DIRECTOR'S REPORT

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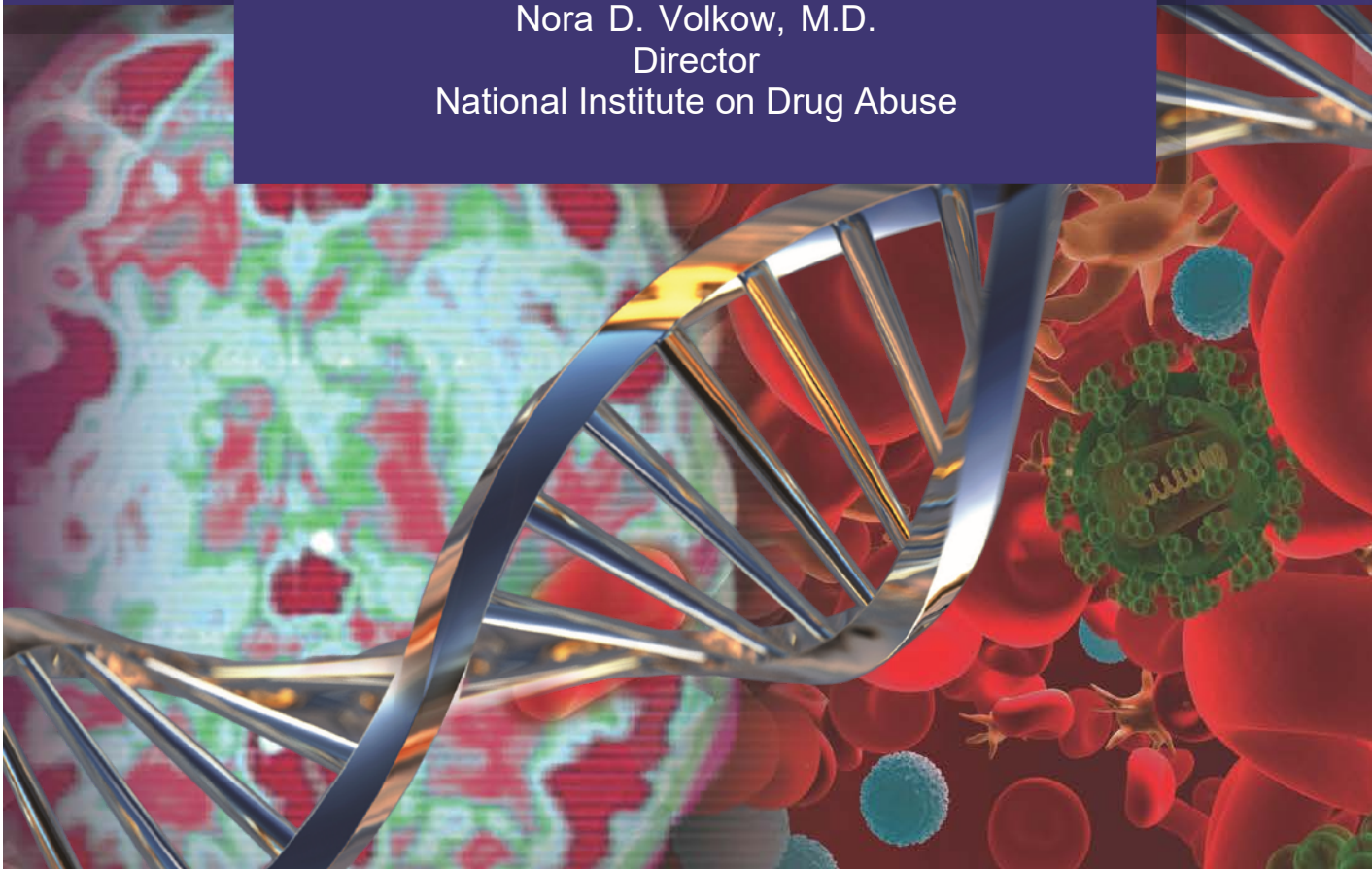
RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Local And Global Consequences Of Reward-Evoked Striatal Dopamine Release Li N, Jasanoff A. Nature. 2020 Apr 1. [Epub ahead of print].
The neurotransmitter dopamine is required for the reinforcement of actions by rewarding stimuli. Neuroscientists have tried to define the functions of dopamine in concise conceptual terms, but the practical implications of dopamine release depend on its diverse brain-wide consequences. Although molecular and cellular effects of dopaminergic signaling have been extensively studied, the effects of dopamine on larger-scale neural activity profiles are less well-understood. Here we combine dynamic dopamine-sensitive molecular imaging and functional magnetic resonance imaging to determine how striatal dopamine release shapes local and global responses to rewarding stimulation in rat brains. We find that dopamine consistently alters the duration, but not the magnitude, of stimulus responses across much of the striatum, via quantifiable postsynaptic effects that vary across subregions. Striatal dopamine release also potentiates a network of distal responses, which we delineate using neurochemically dependent functional connectivity analyses. Hot spots of dopaminergic drive notably include cortical regions that are associated with both limbic and motor function. Our results reveal distinct neuromodulatory actions of striatal dopamine that extend well beyond its sites of peak release, and that result in enhanced activation of remote neural populations necessary for the performance of motivated actions. Our findings also suggest brain-wide biomarkers of dopaminergic function and could provide a basis for the improved interpretation of neuroimaging results that are relevant to learning and addiction.

