hypnotics. The Study Design was a protocol development and retrospective cohort study. Using Kaiser Permanente Northern California (KPNC) electronic health record data, the authors selected patients using prescription opioids in 2011. Opioid and sedative/hypnotic fills, and physical and psychiatric comorbidity diagnoses, were extracted for years 2008 to 2014. Algorithms were developed to identify each patient's daily opioid and sedative/hypnotic use, and morphine daily-dose equivalent. Opioid episodes were classified as long-term, episodic, or acute. Logistic regression was used to predict characteristics associated with becoming a long-term opioid user. In 2011, 18% of KPNC adult members filled at least 1 opioid prescription. Among those patients, 25% used opioids long term and their average duration of use was more than 4 years. Sedative/hypnotics were used by 76% of long-term users. Being older, white, living in a more deprived neighborhood, having a chronic pain diagnosis, and use of sedative/hypnotics were predictors of initiating long-term opioid use. This study established a population-based opioid registry that is flexible and can be used to address important questions of prescription opioid use. It will be used in future studies to answer a broad range of other critical public health issues relating to prescription opioid use.

INTRAMURAL RESEARCH

Glutamate Autoreceptor (mGluR2) Differentially Modulates Cocaine-Taking and Cocaine-Seeking Behavior In Rats Yang HJ, Zhang HY, Bi GH, He Y, Gao JT, Xi ZX. Cell Rep. 2017 Jul 11;20(2):319-332.
Cocaine users show reduced expression of the metabotropic glutamate receptor (mGluR2), but it is not clear whether this is a predisposing trait for addiction or a consequence of drug exposure. In this study, the authors found that a nonsense mutation at the mGluR2 gene decreased mGluR2 expression and altered the seeking and taking of cocaine. mGluR2 mutant rats show reduced sensitivity to cocaine reward, requiring more cocaine to reach satiation when it was freely available and ceasing their drug-seeking behavior sooner than controls when the response requirement was increased. mGluR2 mutant rats also show a lower propensity to relapse after a period of cocaine abstinence, an effect associated with reduced cocaine-induced dopamine and glutamate overflow in the nucleus accumbens. These findings suggest that mGluR2 polymorphisms or reduced availability of mGluR2 might be risk factors for the initial development of cocaine use but could actually protect against addiction by reducing sensitivity to cocaine reward.

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 and Stein, EA. JAMA Psychiatry 74, 632-640, 2017, doi: 10.1001/jamapsychiatry.2017.0400. [Epub ahead of print].
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 aim 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 v arenicline 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.

Local Cues Establish and Maintain Region-Specific Phenotypes of Basal Ganglia Microglia De Biase LM, Schuebel KE, Fusfeld ZH, Jair K, Hawes IA, Cimbro R, Zhang HY, Liu QR, Shen H, Xi ZX, Goldman D, Bonci A. Neuron. 2017 Jul 1. pii: S0896-6273(17)30518-4.
Microglia play critical roles in tissue homeostasis and can also modulate neuronal function and synaptic connectivity. In contrast to astrocytes and oligodendrocytes, which arise from multiple progenitor pools, microglia arise from yolk sac progenitors and are widely considered to be equivalent throughout the CNS. However, little is known about basic properties of deep brain microglia, such as those within the basal ganglia (BG). Here, the authors show that microglial anatomical features, lysosome content, membrane properties, and transcriptomes differ significantly across BG nuclei. Region-specific phenotypes of BG microglia emerged during the second postnatal week and were re-established following genetic or pharmacological microglial ablation and repopulation in the adult, indicating that local cues play an ongoing role in shaping microglial diversity. These findings demonstrate that microglia in the healthy brain exhibit a spectrum of distinct functional states and provide a critical foundation for defining microglial contributions to BG circuit function.

