DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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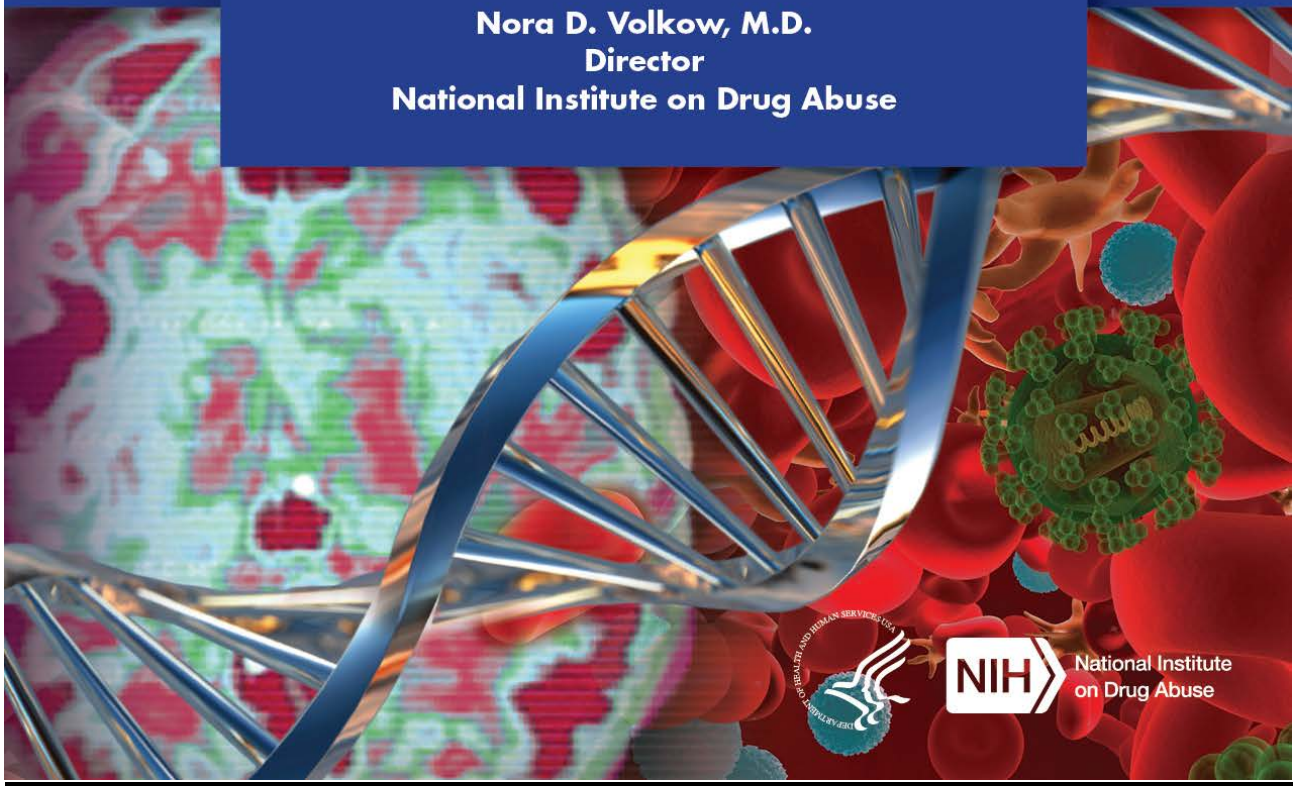

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TABLE OF CONTENTS

RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

In Vivo Brain GPCR Signaling Elucidated by Phosphoproteomics Liu JJ, Sharma K, Zangrandi L, Chen C, Humphrey SJ, Chiu YT, Spetea M, Liu-Chen LY, Schwarzer C, Mann M. Science. 2018 Jun 22;360(6395).
A systems view of G protein-coupled receptor (GPCR) signaling in its native environment is central to the development of GPCR therapeutics with fewer side effects. Using the kappa opioid receptor (KOR) as a model, the authors employed high-throughput phosphoproteomics to investigate signaling induced by structurally diverse agonists in five mouse brain regions. Quantification of 50,000 different phosphosites provided a systems view of KOR in vivo signaling, revealing novel mechanisms of drug action. Thus, the authors discovered enrichment of the mechanistic target of rapamycin (mTOR) pathway by U-50,488H, an agonist causing aversion, which is a typical KOR-mediated side effect. Consequently, mTOR inhibition during KOR activation abolished aversion while preserving beneficial antinociceptive and anticonvulsant effects. These results establish high-throughput phosphoproteomics as a general strategy to investigate GPCR in vivo signaling, enabling prediction and modulation of behavioral outcomes.

NAD+ Cellular Redox and SIRT1 Regulate the Diurnal Rhythms Of Tyrosine Hydroxylase and Conditioned Cocaine Reward Logan RW, Parekh PK, Kaplan GN, Becker-Krail DD, Williams WP 3rd, Yamaguchi S, Yoshino J, Shelton MA, Zhu X, Zhang H, Waplinger S, Fitzgerald E, Oliver-Smith J, Sundarvelu P, Enwright JF 3rd, Huang YH, McClung CA. Mol Psychiatry. 2018 May 4. doi: 10.1038/s41380-018-0061-1. [Epub ahead of print].
The diurnal regulation of dopamine is important for normal physiology and diseases such as addiction. Here the authors find a novel role for the CLOCK protein to antagonize CREB-mediated transcriptional activity at the tyrosine hydroxylase (TH) promoter, which is mediated by the interaction with the metabolic sensing protein, Sirtuin 1 (SIRT1). Additionally, they demonstrate that the transcriptional activity of TH is modulated by the cellular redox state, and daily rhythms of redox balance in the ventral tegmental area (VTA), along with TH transcription, are highly disrupted following chronic cocaine administration. Furthermore, CLOCK and SIRT1 are important for regulating cocaine reward and dopaminergic (DAergic) activity, with interesting differences depending on whether DAergic activity is in a heightened state and if there is a functional CLOCK protein. Taken together, the authors find that rhythms in cellular metabolism and circadian proteins work together to regulate dopamine synthesis and the reward value for drugs of abuse.

Structure Of the μ-Opioid Receptor-G_i Protein Complex Koehl A, Hu H, Maeda S, Zhang Y, Qu Q, Paggi JM, Latorraca NR, Hilger D, Dawson R, Matile H, Schertler GFX, Granier S, Weis WI, Dror RO, Manglik A, Skiniotis G, Kobilka BK.Nature. 2018 Jun;558(7711):547-552. doi: 10.1038/s41586-018-0219-7. Epub 2018 Jun 13.
The μ-opioid receptor (μOR) is a G-protein-coupled receptor (GPCR) and the target of most clinically and recreationally used opioids. The induced positive effects of analgesia and euphoria are mediated by μOR signalling through the adenylyl cyclase-inhibiting heterotrimeric G protein G_i. Here the authors present the 3.5 Å resolution cryo-electron microscopy structure of the μOR bound to the agonist peptide DAMGO and nucleotide-free G_i. DAMGO occupies the morphinan ligand pocket, with its N terminus interacting with conserved receptor residues and its C terminus engaging regions important for opioid-ligand selectivity. Comparison of the μOR-G_i complex to

previously determined structures of other GPCRs bound to the stimulatory G protein G_s reveals differences in the position of transmembrane receptor helix 6 and in the interactions between the G protein α-subunit and the receptor core. Together, these results shed light on the structural features that contribute to the G_i protein-coupling specificity of the μOR.

Opiates Increase the Number Of Hypocretin-Producing Cells In Human and Mouse Brain and Reverse Cataplexy In A Mouse Model Of Narcolepsy Thannickal TC, John J, Shan L, Swaab DF, Wu MF, Ramanathan L, McGregor R, Chew KT, Cornford M, Yamanaka A, Inutsuka A, Fronczek R, Lammers GJ, Worley PF, Siegel JM. Sci Transl Med. 2018 Jun 27;10(447). The changes in brain function that perpetuate opiate addiction are unclear. In the authors' studies of human narcolepsy, a disease caused by loss of immunohistochemically detected hypocretin (orexin) neurons, they encountered a control brain (from an apparently neurologically normal individual) with 50% more hypocretin neurons than other control human brains that they had studied. The authors discovered that this individual was a heroin addict. Studying five postmortem brains from heroin addicts, thy report that the brain tissue had, on average, 54% more immunohistochemically detected neurons producing hypocretin than did control brains from neurologically normal subjects. Similar increases in hypocretin-producing cells could be induced in wild-type mice by long-term (but not short-term) administration of morphine. The increased number of detected hypocretin neurons was not due to neurogenesis and outlasted morphine administration by several weeks. The number of neurons containing melanin-concentrating hormone, which are in the same hypothalamic region as hypocretin-producing cells, did not change in response to morphine administration. Morphine administration restored the population of detected hypocretin cells to normal numbers in transgenic mice in which these neurons had been partially depleted. Morphine administration also decreased cataplexy in mice made narcoleptic by the depletion of hypocretin neurons. These findings suggest that opiate agonists may have a role in the treatment of narcolepsy, a disorder caused by hypocretin neuron loss, and that increased numbers of hypocretin-producing cells may play a role in maintaining opiate addiction.

Phasic Dopamine Signals in the Nucleus Accumbens that Cause Active Avoidance Require Endocannabinoid Mobilization in the Midbrain Wenzel JM, Oleson EB, Gove WN, Cole AB, Gyawali U, Dantrassy HM, Bluett RJ, Dryanovski DI, Stuber GD, Deisseroth K, Mathur BN, Patel S, Lupica CR, Cheer JF.Curr Biol. 2018 May 7;28(9):1392-1404.
Phasic dopamine (DA) release accompanies approach toward appetitive cues. However, a role for DA in the active avoidance of negative events remains undetermined. Warning signals informing footshock avoidance are associated with accumbal DA release, whereas depression of DA is observed with unavoidable footshock. Here, the authors reveal a causal role of phasic DA in active avoidance learning; specifically, optogenetic activation of DA neurons facilitates avoidance, whereas optical inhibition of these cells attenuates it. Furthermore, stimulation of DA neurons during presentation of a fear-conditioned cue accelerates the extinction of a passive defensive behavior (i.e., freezing). Dopaminergic control of avoidance requires endocannabinoids (eCBs), as perturbing eCB signaling in the midbrain disrupts avoidance, which is rescued by optical stimulation of DA neurons. Interestingly, once the avoidance task is learned, neither DA nor eCB manipulations affect performance, suggesting that once acquisition occurs, expression of this behavior is subserved by other anatomical frameworks. These findings establish an instrumental role for DA release in learning active responses to aversive stimuli and its control by eCB signaling.

EPIDEMIOLOGY, PREVENTION AND SERVICES RESEARCH

Substance Use Among American Indian Youths on Reservations Compared With a National Sample of US Adolescents Swaim, Randall C.; Stanley, Linda R. JAMA Network Open. 2018;1(1):e180382.