Nanobody-Enabled Monitoring Of Kappa Opioid Receptor States Che T, English J, Krumm BE, Kim K, Pardon E, Olsen RHJ, Wang S, Zhang S, Diberto JF, Sciaky N, Carroll FI, Steyaert J, Wacker D, Roth BL. Nature. 2020; 11(1): 1145-1157.
Recent studies show that GPCRs rapidly interconvert between multiple states, although our ability to interrogate, monitor and visualize them is limited by a relative lack of suitable tools. We previously reported two nanobodies (Nb39 and Nb6) that stabilize distinct ligand- and efficacy-delimited conformations of the kappa opioid receptor. Here, we demonstrate via X-ray crystallography a nanobody-targeted allosteric binding site by which Nb6 stabilizes a ligand-dependent inactive state. As Nb39 stabilizes an active-like state, we show how these two state-dependent nanobodies can provide real-time reporting of ligand-stabilized states in cells in situ. Significantly, we demonstrate that chimeric GPCRs can be created with engineered nanobody binding sites to report ligand-stabilized states. Our results provide both insights regarding potential mechanisms for allosterically modulating KOR with nanobodies and a tool for reporting the real-time, in situ dynamic range of GPCR activity.

Synergy Of Distinct Dopamine Projection Populations In Behavioral Reinforcement Heymann G, Jo YS, Reichard KL, McFarland N, Chavkin C, Palmiter RD, Soden ME, Zweifel LS Neuron. 2020 Mar 4; 105: 909-920.
Dopamine neurons of the ventral tegmental area (VTA) regulate reward association and motivation. Using mouse genetics, the authors isolated two distinct populations of dopamine-producing VTA neurons with divergent projections to the nucleus accumbens (NAc) core and shell, respectively. Inhibition of VTA-core-projecting neurons disrupted Pavlovian reward learning, and activation of these cells promoted the acquisition of an instrumental response. VTA-shell-projecting neurons did not regulate Pavlovian reward learning and could not facilitate acquisition of an instrumental

response, but their activation could drive robust responding in a previously learned instrumental task. Both populations were found to be activated simultaneously by cues, actions, and rewards, and this co-activation was required for robust reinforcement of behavior. Thus, there are functionally distinct dopamine populations in the VTA for promoting motivation and reward association, which operate on the same timescale to optimize behavioral reinforcement.

[Single-Cell Transcriptome Mapping Identifies Common And Cell-Type Specific Genes Affected By Acute Delta9-tetrahydrocannabinol In Humans](#) Hu Y, Ranganathan M, Shu C, Liang X, Ganesh S, Osafo-Addo A, Yan C, Zhang X, Aouizerat BE, Krystal J, D'Souza D, Xu K. Sci Rep. 2020; 10(1): 3450-3464.
Delta-9-tetrahydrocannabinol (THC) is known to modulate immune response in peripheral blood cells. The mechanisms of THC's effects on gene expression in human immune cells remains poorly understood. Combining a within-subject design with single cell transcriptome mapping, we report that THC acutely alters gene expression in 15,973 blood cells. We identified 294 transcriptome-wide significant genes among eight cell types including 69 common genes and 225 cell-type-specific genes affected by THC administration, including those genes involving in immune response, cytokine production, cell proliferation and apoptosis. We revealed distinct transcriptomic sub-clusters affected by THC in major immune cell types where THC perturbed cell-type-specific intracellular gene expression correlations. Gene set enrichment analysis further supports the findings of THC's common and cell-type-specific effects on immune response and cell toxicity. This comprehensive single-cell transcriptomic profiling provides important insights into THC's acute effects on immune function that may have important medical implications.

[Dopamine-Evoked Synaptic Regulation In The Nucleus Accumbens Requires Astrocyte Activity](#) Corkrum M, Covelo A, Lines J, Bellocchio L, Pisansky M, Loke K, Quintana R, Rothwell PE, Lujan R, Marsicano G, Martin ED, Thomas MJ, Kofuji P, Araque A. Neuron. 2020 March 18; 105: 1036-1047.
Dopamine is involved in physiological processes like learning and memory, motor control and reward, and pathological conditions such as Parkinson's disease and addiction. In contrast to the extensive studies on neurons, astrocyte involvement in dopaminergic signaling remains largely unknown. Using transgenic mice, optogenetics, and pharmacogenetics, we studied the role of astrocytes on the dopaminergic system. We show that in freely behaving mice, astrocytes in the nucleus accumbens (NAc), a key reward center in the brain, respond with Ca^{2+} elevations to synaptically released dopamine, a phenomenon enhanced by amphetamine. In brain slices, synaptically released dopamine increases astrocyte Ca^{2+}, stimulates ATP/adenosine release, and depresses excitatory synaptic transmission through activation of presynaptic A_1 receptors. Amphetamine depresses neurotransmission through stimulation of astrocytes and the consequent A_1 receptor activation. Furthermore, astrocytes modulate the acute behavioral psychomotor effects of amphetamine. Therefore, astrocytes mediate the dopamine- and amphetamine-induced synaptic regulation, revealing a novel cellular pathway in the brain reward system.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