Relationship Between The Aldosterone - Mineralocorticoid Receptor Pathway and Alcohol Drinking: Preliminary Translational Findings Across Monkeys, Rats and Humans E.G. Aoun, V. Jimenez, L.F. Vendruscolo, N.A.R. Walter, E. Barbier, A. Ferrulli, C.L. Haass-Koffler, P. Darakajian, M.R. Lee, G. Addolorato, M. Heilig, R. Hitzemann, G.F. Koob, K.A. Grant, L. Leggio. Molecular Psychiatry 2017.
In this study, the authors examined the relationships between alcohol craving, drinking and anxiety and the aldosterone pathway, as assessed by peripheral aldosterone concentrations and the brain expression of its receptor, the mineralocorticoid receptor (MR). The study showed a relationship between higher aldosterone concentrations and higher craving, drinking and anxiety. On the other hand, the lower was the expression of the MR in the amydgala, the higher was alcohol drinking and anxiety. These results were consistent across three species: a rat model of alcohol dependence, a non-human primate model of excessive alcohol drinking and a clinically-relevant sample of patients with alcohol dependence. The study supports future research to investigate the potential causality link between the aldosterone/MR pathway and alcohol use disorder in order to shed light on the potential role of this pathway towards the development of novel pharmacological treatments.

Dopamine Transients Are Sufficient and Necessary For Acquisition Of Model-Based Associations Sharpe, M.J., Chang, C.Y., Liu, M.A., Batchelor, H.M., Mueller, L.E., Jones, J.L., Niv, Y., and Schoenbaum, G. 2017. Nature Neuroscience 20, 735-742.
Associative learning is driven by prediction errors. Dopamine transients correlate with these errors, which current interpretations limit to endowing cues with a scalar quantity reflecting the value of future rewards. The authors tested whether dopamine might act more broadly to support learning of an associative model of the environment. Using sensory preconditioning, they show that prediction errors underlying stimulus-stimulus learning can be blocked behaviorally and reinstated by optogenetically activating dopamine neurons. They further show that suppressing the firing of these neurons across the transition prevents normal stimulus-stimulus learning. These results establish that the acquisition of model-based information about transitions between nonrewarding events is also driven by prediction errors and that, contrary to existing canon, dopamine transients are both sufficient and necessary to support this type of learning. These findings open new possibilities for how these biological signals might support associative learning in the mammalian brain in these and other contexts.

Salience and Default Mode Network Dysregulation In Chronic Cocaine Users Predict Treatment Outcome Geng X, Hu Y, Gu H, Salmeron BJ, Adinoff B, Stein EA and Yang Y. Brain 2017 140:1513-1527.
While chronic cocaine use is associated with abnormalities in both brain structure and function within and interactions between regions, previous studies have been limited to interrogating structure and function independently, and the detected neural differences have not been applied to independent samples to assess the clinical relevance of results. The authors investigated consequences of structural differences on resting-state functional connectivity in cocaine addiction and tested whether resting-state functional connectivity of the identified circuits predict relapse in an independent cohort. Subjects included 64 non-treatment-seeking cocaine users (NTSCUs) and 67 healthy control subjects and an independent treatment-completed cohort (n = 45) of cocaine-dependent individuals scanned at the end of a 30-day residential treatment programme. Differences in cortical thickness and related resting-state functional connectivity between NTSCUs and healthy control subjects were identified. Survival analysis, applying cortical thickness of the identified regions, resting-state functional connectivity of the identified circuits and clinical characteristics to the treatment cohort, was used to predict relapse. Lower cortical thickness in bilateral insula and

higher thickness in bilateral temporal pole were found in NTSCUs versus healthy control subjects. Whole brain resting-state functional connectivity analyses with these four different anatomical regions as seeds revealed eight weaker circuits including within the salience network (insula seeds) and between temporal pole and elements of the default mode network in NTSCUs. Applying these circuits and clinical characteristics to the independent cocaine-dependent treatment cohort, functional connectivity between right temporal pole and medial prefrontal cortex, combined with years of education, predicted relapse status at 150 days with 88% accuracy. Deficits in the salience network suggest an impaired ability to process physiologically salient events, while abnormalities in a temporal pole–medial prefrontal cortex circuit might speak to the social-emotional functional alterations in cocaine addiction. The involvement of the temporal pole–medial prefrontal cortex circuit in a model highly predictive of relapse highlights the importance of social-emotional functions in cocaine dependence, and provides a potential underlying neural target for therapeutic interventions, and for identifying those at high risk of relapse.