American Indian adolescents attending schools on or near reservations are historically at high risk for substance use. The objective of this study was to compare rates of substance use among reservation-based American Indian adolescents vs rates among national US youths. This was a population-based survey study of 8th-, 10th-, and 12th-grade students attending participating schools on or near reservations, stratified by region, during the 2016-2017 school year. Substance use rates were compared with those of a national sample of comparably aged students from the Monitoring the Future study. The main outcomes and measures obtained were lifetime and last-30-day self-reported use of alcohol, marijuana, and other drugs, using relative risk (RR) ratios with 95% confidence intervals to compare American Indian student rates with Monitoring the Future student rates. Participants included 570 students in eighth grade (49.6% girls; mean age, 13.5 years), 582 in 10th grade (50.0% girls; mean age, 15.4 years), and 508 in 12th grade (53.5% girls; mean age, 17.4 years). American Indian students reported substantially higher lifetime and last-30-day substance use rates compared with the Monitoring the Future students, with greatest disparity at eighth grade: last-30-day substance use RRs for grade 8 were 2.1 (95% CI, 1.4-3.0) for alcohol, 4.2 (95% CI, 3.1-5.8) for marijuana, and 2.4 (95% CI, 1.7-3.3) for other illicit drugs. Compared with 2009 to 2012 data, the RRs between American Indian and Monitoring the Future students for lifetime alcohol and marijuana use did not change substantially from the 2016-2017 school year (alcohol: RR, 1.5 [95% CI, 1.4-1.6] vs RR, 1.3 [95% CI, 1.2-1.4], respectively; marijuana: RR, 2.0 [95% CI, 1.8-2.1] vs RR, 2.1 [95% CI, 1.9-2.3], respectively), but increased substantially for other drugs (RR, 1.8 [95% CI, 1.7-1.9] vs RR, 3.0 [95% CI, 2.9-3.2], respectively). The authors conclude that reservation-based American Indian students are at high risk for substance use compared with US youths in general, making prevention efforts critical. Cultural and value-based characteristics unique to American Indian populations may provide beneficial targets for prevention, but there is limited evidence on how cultural factors work to prevent risky behaviors. Without increased attention to these disparities, the costs to American Indian youths and their communities will remain high.

Electronic Cigarette Use and Progression From Experimentation To Established Smoking Chaffee, Benjamin W; Watkins, Shannon Lea; Glantz, Stanton A. Pediatrics. 2018; 141(4): e20173594.

It has been shown that never-smoking adolescents who try electronic cigarettes (e-cigarettes) are at increased risk of subsequent conventional cigarette smoking. The authors evaluated associations between e-cigarette use and progression to established smoking among adolescents who had already tried cigarettes. Among participants (age 12-17 years) in the nationally representative Population Assessment of Tobacco and Health survey who had smoked a cigarette (≥1 puff) but not yet smoked 100 cigarettes (N = 1295), the authors examined 3 outcomes at 1-year follow-up as a function of baseline e-cigarette use: (1) having smoked ≥100 cigarettes (established smoking), (2) smoking during the past 30 days, and (3) both having smoked ≥100 cigarettes and past 30-day smoking (current established smoking). Survey-weighted multivariable logistic regression models were fitted to obtain odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for smoking risk factors. Versus e-cigarette never use, having ever used e-cigarettes was positively associated with progression to established cigarette smoking (19.3% vs 9.7%), past 30-day smoking (38.8% vs 26.6%), and current established smoking (15.6% vs 7.1%). In adjusted models, e-cigarette ever use

positively predicted current established smoking (OR: 1.80; 95% CI: 1.04-3.12) but did not reach statistical significance (α = .05) for established smoking (OR: 1.57; 95% CI: 0.99-2.49) and past 30-day smoking (OR: 1.32; 95% CI: 0.99-1.76). Among adolescent cigarette experimenters, using e-cigarettes was positively and independently associated with progression to current established smoking, suggesting that e-cigarettes do not divert from, and may encourage, cigarette smoking in this population.

Impact Of Sleep and Circadian Rhythms On Addiction Vulnerability In Adolescents
Logan RW, Hasler BP, Forbes EE, Franzen PL, Torregrossa MM, Huang YH, Buysse DJ, Clark DB, McClung CA. Biol Psychiatry. 2018; 83(12): 987-996.
Sleep homeostasis and circadian function are important maintaining factors for optimal health and well-being. Conversely, sleep and circadian disruptions are implicated in a variety of adverse health outcomes, including substance use disorders. These risks are particularly salient during adolescence. Adolescents require 8 to 10 hours of sleep per night, although few consistently achieve these durations. A mismatch between developmental changes and social/environmental demands contributes to inadequate sleep. Homeostatic sleep drive takes longer to build, circadian rhythms naturally become delayed, and sensitivity to the phase-shifting effects of light increases, all of which lead to an evening preference (i.e., chronotype) during adolescence. In addition, school start times are often earlier in adolescence and the use of electronic devices at night increases, leading to disrupted sleep and circadian misalignment (i.e., social jet lag). Social factors (e.g., peer influence) and school demands further impact sleep and circadian rhythms. To cope with sleepiness, many teens regularly consume highly caffeinated energy drinks and other stimulants, creating further disruptions in sleep. Chronic sleep loss and circadian misalignment enhance developmental tendencies toward increased reward sensitivity and impulsivity, increasing the likelihood of engaging in risky behaviors and exacerbating the vulnerability to substance use and substance use disorders. The authors review the neurobiology of brain reward systems and the impact of sleep and circadian rhythms changes on addiction vulnerability in adolescence and suggest areas that warrant additional research.

Cigarette Use Is Increasing Among People With Illicit Substance Use Disorders In The United States, 2002-14: Emerging Disparities In Vulnerable Populations Weinberger, Andrea H; Gbedemah, Misato; Wall, Melanie M; Hasin, Deborah S; Zvolensky, Michael J; Goodwin, Renee D. Addiction. 2018; 113(4): 719-728.
While cigarette smoking has declined over time, it is not known whether this decline has occurred similarly among individuals with substance use disorders (SUDs) in the United States (US). The current study estimated trends in smoking from 2002 to 2014 among US individuals with and without SUDs. Linear time trends of current smoking prevalence were assessed using logistic regression models. United States; data were drawn from the 2002 to 2014 National Household Survey on Drug Use (NSDUH), an annual US cross-sectional study. A representative, population-based sample of US individuals age 12 years and older (total analytical population: n = 723 283). Past-month current smoking was defined as having smoked at least 100 lifetime cigarettes and reporting smoking part or all of at least one cigarette during the past 30 days. Respondents were classified as having any SUD if they met criteria for abuse or dependence for one or more of the following illicit drugs: cannabis, hallucinogens, inhalants, tranquilizers, cocaine, heroin, pain relievers, simulants and sedatives. A second SUD variable included all drugs listed above excluding cannabis use disorder (CUD). An additional variable included respondents who met criteria for cannabis abuse or dependence. Among those with any SUD, the prevalence of smoking did not change from 2002 to 2014 (P = 0.08). However, when CUDs were separated from other SUDs, a

significant increase in prevalence of smoking was observed among those with SUDs excluding CUDs (P < 0.001), while smoking decreased among those with CUDs (P < 0.001). Smoking declined among those without SUDs (P < 0.001). In 2014, smoking remained significantly more common among those with any SUD (55.48%), SUDs excluding CUDs (63.34%) and CUDs (51.34%) compared with those without these respective disorders (18.16, 18.55 and 18.64%; P < 0.001). The prevalence of cigarette smoking in the United States increased from 2002 to 2014 among people with substance use disorders (SUDs) excluding cannabis use disorders (CUDs) and declined among those with CUDs and without SUDs. In 2014, the prevalence of smoking was multifold higher among those with SUDs, including CUDs, compared with those without SUDs.

A Reciprocal Effects Analysis Of Cannabis Use and Perceptions Of Risk Salloum, Naji C; Krauss, Melissa J; Agrawal, Arpana; Bierut, Laura J; Grucza, Richard A. Addiction. 2018; 113(6): 1077-1085.
Adolescents and young adults increasingly view cannabis as a relatively safe drug. Perception of risk associated with cannabis use is correlated negatively with the prevalence of use, but the causal nature of this association is debated. The aim of this study is to quantitate the reciprocal associations between cannabis use and risk perception in a longitudinal panel of emerging adults. Observational study of longitudinal data from the Monitoring the Future longitudinal study using autoregressive cross-lagged panel analyses to investigate reciprocal associations between cannabis risk perception and frequency of past-year cannabis use. Surveys administered to 12th-grade students from the United States general population. A total of 9929 12th-grade students (mean age 18.0 years) who were surveyed initially during 2000-05 and follow-up data until approximately 23-24 years old (three waves; n = 9929). Perception of risk association with cannabis use and frequency of past-year cannabis use. At baseline, 33% of the 12th-graders used cannabis in the past year versus 28% by the third follow-up; 83% believed that smoking cannabis regularly carried moderate or great risk versus 78% by the third follow-up. All cross-lagged paths in both directions were statistically significant (all P < 0.001), consistent with reciprocal influences between cannabis use and risk perception. The negative association between past-year cannabis use and subsequent risk perception (standardized coefficient range -0.21 to -0.27) was stronger than that between risk perception and subsequent use (standardized coefficient range -0.08 to -0.11; confidence intervals did not overlap with those for the coefficients reported above). Similar results were obtained when the analysis was limited to those who had never used cannabis prior to baseline. Longitudinal associations between cannabis use and perception of risks from cannabis use are reciprocal in nature, with a stronger association between cannabis use and lower subsequent risk perception.

Long-Term Effects Of The Communities That Care Trial On Substance Use, Antisocial Behavior, and Violence Through Age 21 Years Oesterle, Sabrina; Kuklinski, Margaret R; Hawkins, J David; Skinner, Martie L; Guttmannova, Katarina; Rhew, Isaac C. Am J Public Health. 2018; 108(5): 659-665.
The aim of this study was to evaluate whether the effects of the Communities That Care (CTC) prevention system, implemented in early adolescence to promote positive youth development and reduce health-risking behavior, endured through age 21 years. The authors analyzed 9 waves of prospective data collected between 2004 and 2014 from a panel of 4407 participants (grade 5 through age 21 years) in the community-randomized trial of the CTC system in Colorado, Illinois, Kansas, Maine, Oregon, Utah, and Washington State. They used multilevel models to evaluate intervention effects on sustained abstinence, lifetime incidence, and prevalence of past-year substance use, antisocial behavior, and violence. The CTC system increased the likelihood of sustained abstinence from gateway drug use by 49% and antisocial behavior by 18%, and reduced

lifetime incidence of violence by 11% through age 21 years. In male participants, the CTC system also increased the likelihood of sustained abstinence from tobacco use by 30% and marijuana use by 24%, and reduced lifetime incidence of inhalant use by 18%. No intervention effects were found on past-year prevalence of these behaviors. Implementation of the CTC prevention system in adolescence reduced lifetime incidence of health-risking behaviors into young adulthood. Clinicaltrials.gov identifier: NCT01088542.

E-cigarette Advertising Exposure In E-cigarette Naïve Adolescents and Subsequent E-cigarette Use: A Longitudinal Cohort Study Camenga, Deepa; Gutierrez, Kevin M; Kong, Grace; Cavallo, Dana; Simon, Patricia; Krishnan-Sarin, Suchitra. Addict Behav. 2018; 81: 78-83.
Electronic (E-) cigarettes are one of the most popular tobacco products used by adolescents today. This study examined whether exposure to advertisements in (1) social networking sites (Facebook, Twitter, YouTube, Pinterest/Google Plus), (2) traditional media (television/radio, magazines, billboards), or (3) retail stores (convenience stores, mall kiosks, tobacco shops) was associated with subsequent e-cigarette use in a longitudinal cohort of adolescents. Data were drawn from longitudinal surveys conducted in fall 2013 (wave 1) and spring 2014 (wave 2) of a school-based cohort attending 3 high schools and 2 middle schools in Connecticut. Adolescents were asked about tobacco use behaviors and where they had recently seen e-cigarette advertising at wave 1. The authors used logistic regression to determine whether advertising exposure at wave 1 increased the odds of e-cigarette use by wave 2, controlling for demographics and cigarette smoking status at wave 1. Among those who have never used e-cigarettes in wave 1 (n = 1742), 9.6% reported e-cigarette use at wave 2. Multivariate logistic regression demonstrated that exposure to e-cigarette advertising on Facebook (OR 2.12 = $p < 0.02$) at wave 1, but not other venues, significantly increased the odds of subsequent e-cigarette use wave 2. Age, white race, and cigarette smoking at wave 1 also was associated with e-cigarette use at wave 2. This study provides one of the first longitudinal examinations demonstrating that exposure to e-cigarette advertising on social networking sites among youth who had never used e-cigarettes increases the likelihood of subsequent e-cigarette use.

Washington State Retail Marijuana Legalization: Parent and Adolescent Preferences For Marijuana Messages In A Sample Of Low-Income Families Hanson, Koren; Haggerty, Kevin P; Fleming, Charles B; Skinner, Martie L; Casey-Goldstein, Mary; Mason, W Alex; Thompson, Ronald W; Redmond, Cleve. J Stud Alcohol Drugs. 2018; 79(2): 309-317.
As legalization of nonmedical retail marijuana increases, states are implementing public health campaigns designed to prevent increases in youth marijuana use. This study investigated which types of marijuana-related messages were rated most highly by parents and their teens and whether these preferences differed by age and marijuana use. Nine marijuana-focused messages were developed as potential radio, newspaper, or television announcements. The messages fell into four categories: information about the law, general advice/conversation starters, consequences of marijuana use/positive alternatives, and information on potential harmful effects of teen marijuana use. The messages were presented through an online survey to 282 parent (84% female) and 283 teen (54% female) participants in an ongoing study in Washington State. Both parents and youth rated messages containing information about the law higher than other types of messages. Messages about potential harms of marijuana use were rated lower than other messages by both generations. Parents who had used marijuana within the past year (n = 80) rated consequence/positive alternative messages lower than parent nonusers (n = 199). Youth marijuana users (n = 77) and nonusers (n = 202) both rated messages containing information about the law higher than other types of messages. Youth users and nonusers were less likely than parents to believe messages on the harmful effects

of marijuana. The high ratings for messages based on information about the marijuana law highlight the need for informational health campaigns to be established as a first step in the marijuana legalization process.

Socioeconomic Status and Adolescent E-cigarette Use: The Mediating Role Of E-cigarette Advertisement Exposure Simon, Patricia; Camenga, Deepa R; Morean, Meghan E; Kong, Grace; Bold, Krysten W; Cavallo, Dana A; Krishnan-Sarin, Suchitra. Prev Med. 2018; 112: 193-198.
Among adolescents, low socioeconomic status (SES) is associated with greater exposure to tobacco cigarette advertising and cigarette use. However, associations among SES, e-cigarette advertising and e-cigarette use are not well understood. This study examined exposure to e-cigarette advertisements as a mediator of the relationship between SES and adolescent e-cigarette use. Adolescents (N = 3473; 51% Female) from 8 high schools in Connecticut completed an anonymous survey in Spring 2015. Mediation analysis was used to examine whether the total number of sources of recent e-cigarette advertising exposure (e.g., TV, radio, billboards, magazines, local stores [gas stations, convenience stores], vape shops, mall kiosks, tobacco shops, social media) mediated the association between SES (measured by the Family Affluence Scale) and past-month frequency of e-cigarette use. The authors clustered for school and controlled for other tobacco product use, age, sex, race/ethnicity and perceived social norms for e-cigarette use in the model. Their sample recently had seen advertisements via 2.1 (SD = 2.8) advertising channels. Mediation was supported (indirect effect: $\beta = 0.01$, SE = 0.00, 95% CI [0.001, 0.010], $p = 0.02$), such that higher SES was associated with greater recent advertising exposure, which, in turn, was associated with greater frequency of e-cigarette use. This study suggests that regulations to reduce youth exposure to e-cigarette advertisement may be especially relevant to higher SES youth. Future research should examine these associations longitudinally and evaluate which types of advertisements target different SES groups.

Prediction of Future Chronic Opioid Use Among Hospitalized Patients Calcaterra, S L; Scarbro, S; Hull, M L; Forber, A D; Binswanger, I A; Colborn, K L. J Gen Intern Med. 2018 Jun; 33: 898-905.
Opioids are commonly prescribed in the hospital; yet, little is known about which patients will progress to chronic opioid therapy (COT) following discharge. The authors defined COT as receipt of ≥ 90-day supply of opioids with < 30-day gap in supply over a 180-day period or receipt of ≥ 10 opioid prescriptions over 1 year. Predictive tools to identify hospitalized patients at risk for future chronic opioid use could have clinical utility to improve pain management strategies and patient education during hospitalization and discharge. The objective of this study was to identify a parsimonious statistical model for predicting future COT among hospitalized patients not on COT before hospitalization. Retrospective analysis electronic health record (EHR) data from 2008 to 2014 using logistic regression. Hospitalized patients at an urban, safety net hospital. Independent variables included medical and mental health diagnoses, substance and tobacco use disorder, chronic or acute pain, surgical intervention during hospitalization, past year receipt of opioid or non-opioid analgesics or benzodiazepines, opioid receipt at hospital discharge, milligrams of morphine equivalents prescribed per hospital day, and others. Model prediction performance was estimated using area under the receiver operator curve, accuracy, sensitivity, and specificity. A model with 13 covariates was chosen using stepwise logistic regression on a randomly down-sampled subset of the data. Sensitivity and specificity were optimized using the Youden's index. This model predicted correctly COT in 79% of the patients and no COT correctly in 78% of the patients. The authors' model accessed EHR data to predict 79% of the future COT among hospitalized patients. Application of such a predictive model within the EHR could identify patients

at high risk for future chronic opioid use to allow clinicians to provide early patient education about pain management strategies and, when able, to wean opioids prior to discharge while incorporating alternative therapies for pain into discharge planning.

Implementing A Mobile Health System To Integrate The Treatment Of Addiction Into Primary Care: A Hybrid Implementation-Effectiveness Study Quanbeck, Andrew; Gustafson, David H; Marsch, Lisa A; Chih, Ming-Yuan; Kornfield, Rachel; McTavish, Fiona; Johnson, Roberta; Brown, Randall T; Mares, Marie-Louise; Shah, Dhavan V. J Med Internet Res. 2018; 20(1): e37.

Despite the near ubiquity of mobile phones, little research has been conducted on the implementation of mobile health (mHealth) apps to treat patients in primary care. Although primary care clinicians routinely treat chronic conditions such as asthma and diabetes, they rarely treat addiction, a common chronic condition. Instead, addiction is most often treated in the US health care system, if it is treated at all, in a separate behavioral health system. mHealth could help integrate addiction treatment in primary care. The objective of this paper was to report the effects of implementing an mHealth system for addiction in primary care on both patients and clinicians. In this implementation research trial, an evidence-based mHealth system named Seva was introduced sequentially over 36 months to a maximum of 100 patients with substance use disorders (SUDs) in each of three federally qualified health centers (FQHCs; primary care clinics that serve patients regardless of their ability to pay). This paper reports on patient and clinician outcomes organized according to the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework. The outcomes according to the RE-AIM framework are as follows: Reach-Seva reached 8.31% (268/3226) of appropriate patients. Reach was limited by our ability to pay for phones and data plans for a maximum of 100 patients per clinic. Effectiveness-Patients who were given Seva had significant improvements in their risky drinking days (44% reduction, (0.7-1.25)/1.25, P=.04), illicit drug-use days (34% reduction, (2.14-3.22)/3.22, P=.01), quality of life, human immunodeficiency virus screening rates, and number of hospitalizations. Through Seva, patients also provided peer support to one another in ways that are novel in primary care settings. Adoption-Patients sustained high levels of Seva use-between 53% and 60% of the patients at the 3 sites accessed Seva during the last week of the 12-month implementation period. Among clinicians, use of the technology was less robust than use by patients, with only a handful of clinicians using Seva in each clinic and behavioral health providers making most referrals to Seva in 2 of the 3 clinics. Implementation-At 2 sites, implementation plans were realized successfully; they were delayed in the third. Maintenance-Use of Seva dropped when grant funding stopped paying for the mobile phones and data plans. Two of the 3 clinics wanted to maintain the use of Seva, but they struggled to find funding to support this. Implementing an mHealth system can improve care among primary care patients with SUDs, and patients using the system can support one another in their recovery. Among clinicians, however, implementation requires figuring out how information from the mHealth system will be used and making mHealth data available in the electronic health (eHealth) record. In addition, paying for an mHealth system remains a challenge.

Technology and Social Media Use Among Patients Enrolled In Outpatient Addiction Treatment Programs: Cross-Sectional Survey Study Ashford, Robert D; Lynch, Kevin; Curtis, Brenda. J Med Internet Res. 2018; 20(3): e84.

Substance use disorder research and practice have not yet taken advantage of emerging changes in communication patterns. While internet and social media use is widespread in the general population, little is known about how these mediums are used in substance use disorder treatment. The aims of this paper were to provide data on patients with substance use disorders mobile phone

ownership rates, usage patterns on multiple digital platforms (social media, internet, computer, and mobile apps), and their interest in the use of these platforms to monitor personal recovery. The authors conducted a cross-sectional survey of patients in 4 intensive outpatient substance use disorder treatment facilities in Philadelphia, PA, USA. Logistic regressions were used to examine associations among variables. Survey participants (N=259) were mostly male (72.9%, 188/259), African American (62.9%, 163/259), with annual incomes less than US $10,000 (62.5%, 161/259), and averaged 39 (SD 12.24) years of age. The vast majority of participants (93.8%, 243/259) owned a mobile phone and about 64.1% (166/259) owned a mobile phone with app capabilities, of which 85.1% (207/243) accessed the internet mainly through their mobile phone. There were no significant differences in age, gender, ethnicity, or socio-economic status by computer usage, internet usage, number of times participants changed their phone, type of mobile phone contract, or whether participants had unlimited calling plans. The sample was grouped into 3 age groups (Millennials, Generation Xers, and Baby Boomers). The rates of having a social media account differed across these 3 age groups with significant differences between Baby Boomers and both Generation Xers and Millennials (P<.001 in each case). Among participants with a social media account (73.6%, 190/259), most (76.1%, 144/190) reported using it daily and nearly all (98.2%, 186/190) used Facebook. Nearly half of participants (47.4%, 90/190) reported viewing content on social media that triggered substance cravings and an equal percentage reported being exposed to recovery information on social media. There was a significant difference in rates of reporting viewing recovery information on social media across the 3 age groups with Baby Boomers reporting higher rates than Millennials (P<.001). The majority of respondents (70.1%, 181/259) said they would prefer to use a relapse prevention app on their phone or receive SMS (short message service) relapse prevention text messages (72.3%, 186/259), and nearly half (49.1%, 127/259) expressed an interest in receiving support by allowing social media accounts to be monitored as a relapse prevention technique. To the authors' knowledge, this is the first and largest study examining the online behavior and preferences regarding technology-based substance use disorder treatment interventions in a population of patients enrolled in community outpatient treatment programs. Patients were generally receptive to using relapse prevention apps and text messaging interventions and a substantial proportion supported social media surveillance tools. However, the design of technology-based interventions remains as many participants have monthly telephone plans which may limit continuity.