GRANTEE HONORS AND AWARDS

Dr. Gene Brody and the team at the Center for Family Research, University of Georgia Athens, received the Society for Prevention Research 2017 Advances in Culture and Diversity in Prevention Science Award. This award is given for contributions to the field of prevention science in the area of community and culture.

Dr. Patricia Chamberlain received the Presidential Award at the 2017 Society for Prevention Research. This award is given to those who have made a major lifetime contribution to prevention science research.

Dr. Benjamin F. Cravatt, The Scripps Research Institute, Winner of the The Robert M. Scarborough Award for Excellence in Medicinal Chemistry and 2017 ACS Chemical Biology Lectureship Award. He is recognized for his development of activity-based protein profiling technology. Through post-genomic profiling of the functional state of enzymes in complex proteomes, he identified key enzymes involved in regulation of lipid signaling pathways.

Dr. Daniel Max Crowley received the Society for Prevention Research 2017 ECPN John B. Reid Early Career Award. This award is presented to someone who has shown a commitment to prevention science through outstanding contributions to research, policy or practice.

Drs. Kenneth Dodge, **Mark Greenberg**, and **John Lochman**, along with **Drs. Karen Bierman**, **Robert McMahon**, and **John Coie** (posthumously) received the Society for Prevention Research 2017 Service to SPR Award for their generous contribution of their royalties from the Conduct Problems Prevention Research Group (CPPRG) Fast Track program for the past seven years to SPR. The royalties support SPR's training and professional development programs and activities for early career prevention scientists.

Dr. Honora Englander, OHSU physician, was honored by CODA, a charter CTN community treatment program and frequent participant in CTN protocols, with the 2017 Advocacy Award for her role in the development and leadership of OHSU's Improving Addiction Care Team (IMPACT). IMPACT addresses the multi-faceted needs of hospitalized patients with alcohol and drug use disorders that complicate medical care for co-morbid conditions. IMPACT initiates addiction treatment services while patients are hospitalized and links them with community-based services for substance use disorders, housing, employment, and criminal justice. Many IMPACT patients continue medical and substance abuse services at CODA. Dr. Englander received the award at CODA's annual Advocacy Awards Luncheon on April 4, 2017.

Dr. Thomas H. Everett, Arrhythmotech, won the Innovation of The Year Mira Award During The 18th Annual "Best of Tech in Indiana" for the project, "Skin Sympathetic Nerve Activity and Cardiac Arrhythmias." Arrhythmotech's neuECG(TM) platform is a novel medical device and software platform capable of detecting sympathetic nerve signaling (fight-or-flight activity) non-invasively on the skin (SKNA). SKNA is a novel continuous digital biomarker for stress that will have an impact clinical research, therapeutic development and wearable technology markets. This early-stress-response biomarker and wearable device may be applied to the detection of stress related factors that contribute relapse.

Dr. Mark Feinberg, The Pennsylvania State University, received the Society for Prevention Research 2017 Prevention Science Award. This award is given for the work of developing and testing prevention strategies.

Drs. Diana Fishbein, The Pennsylvania State University, **John Lochman**, The University of Alabama, and **Sharlene Wolchik**, Arizona State University, were inducted into the 2017 cohort of Fellows of the Society for Prevention Research. Fellows represent a select group of members of SPR who have a distinguished record of contributions in the field of prevention research that reflects a substantial body of work that has a broad and significant impact.

Dr. Samie Jaffrey is the 2017 winner of the John J. Abel Award in Pharmacology.

Dr. Douglas Owens of Stanford University, was just appointed Vice Chair of the U.S. Prevention Services Task Force; his next appointment will be that of Chair. The Task Force is an elite group of 16 experts in public health and medicine whose task includes but is not limited to developing screening guidelines for various health problems. Dr. Owens has led the development of national guidelines for measuring HIV, HCV, and HBV.

Dr. Marina Picciotto, Professor of Psychiatry Yale Department of Psychiatry, was elected as President of the Society for Research on Nicotine & Tobacco (SRNT) in the Spring of 2017.