Predictors of Daily Pain Medication Use in Individuals with Recurrent Back Pain Sturgeon, John A; Hah, Jennifer M; Sharifzadeh, Yasamin; Middleton, Stephanie K; Rico, Thomas; Johnson, Kevin A; Mackey, Sean C. Int J Behav Med; 2018 Apr; 25: 252-258.
A key component to chronic pain management regimens is the use of analgesic medications. Psychological factors, such as mood states, may also affect the use of pain medications for individuals with chronic pain, but few observational studies have examined how these factors may predict pain medication use at the daily level. Daily assessments from 104 individuals with back pain were used to examine fluctuations in daily pain intensity, mood, sleep quality, and physical activity as predictors of the likelihood of pain medication (opioid and non-opioid) use and levels of medication use on the same day. Pain intensity and mood ratings significantly predicted whether participants used pain medication on the same day, while only pain intensity predicted whether participants used more medication than usual. Further, current opioid users were more likely to increase the amount of their medication use on days of higher pain. This article identifies fluctuations in daily pain intensity and mood as salient predictors of daily pain medication use in individuals with recurrent back pain. The current study is among the first to highlight both pain and mood states as predictors of daily pain medication use in individuals with back pain, though future

studies may expand on these findings through the use of higher-resolution daily medication use variables.

TREATMENT RESEARCH

An RCT With The Combination Of Varenicline and Bupropion For Smoking Cessation: Clinical Implications For Front Line Use Cinciripini, Paul M; Minnix, Jennifer A; Green, Charles E; Robinson, Jason D; Engelmann, Jeffrey M; Versace, Francesco; Wetter, David W; Shete, Sanjay; Karam-Hage, Maher. Addiction. 2018.
Despite the availability of several efficacious smoking cessation treatments, fewer than 25% of smokers who quit remain abstinent 1year post-treatment. This study aimed to determine if varenicline and bupropion combination treatment would result in higher abstinence rates than varenicline alone. A double-blind, randomized, parallel-group smoking cessation clinical trial in which participants were exposed to 12 weeks of treatment and followed for 12 months. Hospital-based out-patient clinic in Texas, USA specializing in cancer prevention. A total of 385 community smokers (58.44% male) who smoked 1 pack of cigarettes/day [mean = 19.66 cigarettes/day, standard deviation (SD) = 9.45]; had average carbon monoxide (CO) of 26.43 parts per million (SD = 13.74); and were moderately dependent (Fagerström Test for Cigarette Dependence = 4.79; SD = 2.07).Smokers were randomized in a 3 : 1 (active: Placebo) ratio to 12 weeks of treatment as follows: placebo (n = 56), varenicline (Var; n = 166), and varenicline + bupropion (Combo; n = 163).A priori primary outcome: prolonged abstinence at 12 months.7-day point prevalence abstinence and continuous abstinence; all abstinence measures at end of treatment and 6-month follow-ups. Intention-to-treat analysis: the Combo group (n = 163) failed to demonstrate superiority to the Var group (n = 166) for prolonged abstinence at 12 months [odds ratio (OR) = 0.91, 95% confidence interval (CI) = 0.50-1.64], supported by Bayes factor = 0.06. Both the Var (OR = 6.66, 95% CI = 1.61-59.27) and Combo groups (OR = 6.06, 95% CI = 1.45-54.09) demonstrated superiority to the Placebo group (n = 56; score = 8.38, P < 0.016). The addition of bupropion to varenicline treatment does not appear to increase smoking abstinence rates above that of varenicline alone. The findings support previous research showing a consistently favorable effect of both varenicline and the combination of varenicline and bupropion on smoking cessation compared with placebo.

Concurrent Assessment Of the Antinociceptive and Behaviorally Disruptive Effects Of Opioids In Squirrel Monkeys Withey, Sarah L; Paronis, Carol A; Bergman, Jack. J Pain. 2018; 19(7): 728-740.
Although the clinical application of opioids for pain management is often hindered by undesired behavioral impairment, preclinical assays of antinociception typically do not provide information regarding the behaviorally disruptive effects of opioids that may accompany their antinociceptive effects. To address this, the authors modified a warm water tail withdrawal procedure to determine concurrently the effects of opioids on tail withdrawal latency (antinociception) and indices of food-maintained operant behavior (rates of responding and reinforcement density) in squirrel monkeys. Six opioid agonists were tested, and all produced dose-dependent antinociception and impairment of operant behavior. The ratio of median effective dose (ED50) values for both measures (behavioral impairment:antinociception) was used as a quantitative measure of therapeutic index. Nalbuphine had the highest ED50 ratio (4.88), reflecting antinociception with minimal behavioral disruption. Oxycodone, heroin, buprenorphine, and methadone all produced similar ED50 ratios (.82-1.14), whereas butorphanol yielded a significantly lower ED50 ratio (.17) reflecting behavioral disruption

at doses producing only minimal antinociception. The antinociceptive and behaviorally disruptive effects of oxycodone and buprenorphine were further characterized using Schild analysis to calculate apparent pA2 values for antagonism of the 2 drugs by naltrexone. These analyses suggest that μ-receptor mechanisms likely mediate the antinociceptive as well as behaviorally disruptive effects of oxycodone (pA2 values: 8.13 and 8.57) and buprenorphine (pA2 values: 8.6 and 7.9). This article presents an assay that allows for the concurrent assessment of the antinociceptive and behaviorally disruptive effects of opioids. These results show that the tail withdrawal assay in squirrel monkeys can provide a useful index of the behavioral selectivity with which opioids produce antinociception.

Opioid Dose- and Route-Dependent Efficacy Of Oxycodone and Heroin Vaccines In Rats
Raleigh, Michael D; Laudenbach, Megan; Baruffaldi, Federico; Peterson, Samantha J; Roslawski, Michaela J; Birnbaum, Angela K; Carroll, F Ivy; Runyon, Scott P; Winston, Scott; Pentel, Paul R; Pravetoni, Marco. J Pharmacol Exp Ther. 2018; 365(2): 346-353.
Heroin and oxycodone abuse occurs over a wide range of drug doses and by various routes of administration characterized by differing rates of drug absorption. The current study addressed the efficacy of a heroin vaccine [morphine hapten conjugated to keyhole limpet hemocyanin (M-KLH)] or oxycodone vaccine [oxycodone hapten conjugated to keyhole limpet hemocyanin (OXY-KLH)] for reducing drug distribution to brain after intravenous heroin or oxycodone, or subcutaneous oxycodone. Rats immunized with M-KLH or keyhole limpet hemocyanin (KLH) control received an intravenous bolus dose of 0.26 or 2.6 mg/kg heroin. Vaccination with M-KLH increased retention of heroin and its active metabolites 6-acetylmorphine (6-AM) and morphine in plasma compared with KLH controls, and reduced total opioid (heroin + 6-AM + morphine) distribution to brain but only at the lower heroin dose. Immunization also protected against respiratory depression at the lower heroin dose. Rats immunized with OXY-KLH or KLH control received 0.22 or 2.2 mg/kg oxycodone intravenously, the molar equivalent of the heroin doses. Immunization with OXY-KLH significantly reduced oxycodone distribution to brain after either oxycodone dose, although the magnitude of effect of immunization at the higher oxycodone dose was small (12%). By contrast, vaccination with OXY-KLH was more effective when oxycodone was administered subcutaneously rather than intravenously, reducing oxycodone distribution to brain by 44% after an oxycodone dose of 2.3 mg/kg. Vaccination also reduced oxycodone-induced antinociception. These data suggest that the efficacy of OXY-KLH and M-KLH opioid vaccines is highly dependent upon opioid dose and route of administration.

Approach Bias Modification For Cannabis Use Disorder: A Proof-of-principle Study Sherman, Brian J; Baker, Nathaniel L; Squeglia, Lindsay M; McRae-Clark, Aimee L. J Subst Abuse Treat. 2018; 87: 16-22.
More effective treatments for cannabis use disorder (CUD) are needed. Evidence suggests that biases in cognitive processing of drug-related stimuli are central to the development and maintenance of addiction. The current study examined the feasibility and effect of a novel intervention - approach bias modification (ApBM) - on cannabis approach bias and cue-reactivity. A randomized, double-blind, sham-controlled proof-of-principle laboratory experiment investigated the effect of a four-session computerized ApBM training protocol on cannabis approach bias and cue-reactivity in non-treatment seeking adults age 18-65 with CUD (N = 33). ApBM procedures involved responding to cannabis or neutral stimuli using a computer joystick to model approach or avoidance behavior. Reactivity to tactile, olfactory, and auditory cue sets was assessed with physiological (blood pressure and heart rate) and subjective (cannabis craving) measures. Cannabis use was assessed via self-report. Participants receiving ApBM showed blunted cannabis cue-

induced craving at the end of training compared to those in the sham-ApBM condition (p = .05). A preliminary gender effect on cannabis use was also found; men receiving ApBM reported fewer cannabis use sessions per day at the end of training compared to women (p = .02), while there were no differences between men and women in the sham condition. ApBM did not attenuate cannabis approach bias following training.Preliminary results indicate that ApBM may be efficacious in reducing cannabis cue-reactivity and improving cannabis use outcomes. While encouraging, the results should be interpreted with caution. Investigation of ApBM as an adjunct to psychosocial treatments for treatment-seeking adults with CUD is warranted.

Influence Of Tiagabine Maintenance On Cannabis Effects and Related Behaviors In Daily Cannabis Users Wesley, Michael J; Westgate, Philip M; Stoops, William W; Kelly, Thomas H; Hays, Lon R; Lile, Joshua A. Exp Clin Psychopharmacol. 2018; 26(3): 310-319.
No medications are approved for cannabis use disorder (CUD). Gamma-aminobutyric acid (GABA) reuptake is modulated by cannabinoid (CB) receptor agonists, and there are shared effects between CB agonists and the GABA reuptake inhibitor tiagabine. This overlapping neuropharmacology suggested that tiagabine might be useful for CUD. The study determined the ability of tiagabine maintenance to reduce cannabis self-administration using a placebo-controlled, double-blind, counterbalanced, within-subjects design. Nontreatment-seeking daily cannabis users (N = 12; 3 female, 9 male) completed two 12-day outpatient maintenance phases (0 or 12 mg of tiagabine/day). Each phase consisted of a safety session, 7 maintenance days, and 4 experimental sessions. During experimental sessions, maintenance continued and participants completed two 2-day blocks of sampling and self-administration sessions to determine the reinforcing effects of smoked cannabis (0% and 5.9% Δ9-tetrahydrocannabinol). Naturalistic cannabis use, the subjective, performance and physiological response to cannabis, as well as side effects, sleep quality, craving, other self-reported substance use, and observer ratings were also measured. Cannabis functioned as a reinforcer and produced prototypical effects (e.g., increased heart rate and ratings of "high"), but tiagabine generally did not impact the effects of cannabis, or alter naturalistic use. Furthermore, tiagabine produced small, but significant, increases on 2 subscales of a Marijuana Craving Questionnaire, and reductions in both the amount of time slept in the past 24 hr and ratings of positive mood upon awakening. These human laboratory results from a sample of nontreatment-seeking cannabis users do not support the potential efficacy of 12 mg of tiagabine as a stand-alone pharmacotherapy for CUD.

A Preliminary Investigation Into the Effects Of Doxazosin On Cognitive Functioning In Tobacco-deprived and -satiated Smokers Roberts, Walter; Verplaetse, Terril L; Moore, Kelly E; Oberleitner, Lindsay M; McKee, Sherry A. Hum Psychopharmacol. 2018; 33(3): e2660.
The objective of this study was to test the effects of doxazosin, an α1 antagonist, on cognitive functioning during tobacco withdrawal in smokers. Participants (n = 35) were randomly assigned to receive placebo, 4-mg/day, or 8-mg/day doxazosin. They completed a continuous performance task and self-reported their withdrawal symptoms at baseline and twice following a medication titration period: once in a tobacco-deprived state and again in a nondeprived state. Ability to resist smoking was assessed using a laboratory smoking-lapse paradigm. Participants showed poorer cognitive performance on most measures taken from the continuous performance task when tobacco deprived. Eight-mg/day doxazosin improved inhibitory control during the nondeprivation session but did not affect sustained attention or reaction time. Participants receiving doxazosin reported fewer withdrawal symptoms during deprivation than those on placebo. Those showing the greatest improvement of inhibitory control under doxazosin were better able to resist smoking (i.e., latency to smoke) during a smoking lapse task. Self-reported withdrawal symptoms also were negatively

associated with time to smoking. Doxazosin reduced symptoms of tobacco withdrawal according to self-report and cognitive assessment and improved inhibitory control above predrug levels. This research identifies potential mechanisms by which doxazosin might improve smoking outcomes.

HIV/AIDS RELATED RESEARCH

Influence Of Injection Drug Use-Related HIV Acquisition On CD4 Response To First Antiretroviral Therapy Regimen Among Virally Suppressed Individuals Calkins, Keri L; Lesko, Catherine R; Chander, Geetanjali; Moore, Richard D; Lau, Bryan. J Acquir Immune Defic Syndr. 2018; 77(3): 317-324.

The inflammatory effects of injection drug use (IDU) may result in an impaired immune response to antiretroviral therapy (ART). The authors examined CD4 response to first ART regimen among individuals in routine HIV care, stratified by IDU-related HIV acquisition. This was a cohort study including patients who initiated ART between 2000 and 2015 in the Johns Hopkins HIV Clinic. The authors followed individuals from ART initiation until death, loss to follow-up, loss of viral load suppression (<500 copies/mL), or administrative censoring. They described CD4 trajectories after ART initiation using inverse probability weighted quantile regression models with restricted cubic splines for time. Weights accounted for differences in baseline characteristics of persons comparing those with IDU-related HIV acquisition to those with other HIV acquisition risks (non-IDU) and possible nondifferential censoring due to death, loss to follow-up, or loss of viral load suppression. The authors also examined CD4 response by strata of CD4 at ART initiation (≤200, 201-350, >350).Of 1244 patients initiating ART, 30.4% were IDU. Absolute CD4 cell difference at the 50th percentile comparing IDU with non-IDU was -25 cells [95% confidence interval (CI): -63 to 35], -66 cells (95% CI: -141 to 16), and -91 cells (95% CI: -190 to -5) at 2, 4, and 6 years after ART initiation, respectively. Results were similar (non-IDU with slightly higher CD4 count, but not statistically significant differences) at other percentiles and stratified by baseline CD4.CD4 recovery after ART initiation was similar for IDU and non-IDU, conditional on consistent viral load suppression.

Missed Opportunities For HIV Testing Among STD Clinic Patients Traynor, Sharleen M; Rosen-Metsch, Lisa; Feaster, Daniel J. J Community Health. 2018.

Current HIV testing guidelines recommend that all adolescents and adults aged 13-64 be routinely screened for HIV in healthcare settings. Sexually transmitted disease (STD) clinic patients represent a population at increased risk for HIV, justifying more frequent risk assessment and testing. This analysis describes missed opportunities for HIV testing among a sample of STD clinic patients to identify areas where HIV testing services may be improved. Secondary analysis was conducted using data from Project AWARE, a randomized trial of 5012 adult patients from 9 STD clinics in the United States, enrolled April-December 2010. HIV testing history, healthcare service utilization, and behavioral risks were obtained through audio computer-assisted self-interview. Missed opportunities for HIV testing, defined as having a healthcare visit but no HIV test in the last 12 months, were characterized by location and frequency. Of 2315 (46.2%) participants not tested for HIV in the last 12 months, 1715 (74.1%) had a missed opportunity for HIV testing. These missed opportunities occurred in both traditional (54.9% at family doctor, 20.3% at other medical doctor visits) and non-traditional (28.5% at dental, 19.0% at eye doctor, 13.9% at correctional facility, and 13.3% at psychology visits) testing settings. Of 53 participants positive for HIV at baseline, 16 (30.2%) had a missed testing opportunity. Missed opportunities for HIV testing were

common in this population of STD clinic patients. There is a need to increase routinized HIV screening and expand testing services to a broader range of healthcare settings.

Extended-Release Naltrexone Improves Viral Suppression Among Incarcerated Persons Living With HIV With Opioid Use Disorders Transitioning To The Community: Results Of A Double-Blind, Placebo-Controlled Randomized Trial Springer SA, Di Paola A, Azar MM, Barbour R, Biondi BE, Desabrais M, Lincoln T, Skiest DJ, Altice FL. J Acquir Immune Defic Syndr. 2018; 78(1): 43-53.
To determine whether extended-release naltrexone (XR-NTX) would improve or maintain viral suppression (VS) among prisoners or jail detainees with HIV and opioid use disorder (OUD) transitioning to the community a 4-site, prospective randomized double-blind, placebo-controlled trial was conducted among prison and jail inmates with HIV and OUD transitioning to the community from September 2010 through March 2016. Eligible participants (N = 93) were randomized 2:1 to receive 6 monthly injections of XR-NTX (n = 66) or placebo (n = 27) starting at release and observed for 6 months. The primary outcome was the proportion that maintained or improved VS (<50 copies/mL) from baseline to 6 months. Participants allocated to XR-NTX significantly improved to VS (<50 copies/mL) from baseline (37.9%) to 6 months (60.6%) (P = 0.002), whereas the placebo group did not (55.6% at baseline to 40.7% at 6 months P = 0.294). There was, however, no statistically significant difference in VS levels at 6 months between XR-NTX (60.6%) vs. placebo (40.7%) (P = 0.087). After controlling for other factors, only allocation to XR-NTX (adjusted odds ratio = 2.90; 95% confidence interval = 1.04 to 8.14, P = 0.043) was associated with the primary outcome. Trajectories in VS from baseline to 6 months differed significantly (P = 0.017) between treatment groups, and the differences in the discordant values were significantly different as well (P = 0.041): the XR-NTX group was more likely than the placebo group to improve VS (30.3% vs. 18.5%), maintain VS (30.3% vs. 27.3), and less likely to lose VS (7.6% vs. 33.3%) by 6 months. XR-NTX improves or maintains VS after release to the community for incarcerated people living with HIV with OUD.

Reducing Opioid Overdose In Kazakhstan: A Randomized Controlled Trial Of A Couple-based Integrated HIV/HCV and Overdose Prevention Intervention "Renaissance" Gilbert, Louisa; Hunt, Timothy; Primbetova, Sholpan; Terlikbayeva, Assel; Chang, Mingway; Wu, Elwin; McCrimmon, Tara; El-Bassel, Nabila. Int J Drug Policy. 2018; 54: 105-113.
The aim of this study was to evaluate the efficacy of a couple-based integrated HIV/HCV and overdose prevention intervention on non-fatal and fatal overdose and overdose prevention behaviors among people who use heroin or other opioids in Almaty, Kazakhstan. The authors selected 479 participants who reported lifetime heroin or opioid use from a sample of 600 participants (300 couples) enrolled in a randomized controlled trial (RCT) conducted between May 2009 and February 2013. Participants were randomized to either (1) a 5-session couple-based HIV/HCV and overdose prevention intervention condition or (2) a 5-session Wellness Promotion and overdose prevention comparison condition. The authors used multilevel mixed-effects model with modified Poisson regression to estimate effects of the intervention as risk ratios (RR) and the corresponding 95% CIs. About one-fifth (21.9%) of the sample reported that they had experienced an opioid overdose in the past 6 months at baseline. At the 12-month follow-up, both the intervention and comparison conditions reported significant reductions in non-fatal overdose and injection heroin/opioid use and significant increases in drug treatment attendance and naloxone use to prevent death from overdose. However, the authors found no differences between the study arms on any of these outcomes. There were three intervention condition participants (1.3%), compared to seven comparison condition participants (2.9%) who died from opioid overdose during the 12-month

follow up period although this difference was not significant. There were no significant conditions on any outcomes: both conditions showed promising effects of reducing non-fatal overdose and overdose risks. Integrating overdose prevention into a couple-based HIV/HCV intervention may be an efficient strategy to target the syndemic of opioid overdose, HIV and HCV in Kazakhstan.

CTN-RELATED RESEARCH

Prevalence of Behavioral Health Conditions Across Frequency of Cannabis Use Among Adult Primary Care Patients in Washington State Lapham GT, Lee AK, Caldeiro RM, Glass JE, Carrell DS, Richards JE, Bradley KA. J Gen Intern Med. 2018 Jul 10. doi: 10.1007/s11606-018-4558-8. [Epub ahead of print].
Individuals who use cannabis have increased risk of behavioral health conditions, including depression, anxiety, and tobacco, alcohol, and other substance use disorders, but little is known about the association between frequency of cannabis use and behavioral health conditions among primary care patients. This population-based study of primary care patients reports on the prevalence of common behavioral health conditions across cannabis use frequency. Kaiser Permanente Washington, a large health system in Washington State where medical and nonmedical cannabis use is legal, implemented annual behavioral health screening, including a single-item about the frequency of past-year cannabis use, in three primary care sites beginning March 2015. Data are from electronic health record (EHR) and claims. Tobacco and unhealthy alcohol use were most common among young adult patients who reported daily and any past-year cannabis use, respectively. Among patients who used cannabis daily, nearly 50% reported depression symptoms and more than 35% had a past-year mental health disorder diagnosis. Integrating routine assessment of cannabis use into primary behavioral health care will become increasingly important to understand patients' needs as legalization expands.

Enhancing Patient Navigation with Contingent Incentives to Improve Healthcare Behaviors and Viral Load Suppression of Persons with HIV and Substance Use Stitzer ML, Hammond AS, Matheson T, Sorensen JL, Feaster DJ, Duan R, Gooden L, Del Rio C, Metsch LR. AIDS Patient Care STDS. 2018 Jul;32(7):288-296. doi: 10.1089/apc.2018.0014. Epub 2018 Jun 8.
This secondary analysis compares health behavior outcomes for two groups of HIV+ substance users randomized in a 3-arm trial [1] to receive Patient Navigation with (PN+CM) or without (PN) contingent financial incentives (CM). Mean age of participants was 45 years; the majority was male (67%), African American (78%), unemployed (35%), or disabled (50%). Behaviors incentivized for PN+CM were (1) attendance at HIV care visits and (2) verification of an active HIV medication prescription. Incentives were associated with shorter time to treatment initiation and higher rates of behaviors during the 6-month intervention with exception of month 6 HIV care visits. Median HIV care visits were 3 (IQR 2-4) for PN+CM versus 1.5 (IQR 0-3) for PN (Wilcoxon $p < 0.001$); median validated medication checks were 4 (IQR 2-6) for PN+CM versus 1 (IQR 0-3) for PN (Wilcoxon $p < 0.001$). Viral suppression rates at end of treatment were not significantly different for the two groups but were directly related to the number of behaviors completed for both care visits ($\chi^2(1) = 7.69$, $p = 0.006$) and validated medication ($\chi^2(1) = 8.49$, $p = 0.004$). Results support use of incentives to increase performance of key healthcare behaviors. Adjustments to the incentive program may be needed to achieve greater rates of sustained health behavior change that result in improved viral load outcomes.