Dr. Danielli Piomelli of the Dept. of Anatomy and Neurobiology at UC Irvine was awarded the Mechulam award form ICRS, 2017 Meeting at Montreal for contributions to cannabinioid research.

Dr. Guillermo "Willy" Prado received the Society for Prevention Research 2017 Friend of ECPN (Early Career Preventionist Network) Award. This award is presented to a mid-career or senior preventionist who has supported and encouraged early career prevention scientists or issues.

Dr. Richard Spoth, Iowa State University, was awarded the Society for Prevention Research Translation Science Award, in recognition for contributions to the field of prevention science in the area of Type 1 or Type 2 translational research.

Dr. Ilana Witten, DP2 awardee who won the 2017 Freedman Prize for exceptional basic Resesarch from the Brain Behavior Research Foundation, formerly NARSAD.

STAFF HONORS AND AWARDS

Dr. Alessandro Bonifazi, IRP, was awarded an FY18 NIH FARE Travel Award.

Allison Daurio, IRP, received a 2017 Research Society on Alcoholism (RSA) Student Merit Award.

Lisa Farinelli, IRP, received a certification in Officer Health Care Compliance (OHCC).

Dr. Mehdi Farokhnia, IRP, was one of the NIH FARE awardees.

Dr. Mehdi Farokhnia was one of six 2017 RSA Gordis Awards Finalists.

Dr. Yi He, IRP, was awarded an FY18 NIH FARE Travel Award.

Dr. Jinhee Lee, OSPC, was recently promoted from Commander to the rank of Captain in the U.S. Public Health Service Commissioned Corps.

Dr. Mary Lee, IRP, was invited to become a Corresponding Member of the Addictions Council of the American Psychiatric Association.

Dr. Mary Lee was invited to join the RSA Membership Committee.

Dr. Lorenzo Leggio, IRP, was invited to join the newly formed Advisory Council of the Peter G. Dodge Foundation (PGDF).

Dr. Da-Ting Lin, IRP, was awarded the 2016 HHS Green Champion Award.

Dr. Roger Little, DNB, has been asked to serve on the Scientific Advisory Board of VA's National PTSD Brain Bank (NPBB). He is also participating in an Institute of Medicine workshop "Enabling Novel Treatments for Nervous System Disorders by Improving Methods for Traversing the Blood-Brain Barrier."

Brandon Warren, IRP, received a K99 award.

Dr. Rita Valentino, Director, DNB, was re-elected to the Scientific Advisory Board of the Brain Behavior Research Foundation.

STAFF CHANGES

Separations

Gweniffer Epps, a Contract Specialist in the Office of Management, Office of Acquisitions left NIDA on July 22, 2017 for a position with the Veteran's Administration.

Keisha McDonald, a Contract Specialist in the Office of Management, Office of Acquisition's Station Support Branch, left NIDA on August 5, 2017 for a position with the US Courts.

Lauren Phelps, a Contract Specialist in the Office of Management, Office of Acquisition's Station Support Branch, left NIDA on September 2, 2017 for a position with the Federal Retirement Thrift Savings Program.

Retirements

Shou Hua Li, a Mathematical Statistician in the Clinical/Medical Branch of NIDA's Division of Therapeutics and Medical Consequences, retired from Federal service on June 30, 2017.

Cathrine Sasek, Ph.D., Health Scientist Administrator, Science Policy Branch, OSPC, retired from federal service on June 30, 2017, after a distinguished career spanning nearly 27 years. Cathrine had a role in many of NIDA's activities, including science education grants and contracts and more recently, the NIDA Loan Repayment Program (LRP). Cathrine was project officer on numerous widely distributed science education projects such as NIDA's Brain Power Junior Scientists series, the Mind Over Matter Series, The Brain: Understanding Neurobiology through the Study of Addiction, and NIDA's Easy to Read web site. Cathrine also organized Take Your Child to Work Day, the USA Science & Engineering Festival and Brain Awareness Week for many years. Cathrine plans on doing volunteer work, taking courses at Montgomery College and nurturing and expanding her interest in nature photography.

National Institute
on Drug Abuse