Sex Differences In Opioid Use and Medical Issues During Buprenorphine/Naloxone Treatment Barbosa-Leiker C, McPherson S, Layton ME, Burduli E, Roll JM, Ling W. Am J Drug Alcohol Abuse. 2018;44(4):488-496. doi: 10.1080/00952990.2018.1458234. Epub 2018 Apr 19.
There are sex differences in buprenorphine/naloxone clinical trials for opioid use. While women have fewer opioid-positive urine samples, relative to men, a significant decrease in opioid-positive samples was found during treatment for men, but not women. In order to inform sex-based approaches to improve treatment outcomes, research is needed to determine if opioid use, and predictors of opioid use, differs between men and women during treatment. The objectives of this study were to test for sex differences in opioid use during a buprenorphine/naloxone clinical trial and determine if sex differences exist in the associations between addiction-related problem areas and opioid use over the course of the trial. This secondary data analysis of the National Drug Abuse Treatment Clinical Trials Network (CTN) 0003 examined sex differences (men = 347, women = 169) in opioid-positive samples in a randomized clinical trial comparing 7-day vs. 28-day buprenorphine/naloxone tapering strategies. Addiction-related problem areas were defined by Addiction Severity-Lite (ASI-L) domain composite scores. Women were more likely than men to use opioids during the course of the buprenorphine/naloxone clinical trial (B = .33, p = .01) and medical issues were positively related to submitting an opioid-positive sample during treatment for women (B = 1.67, p = .01). No ASI-L domain composite score was associated with opioid-positive samples during treatment for men. The authors conclude that women were more likely than men to use opioids during the course of the buprenorphine/naloxone clinical trial, and medical issues predicted opioid use during treatment for women but not men. Complementary treatment for medical problems during opioid replacement therapy may benefit women.

The Effect Of N-Acetylcysteine On Alcohol Use During A Cannabis Cessation Trial Squeglia LM, Tomko RL, Baker NL, McClure EA, Book GA, Gray KM. Drug Alcohol Depend. 2018 Apr 1;185:17-22. doi: 10.1016/j.drugalcdep.2017.12.005. Epub 2018 Feb 1.
Individuals with alcohol use disorder (AUD) do not always respond to currently available treatments, and evaluation of new candidate pharmacotherapies is indicated. N-acetylcysteine (NAC), an over-the-counter supplement, has shown promise in treating a variety of substance use disorders, but little research has evaluated its merits as a treatment for AUD. This secondary analysis from the National Drug Abuse Treatment Clinical Trials Network examined the effects of NAC versus placebo on alcohol use among participants with cannabis use disorder (CUD) enrolled in a 12-week, multi-site cannabis cessation trial. Participants (N = 302, ages 18-50) were randomized to double-blind NAC (1200 mg, twice daily) or placebo. Neither alcohol use nor desire for alcohol cessation were requirements for participation. Participants that returned for at least one treatment visit and had recorded alcohol use data (i.e., total drinks per week, drinking days per week, and binge drinking days per week) were included in the analysis (n = 277). Compared to the placebo group, participants in the NAC group had increased odds of between-visit alcohol abstinence [OR = 1.37; 95% CI = 1.06-1.78; p = 0.019], fewer drinks per week [RR = 0.67; 95% CI = 0.48-0.99; p = 0.045], and fewer drinking days per week [RR = 0.69; 95% CI = 0.51-0.92; p = 0.014]. Changes in concurrent cannabis use amounts were not correlated to any of the alcohol use variables. These findings indicate that NAC may be effective at reducing consumption of alcohol by ~30% among treatment-seeking adults with CUD, suggesting a need for further trials focused on the effects of NAC on alcohol consumption among individuals seeking treatment for AUD.

Barriers and Facilitators Affecting the Implementation Of Substance Use Screening In Primary Care Clinics: A Qualitative Study Of Patients, Providers, and Staff McNeely J, Kumar PC, Rieckmann T, Sedlander E, Farkas S, Chollak C, Kannry JL, Vega A, Waite EA, Peccoralo LA, Rosenthal RN, McCarty D, Rotrosen J. Addict Sci Clin Pract. 2018 Apr 9;13(1):8. doi: 10.1186/s13722-018-0110-8.

Alcohol and drug use are leading causes of morbidity and mortality that frequently go unidentified in medical settings. As part of a multi-phase study to implement electronic health record-integrated substance use screening in primary care clinics, the authors interviewed key clinical stakeholders to identify current substance use screening practices, barriers to screening, and recommendations for its implementation. Focus groups and individual interviews were conducted with 67 stakeholders, including patients, primary care providers (faculty and resident physicians), nurses, and medical assistants, in two urban academic health systems. Themes were identified using an inductive approach, revised through an iterative process, and mapped to the Knowledge to Action (KTA) framework, which guides the implementation of new clinical practices (Graham et al. in J Contin Educ Health Prof 26(1):13-24, 2006). Factors affecting implementation based on KTA elements were identified from participant narratives. Identifying the problem: Participants consistently agreed that having knowledge of a patient's substance use is important because of its impacts on health and medical care, that substance use is not properly identified in medical settings currently, and that universal screening is the best approach. Assessing barriers: Patients expressed concerns about consequences of disclosing substance use, confidentiality, and the individual's own reluctance to acknowledge a substance use problem. Barriers identified by providers included individual-level factors such as lack of clinical knowledge and training, as well as systems-level factors including time pressure, resources, lack of space, and difficulty accessing addiction treatment. Adapting to the local context: Most patients and providers stated that the primary care provider should play a key role in substance use screening and interventions. Opinions diverged regarding the optimal approach to delivering screening, although most preferred a patient self-administered approach. Many providers reported that taking effective action once unhealthy substance use is identified is crucial. Participants expressed support for substance use screening as a valuable part of medical care, and identified individual-level as well as systems-level barriers to its implementation. These findings suggest that screening programs should clearly communicate the goals of screening to patients and proactively counteract stigma, address staff concerns regarding time and workflow, and provide education as well as treatment resources to primary care providers.

INTRAMURAL RESEARCH

Synaptic Plasticity Section, Cellular Neurobiology Research Branch

Ventral Midbrain Astrocytes Display Unique Physiological Features and Sensitivity To Dopamine D2 Receptor Signaling Xin W, Schuebel KE, Jair K, Cimbro R, De Biase LM, Goldman D, Bonci A. Neuropsychopharmacology (2018) 13 July 2018.

Astrocytes are ubiquitous CNS cells that support tissue homeostasis through ion buffering, neurotransmitter recycling, and regulation of CNS vasculature. Yet, despite the essential functional roles they fill, very little is known about the physiology of astrocytes in the ventral midbrain, a region that houses dopamine-releasing neurons and is critical for reward learning and motivated behaviors. Here, using a combination of whole-transcriptome sequencing, histology, slice electrophysiology, and calcium imaging, the authors performed the first functional and molecular profiling of ventral midbrain astrocytes and observed numerous differences between these cells and

their telencephalic counterparts, both in their gene expression profile and in their physiological properties. Ventral midbrain astrocytes have very low membrane resistance and inward-rectifying potassium channel-mediated current, and are extensively coupled to surrounding oligodendrocytes through gap junctions. They exhibit calcium responses to glutamate but are relatively insensitive to norepinephrine. In addition, their calcium activity can be dynamically modulated by dopamine D2 receptor signaling. Taken together, these data indicate that ventral midbrain astrocytes are physiologically distinct from astrocytes in cortex and hippocampus. This work provides new insights into the extent of functional astrocyte heterogeneity within the adult brain and establishes the foundation for examining the impact of regional astrocyte differences on dopamine neuron function and susceptibility to degeneration.

Drug Design and Synthesis Section, Molecular Targets and Medications Discovery Branch

A Rapid Solution-Based Method For Determining the Affinity Of Heroin Hapten-Induced Antibodies To Heroin, Its Metabolites, and Other Opioids Torres OB, Duval AJ, Sulima A, Antoline JFG, Jacobson AE, Rice KC, Alving CR, Matyas GR. Anal Bioanal Chem. 2018 Jun;410(16):3885-3903.
The authors describe for the first time a method that utilizes microscale thermophoresis (MST) technology to determine polyclonal antibody affinities to small molecules. Using a novel type of heterologous MST, they have accurately measured a solution-based binding affinity of serum antibodies to heroin which was previously impossible with other currently available methods. Moreover, this mismatch approach (i.e., using a cross-reactive hapten tracer) has never been reported in the literature. When compared with equilibrium dialysis combined with ultra-performance liquid chromatography/tandem mass spectrometry (ED-UPLC/MS/MS), this novel MST method yields similar binding affinity values for polyclonal antibodies to the major heroin metabolites 6-AM and morphine. Additionally, the authors herein report the method of synthesis of this novel cross-reactive hapten, MorHap-acetamide-a useful analog for the study of heroin hapten-antibody interactions. Using heterologous MST, they were able to determine the affinities, down to nanomolar accuracies, of polyclonal antibodies to various abused opioids. While optimizing this method, the authors further discovered that heroin is protected from serum esterase degradation by the presence of these antibodies in a concentration-dependent manner. Lastly, using affinity data for a number of structurally different opioids, they were able to dissect the moieties that are crucial to antibody binding. The novel MST method that is presented herein can be extended to the analysis of any ligand that is prone to degradation and can be applied not only to the development of vaccines to substances of abuse but also to the analysis of small molecule/protein interactions in the presence of serum. Graphical abstract Strategy for the determination of hapten-induced antibody affinities using Microscale thermophoresis.

Molecular Neuropsychiatry Research Branch

Selective Activation of Striatal NGF-TrkA/p75NTR/MAPK Intracellular Signaling in Rats That Show Suppression of Methamphetamine Intake 30 Days following Drug Abstinence Torres OV, Jayanthi S, McCoy MT, Cadet JL. Int J Neuropsychopharm, 2018 Mar 1;21(3):281-290.
The continuing epidemic of methamphetamine addiction has prompted research aimed at understanding striatal dysfunctions potentially associated with long-term methamphetamine use.

Here, the authors investigated transcriptional and translational alterations in the expression of neurotrophic factors in the rat striatum at 30 days following methamphetamine self-administration and footshock punishment. Male Sprague-Dawley rats were trained to self-administer methamphetamine (0.1 mg/kg/injection, i.v.) or saline during twenty-two 9-hour sessions. Subsequently, rats were subjected to incremental footshocks for 13 additional methamphetamine self-administration sessions. This paradigm led to the identification of rats with shock-resistant and shock-sensitive phenotypes. Thirty days following the last footshock session, the dorsal striatum was dissected and processed for gene expression and protein analyses. PCR arrays revealed significant differences in neurotrophins and their receptors between the 2 phenotypes. Brain-derived neurotrophic factor and nerve growth factor protein levels were increased in the dorsal striatum of both shock-resistant and shock-sensitive rats. However, neurotrophic receptor tyrosine kinase 1 phosphorylation and nerve growth factor receptor protein expression were increased only in the shock-sensitive phenotype. Moreover, shock-sensitive rats showed increased abundance of several phosphorylated proteins known to participate in Ras/Raf/MEK/ERK signaling cascade including cRaf, ERK1/2, MSK1, and CREB. These findings support the notion that animals with distinct phenotypes for methamphetamine intake in the presence of adverse consequences also display differential changes in an intracellular signaling cascade activated by nerve growth factor-TrkA/p75NTR interactions. Thus, the development of pharmacological agents that can activate nerve growth factor-dependent pathways may be a promising therapeutic approach to combat methamphetamine addiction.

Neuronal Ensembles in Addiction Section, Behavioral Neuroscience Branch

Bidirectional Modulation Of Intrinsic Excitability In Rat Prelimbic Cortex Neuronal Ensembles and Non-Ensembles After Operant Learning Whitaker LR, Warren BL, Venniro M, Harte TC, McPherson KB, Beidel J, Bossert JM, Shaham Y, Bonci A, Hope BT. J. Neurosci. 2017 Sep 6;37(36):8845-8856.

Learned associations between environmental stimuli and rewards drive goal-directed learning and motivated behavior. These memories are thought to be encoded by alterations within specific patterns of sparsely distributed neurons called neuronal ensembles that are activated selectively by reward-predictive stimuli. Here, the authors use the Fos promoter to identify strongly activated neuronal ensembles in rat prelimbic cortex (PLC) and assess altered intrinsic excitability after 10 d of operant food self-administration training (1 h/d). First, they used the Daun02 inactivation procedure in male FosLacZ-transgenic rats to ablate selectively Fos-expressing PLC neurons that were active during operant food self-administration. Selective ablation of these neurons decreased food seeking. The authors then used male FosGFP-transgenic rats to assess selective alterations of intrinsic excitability in Fos-expressing neuronal ensembles (FosGFP+) that were activated during food self-administration and compared these with alterations in less activated non-ensemble neurons (FosGFP-). Using whole-cell recordings of layer V pyramidal neurons in an ex vivo brain slice preparation, the authors found that operant self-administration increased excitability of FosGFP+ neurons and decreased excitability of FosGFP- neurons. Increased excitability of FosGFP+ neurons was driven by increased steady-state input resistance. Decreased excitability of FosGFP- neurons was driven by increased contribution of small-conductance calcium-activated potassium (SK) channels. Injections of the specific SK channel antagonist apamin into PLC increased Fos expression but had no effect on food seeking. Overall, operant learning increased intrinsic excitability of PLC Fos-expressing neuronal ensembles that play a role in food seeking but decreased intrinsic excitability of Fos- non-ensembles.

RAPT Unit, Clinical Pharmacology and Therapeutics Research Branch

Does Human Language Limit Translatability Of Clinical and Preclinical Addiction Research? de Wit H, Epstein DH, and Preston KL. Neuropsychopharmacology, epub 2018, doi:10.1038/s41386-018-0095-8.

Great progress has been made in animal models of addiction—specifically, incorporation of features such as the conflicting drives or delayed outcomes that characterize human drug use. As these models improve, they are likely to collide with an important limitation: the inability of nonhuman animals to learn through language. In humans, language is a fast lane for acquiring knowledge about the multitude of proximal and distal outcomes that inform initiation, continuation, and cessation of drug use. Language less animals can learn about complex outcomes of drug use, but only through direct experience. The two forms of learning - learning by experience versus learning through instruction and culture – may differ in resilience to perturbation, or in susceptibility to variance related to individual differences. The question of how language, vs experience, alters behavior in humans is to some extent open to empirical investigation. There is no question that animal models have improved our understanding of addiction, but further progress calls for clear thinking about the role of language in human learning, and its absence in laboratory animals.

Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section

The Novel Ghrelin Receptor Inverse Agonist PF-5190457 Administered With Alcohol: Preclinical Safety Experiments and A Phase 1b Human Laboratory Study Lee MR, Tapocik JD, Ghareeb M, Schwandt ML, Dias AA, Le AN, Cobbina E, Farinelli LA, Bouhlal S, Farokhnia M, Heilig M, Akhlaghi F, Leggio L. Mol Psychiatry. 2018 May 4. doi:10.1038/s41380-018-0064-y. [Epub ahead of print].

Rodent studies indicate that ghrelin receptor blockade reduces alcohol consumption. However, no ghrelin receptor blockers have been administered to heavy alcohol drinking individuals. Therefore, the authors evaluated the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD) and behavioral effects of a novel ghrelin receptor inverse agonist, PF-5190457, when co-administered with alcohol. They tested the effects of PF-5190457 combined with alcohol on locomotor activity, loss-of-righting reflex (a measure of alcohol sedative actions), and on blood PF-5190457 concentrations in rats. Then, they performed a single-blind, placebo-controlled, within-subject human study with PF-5190457 (placebo/0 mg b.i.d., 50 mg b.i.d., 100 mg b.i.d.). Twelve heavy drinkers during three identical visits completed an alcohol administration session, subjective assessments, and an alcohol cue-reactivity procedure, and gave blood samples for PK/PD testing. In rats, PF-5190457 did not interact with the effects of alcohol on locomotor activity or loss-of-righting reflex. Alcohol did not affect blood PF-5190457 concentrations. In humans, all adverse events were mild or moderate and did not require discontinuation or dose reductions. Drug dose did not alter alcohol concentration or elimination, alcohol-induced stimulation or sedation, or mood during alcohol administration. Potential PD markers of PF-5190457 were acyl-to-total ghrelin ratio and insulin-like growth factor-1. PF-5190457 (100 mg b.i.d.) reduced alcohol craving during the cue-reactivity procedure. This study provides the first translational evidence of safety and tolerability of the ghrelin receptor inverse agonist PF-5190457 when co-administered with alcohol. PK/PD/behavioral findings support continued research of PF-5190457 as a potential pharmacological agent to treat alcohol use disorder.

Neurobiology of Relapse Section, Behavioral Neuroscience Branch

Opposite Effects Of Basolateral Amygdala Inactivation On Context-Induced Relapse To Cocaine Seeking After Extinction Versus Punishment Pelloux Y, Minier-Toribio A, Hoots JK, Bossert JM, Shaham Y (2018) The Journal of Neuroscience 38:51–59.
Studies using the renewal procedure showed that basolateral amygdala (BLA) inactivation inhibits context-induced relapse to cocaine-seeking after extinction. Here, the authors determined whether BLA inactivation would also inhibit context-induced relapse after drug-reinforced responding is suppressed by punishment, an animal model of human relapse after self-imposed abstinence due to adverse consequences of drug use. They also determined the effect of central amygdala (CeA) inactivation on context-induced relapse. The authors trained rats to self-administer cocaine for 12 days (6-h/day) in context A and then exposed them to either extinction or punishment training for 8 days in context B. During punishment, 50% of cocaine-reinforced lever-presses produced an aversive footshock of increasing intensity (0.1 to 0.5 or 0.7 mA). They then tested the rats for relapse to cocaine-seeking in the absence of cocaine or shock in contexts A and B after BLA or CeA injections of vehicle or GABA agonists (muscimol-baclofen). The authors then retrained the rats for cocaine self-administration in context A, repunished or reextinguished lever pressing in context B, and retested for relapse after BLA or CeA inactivation. BLA or CeA inactivation decreased context-induced relapse in context A after extinction in context B. BLA, but not CeA, inactivation increased context-induced relapse in context A after punishment in context B. BLA or CeA inactivation provoked relapse in context B after punishment but not extinction. Results demonstrate that amygdala's role in relapse depends on the method used to achieve abstinence, and highlights the importance of studying relapse under abstinence conditions that more closely mimic the human condition.

Neuronal Networks Section, Integrative Neuroscience Research Branch

Selective Brain Distribution and Distinctive Synaptic Architecture of Dual Glutamatergic-GABAergic Neurons David H. Root, Shiliang Zhang, David J. Barker, Jorge Miranda-Barrientos, Bing Liu, Hui-Ling Wang, and Marisela Morales. Cell Reports 23, 3465–3479, 2018.
For decades, it has been thought that glutamate and GABA are released by distinct neurons. However, some mouse neurons innervating the lateral habenula (LHb) co-release glutamate and GABA. Here, the authors mapped the distribution of neurons throughout the rat brain that co-express vesicular transporters for the accumulation of glutamate (VGluT2) or GABA (VGaT) and for GABA synthesis (GAD). They found concentrated groups of neurons that co-express VGluT2, VGaT, and GAD mRNAs within subdivisions of the ventral tegmental area (VTA), entopeduncular (EPN), and supramammillary (SUM) nuclei. Single axon terminals established by VTA, EPN, or SUM neurons form a common synaptic architecture involving asymmetric (putative excitatory) and symmetric (putative inhibitory) synapses. Within the LHb, which receives co-transmitted glutamate and GABA from VTA and EPN, VGluT2 and VGaT are distributed on separate synaptic vesicles. The authors conclude that single axon terminals from VGluT2 and VGaT co-expressing neurons co-transmit glutamate and GABA from distinct synaptic vesicles at independent synapses.

Structural Biology Unit, Integrative Neuroscience Branch

Imaging of Lipids using 2,6 Dihydroxyacetophenone with an AP-MALDI Source Jackson, SN, Muller, L, Roux, A, Oktem, B, Moskovets, E, Doroshenko, V, Woods, AS. JASMS E-pub March 2018.

Matrix-assisted laser/desorption ionization (MALDI) mass spectrometry imaging (MSI) is widely used as a unique tool to record the distribution of a large range of biomolecules in tissues. 2,6-Dihydroxyacetophenone (DHA) matrix has been shown to provide efficient ionization of lipids, especially gangliosides. The major drawback for DHA as it applies to MS imaging is that it sublimes under vacuum (low pressure) at the extended time necessary to complete both high spatial and mass resolution MSI studies of whole organs. To overcome the problem of sublimation, the authors used an atmospheric pressure (AP)-MALDI source to obtain high spatial resolution images of lipids in the brain using a high mass resolution mass spectrometer. Additionally, the advantages of atmospheric pressure and DHA for imaging gangliosides are highlighted. The imaging of [M–H]− and [M–H2O–H]− mass peaks for GD1 gangliosides showed different distribution, most likely reflecting the different spatial distribution of GD1a and GD1b species in the brain.

GRANTEE HONORS AND AWARDS

Dr. Kenneth Dodge, Duke University, was selected into the 2018 cohort of the Society for Prevention Research Fellows, in honor of his distinguished record of contributions in the field of prevention research.

Dr. Thomas E Eissenberg of Virginia Commonwealth University has been selected as the 2018 recipient of the American Psychological Association Prize for Interdisciplinary Team Research. This prize was developed to recognize interdisciplinary research teams that include one or more psychological scientists in major roles and that have produced significant scientific work.

Dr. Abigail Gewirtz, University of Minnesota, received the 2018 Translational Science Award from the Society for Prevention Research in recognition of her contributions to the field of prevention science in the area of Type 1 or Type 2 translational research.

Dr. Deborah Gorman-Smith, University of Chicago, was selected into the 2018 cohort of the Society for Prevention Research Fellows, in honor of her distinguished record of contributions in the field of prevention research.

Dr. Mary Hatch-Maillette was named Co-Director of the CTN Pacific Northwest Node (PNW) in March 2018. Having joined the University of Washington's Alcohol & Drug Abuse Institute in 2003 to work on CTN-0018, Safer Sex for Men**,** she has since held a variety of local and national roles in seven additional CTN protocols and two platform studies, including the BEing Safe in Treatment (BEST) study. In addition, she maintains a private psychotherapy practice in Seattle. Her primary research interests are in substance use treatment and HIV risk behavior. Now one of the longest-serving members of the Pacific Northwest Node and a CTN "veteran," Dr. Hatch-Maillette has co-authored 45 papers, posters, and presentations for the CTN. She is excited to join the CTN leadership and continue the PNW Node's tradition of blending science and practice in the treatment of substance use disorders.

Dr. David MacKinnon, Arizona State University, received the 2018 Prevention Science Award from the Society for Prevention Research for the application of scientific methods to developing and testing prevention strategies.

Dr. Flavio Marsiglia, Arizona State University, and **Dr. Maria Elena Medina Mora**, National Psychiatric Institute, received the International Collaborative Prevention Research Award from the Society for Prevention Research in recognition of the US and Mexico, binational collaboration.

Dr. Kirill Martemyanov, professor of neuroscience at the Scripps Research Institute (Florida), has been named the recipient of the 2018 ASPET John J. Abel award in pharmacology, presented at the April 2018 ASPET annual meeting of experimental biology. Dr. Martemyanov has been studying the structure and function of RGS complexes in the CNS, especially those affecting opioid signaling in the brain. https://www.aspet.org/aspet/meetings-awards/aspet-awards/aspet-scientific-achievement-awards/aspet-award-winners/2018-scientific-achievement-award-winners

Dr. Dennis McCarty of the CTN Western States Node, retired from the OHSU-PSU School of Public Health, Oregon Health and Science University on July 1, 2018. The school held a retirement reception on March 23 in his honor. The event celebrated decades of contributions Dr. McCarty has given to the field of Addiction.

Dr. Bryan Roth, of the University of North Carolina was the recipient of the IUPHAR Analytical Pharmacology Award, July 2018, Kyoto, Japan**.** This award is given once every 4 years at the World Congress of Pharmacology and Roth presented the Analytical Pharmacology Lecture, "A molecular understanding of drug actions at G protein coupled receptors".

STAFF HONORS AND AWARDS

NIH DIRECTOR'S AWARDS

Gayathri Dowling: In recognition of her extraordinary leadership and commitment to the success and scientific impact of the Adolescent Brain Cognitive Development (ABCD) Study.

NIDA Lofexidine Team: For scientific leadership and support in advancing the development of Lofexidine as an FDA approved medication for the treatment of the symptoms of opioid withdrawal:

- Chia-Whei Chiang
- Aidan Hampson
- Barbara Herman
- Ivan Montoya
- Robert Walsh
- Liza Zeinert

Group Awards: NIDA staff included in other ICs' Group Award Nominations

- **HHS-VA-DOD Collaboratory,** Scientific/Medical, Nominated by NCCIH: **Will Aklin.** Extraordinary multiagency collaboration and leadership in facilitating research on the treatment of chronic pain with nonpharmacologic approaches within the HHS-VA-DoD Collaboratory project.

- **NIH Opioids Epidemic Leadership Team**, Scientific/Medical, Nominated by OD: **Emily Jones, Geoffrey Laredo, Jack Stein, and David Thomas.** For extraordinary leadership and management of NIH's efforts to address the nationwide opioid epidemic through development of a public-private partnership and NIH Director engagement.

- **Optimize NIH IC POC Team,** Administrative, Nominated by OD: **Joellen Austin**. For outstanding work to communicate and engage stakeholders in the Optimize NIH Phase I implementation of Ethics, Freedom of Information Act, and Committee Management.

- **Optimize NIH Subcommittee Team**, Administrative, Nominated by OD: **Jessica Hemmati and Lanette Palmquist**. For exceptional contributions in data gathering and process mapping for Optimize NIH Phase I Implementation of Ethics, Freedom of Information Act, and Committee Management.

Dr. Chloe Jordan, Targets and Medications Discovery Branch, IRP, won a travel award to present a paper at the ICRS (International Cannabinoid Research Society) Symposium in Leiden, The Netherlands, July 1-4, 2018.

Dr. Ivan Montoya received the Michael Morrison Award from the College on Problems of Drug Dependence, for his outstanding contributions in the area of scientific administration related to drug abuse research.

Adam Moreno-Mendelson, Clinical Pharmacology and Therapeutics Research Branch, IRP, received the NIDA Scientific Director's Fellowship for Diversity in Research.

Dr. Rao Rapaka was awarded the inaugural Hall of Fame award from the Society for Chemistry and Pharmacology of Drug Abuse for contributions and service to the field of Drug Abuse and Medication Discovery. This was present in August at the annual meeting in Boston, MA.

Dr. David Reiner, Behavioral Neuroscience Branch, IRP, received the prestigious PRAT post-doctoral training award.

Dr. Jayanthi Subramaniam, Molecular Neuropsychiatry Research Branch, IRP, received the NIDA Staff Scientist Mentor Award.

At the NIDA Poster Day and Mentoring Awards Ceremony held on May 9, 2018, Mentoring Awards were presented to: **Drs. Brendan Tunstall** (Postdoctoral Fellow Award), **Jayanthi Sankar** (Staff Scientist Award), **David Epstein** (Investigator Award), and **Hugo Tejeda** (Diversity Award).

STAFF CHANGES

Bethany Griffin Deeds, Ph.D., was previously the Prevention Branch Chief in the Division of Epidemiology, Services and Prevention Research at the National Institute on Drug Abuse for 3 years. She was also the Deputy Branch Chief within Epidemiology Branch at NIDA for 6 years. She recently accepted the role as Deputy Director of the Division of Epidemiology, Services and Prevention Research.

Emily Jones, Ph.D., was selected as the Chief for the Science Policy Branch, Office of Science Policy and Communications. Dr. Jones joined OSPC in January 2017 as the Deputy Branch Chief and has been serving as Acting Branch Chief since January 2018. Since joining the Science Policy Branch, she has worked to ensure that NIDA's research findings are translated into policy, and that policy supports NIDA's scientific efforts to prevent and treat addiction. Previously, Emily was a policymaker and health services researcher at the HHS Office of the Assistant Secretary of Planning and Evaluation (ASPE), Team Lead for HITECH Act evaluation at the HHS Office of the National Coordinator (ONC) for Health IT, and part of the team implementing the Affordable Care Act in federally-qualified health centers (FQHCs) at HRSA. Prior to joining HHS, she conducted health services and policy research at the Urban Institute, Georgetown University, and George Washington University, as well as health care antitrust investigations at the Federal Trade Commission.

Emily Einstein, Ph.D., has been named Deputy Branch Chief of the Science Policy Branch within the Office of Science Policy and Communications. Emily came to NIDA in 2015 following her American Association for the Advancement of Science (AAAS) fellowship in the Office of Autism Research Coordination at NIMH. Her B.S. is in English and biology from The College of William and Mary, and her Ph.D. is in neuroscience from Yale University, where she trained faculty on evidence-based pedagogical practices and conducted research focused on mechanisms of opioid drug reward.

Janet Linton has been named Deputy Branch Chief of the Digital Communications Branch within the Office of Science Policy and Communications. Janet was previously a NIDA contractor and joined NIDA as a federal employee in 2012. She has completed her B.S. degree in computer animation and is currently working on her M.A. degree in program management.

New Staff

Stuart Berlin joined NIDA's Information Resources and Management Branch as an IT Specialist on August 19th. Stuart comes to NIDA from a position in the private sector.

David Bochner, Ph.D., joined the Science Policy Branch, Office of Science Policy and Communications, in June 2018. Dr. Bochner joins us from the Office of Science Policy (OSP), OD/NIH where he was responsible for analyzing data and evidence, briefing leadership, and communicating information to Congress and the public on a variety of topics, from NIH-wide priority setting and its relationship to disease burden to the impact of NIH research on health and the economy. Dr. Bochner received his Ph.D. in Neuroscience at Stanford University, studying neural plasticity, and joined NIH as a AAAS Science and Technology Policy Fellow at OSP in 2014 before being hired on full time in the same office.

Dr. Albert Burgess-Hull, joined IRP's RAPT Unit, Clinical Pharmacology and Therapeutics Research Branch as a postdoc in August 2018. Albert just received his doctorate in Human Development and Family Studies (with a minor in Quantitative Methods and Statistics) from the University of Wisconsin – Madison. He will be instrumental in the unit's ongoing work with machine-learning methods for detection and prediction of craving and lapse, validation of natural categories of drug-use trajectory and treatment response, and (in one of our high-priority OAR-funded projects) automated detection and prediction of HIV transmission hotspots at a citywide level.

Cynthia Fortis joined the Office of Management's Office of Financial Management as a Budget Analyst on July 8th. Cynthia comes to NIDA from the NIH Office of the Director.

Penny Greene joined the Division of Extramural Research as a Grants Management Specialist in July. She earned a B.S. in Business Administration from Towson University. In July 2004, joined the NIH, National Cancer Institute and then the National Institute of Allergy and Infectious Diseases gaining 8 years of experience as an NIH Grants Management Specialist. In September 2012, she moved to the Center for Medicare and Medicaid Services, Office of Acquisitions and Grants Management as a Grants Management Specialist. In September 2014, she went to Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drug Policy as a Project Manager helping to provide oversight of a variety of administrative projects related to the generic drug policy development. In September 2016, she left Federal Service to work in the private sector and start a family. Penny brings to NIDA ten years of experience as a Grants Management Specialist.

Garlin R. Hallas joined the Division of Extramural Research as a Grants Management Specialist in July. She earned a B.A. in Criminal Justice from the University of Maryland, College Park. She worked for the US Department of Justice, Office of the Inspector as an Auditor, before coming to the NIH, Office of Management Assessment, Division of Program Integrity as a Management Analyst. In January 2009, Garlin came to NIDA in the Management Analysis Branch managing the Institute's risk management program. In January 2013, she went to the Food and Drug Administration managing their risk management and ethics program, before coming back to NIH's Office of Management Assessment, Division of Program Integrity conducting reviews of allegations of complex grant issues. Garlin brings to NIDA her vast knowledge of grant reviews and auditing.

Adam Moreno-Mendelson, joined IRP's RAPT Unit, Clinical Pharmacology and Therapeutics Research Branch as a postbac in August 2018. Adam is the recipient of an SD fellowship award.

Stacey Novelli joined the Office of Management's Office of Financial Management as a Budget Analyst on August 5th. Stacey comes to NIDA from the National Oceanic and Atmospheric Administration.

Dr. Vasundhara Varthakavi joined NIDA's AIDS Research Program on May 27th as a Health Scientist Administrator. Vasundhara comes to NIDA from The National Institute of Allergy and Infectious Diseases (NIAID).

Dr. Susan Wright joined NIDA as a Program Officer in the Division of Neuroscience and Behavior in July. She will pioneer initiatives in Data Science and develop a portfolio in that area.

Staff Departures

Kathleen Elliott, a Pathways Intern in the Science Policy Branch, OSPC, left NIDA for a position in the private sector.

Stacey Gills, an Administrative Officer with the Office of Management's Administrative Management and Analysis Branch left NIDA on May 12th for a position with the Food and Drug Administration (FDA).

Dr. Sam Golden, Behavioral Neuroscience Branch, IRP, accepted a tenure-track position at the University of Washington, Seattle.

Donna Inman, a Program Analyst from DPMC left NIDA on May 12th for a position with the Food and Drug Administration (FDA).

Michelle Morelli, a Contract Specialist in the Office of Administration's Station Support Branch left NIDA on May 12th for a position with CNS.

Dr. Jose Ruiz, a Health Scientist Administrator from the Office of the Director's Office of Diversity and Health Disparities left NIDA on July 7th for a position with the NIH OD OER.

Dr. Brandon Warren, Behavioral Neuroscience Branch, IRP, obtained a tenure-track position at the University of Florida, Gainesville.

Amanda Wasson, a Budget Analyst in the Office of Management's Financial Management Branch left NIDA on May 26th for a position with the Department of Defense.

Retirements

Geoff Laredo, M.P.A., NIDA's Legislative Liaison and Senior Advisor to the OSPC Director, retired in August 2018, after 30 years in the government (22 at NIH; 14 at NIDA). Geoff was involved in a broad variety of intergovernmental initiatives and constituent relations, and was the Institute's point of contact for the U.S. Congress. Before joining NIDA in late 2004, Geoff spent a year working as a policy fellow for the U.S. Senate Committee on Health, Education, Labor and Pensions, Subcommittee on Substance Abuse and Mental Health Services. Prior to that, he was the Director of the Office of Policy and Public Liaison at NIAAA. He also worked as a senior analyst in the Office of the Administrator at SAMHSA. Geoff began his federal career as a program specialist with the National Institute of Justice, U.S. Department of Justice, working primarily on drugs and crime issues.


NIH
National Institute
on Drug Abuse