[Comparative Effectiveness Of Different Treatment Pathways For Opioid Use Disorder](#)
Wakeman SE, Larochelle MR, Ameli O, Chiasson CE, Thomas J, McPheeters T, Crown W, Azocar F, Sanghavi DM. JAMA Netw Open, 2020; 3(2): e1920622.
Importance: Although clinical trials demonstrate the superior effectiveness of medication for opioid use disorder (MOUD) compared with nonpharmacologic treatment, national data on the

comparative effectiveness of real-world treatment pathways are lacking. Objective: To examine associations between opioid use disorder (OUD) treatment pathways and overdose and opioid-related acute care use as proxies for OUD recurrence. Design, setting, and participants: This retrospective comparative effectiveness research study assessed deidentified claims from the OptumLabs Data Warehouse from individuals aged 16 years or older with OUD and commercial or Medicare Advantage coverage. Opioid use disorder was identified based on 1 or more inpatient or 2 or more outpatient claims for OUD diagnosis codes within 3 months of each other; 1 or more claims for OUD plus diagnosis codes for opioid-related overdose, injection-related infection, or inpatient detoxification or residential services; or MOUD claims between January 1, 2015, and September 30, 2017. Data analysis was performed from April 1, 2018, to June 30, 2019. Exposures: One of 6 mutually exclusive treatment pathways, including (1) no treatment, (2) inpatient detoxification or residential services, (3) intensive behavioral health, (4) buprenorphine or methadone, (5) naltrexone, and (6) nonintensive behavioral health. Main outcomes and measures: Opioid-related overdose or serious acute care use during 3 and 12 months after initial treatment. Results: A total of 40 885 individuals with OUD (mean [SD] age, 47.73 [17.25] years; 22 172 [54.2%] male; 30 332 [74.2%] white) were identified. For OUD treatment, 24 258 (59.3%) received nonintensive behavioral health, 6455 (15.8%) received inpatient detoxification or residential services, 5123 (12.5%) received MOUD treatment with buprenorphine or methadone, 1970 (4.8%) received intensive behavioral health, and 963 (2.4%) received MOUD treatment with naltrexone. During 3-month follow-up, 707 participants (1.7%) experienced an overdose, and 773 (1.9%) had serious opioid-related acute care use. Only treatment with buprenorphine or methadone was associated with a reduced risk of overdose during 3-month (adjusted hazard ratio [AHR], 0.24; 95% CI, 0.14-0.41) and 12-month (AHR, 0.41; 95% CI, 0.31-0.55) follow-up. Treatment with buprenorphine or methadone was also associated with reduction in serious opioid-related acute care use during 3-month (AHR, 0.68; 95% CI, 0.47-0.99) and 12-month (AHR, 0.74; 95% CI, 0.58-0.95) follow-up. Conclusions and relevance: Treatment with buprenorphine or methadone was associated with reductions in overdose and serious opioid-related acute care use compared with other treatments. Strategies to address the underuse of MOUD are needed.

[Prospective Association Of E-cigarette And Cigarette Use With Alcohol Use In Two Waves Of The Population Assessment Of Tobacco And Health](#) Roberts W, Verplaetse T, Peltier MR, Moore KE, Gueorguieva R, McKee SA. Addiction. January 24, 2020. [Epub ahead of print]. Prior cross-sectional research finds that electronic cigarette (e-cigarette) use clusters with higher rates of harmful alcohol consumption in the United States adult population. The current study examined prospectively the association between e-cigarette use, cigarette use and the combined use of e-cigarettes and tobacco cigarettes and alcohol use outcomes. A nationally representative multi-wave cohort survey (wave 1: September 2013-December 2014, wave 2: October 2014-October 2015). United States. A representative sample of civilian, non-institutionalized adults who completed waves 1 and 2 of the Population Assessment of Tobacco and Health survey (n = 26 427). Participants were categorized into exposure groups according to their e-cigarette and cigarette use during wave 1. Past 30-day alcohol use outcomes were (1) National Institute on Alcohol Abuse and Alcoholism (NIAAA)–defined hazardous alcohol use, (2) total alcohol drinks consumed, and (3) alcohol-related consequences. After controlling for sociodemographic risk factors and alcohol use at wave 1, all exposure groups showed higher odds of hazardous alcohol use [adjusted odds ratios (aORs) = 2.05-2.12, all P < 0.001] and reported higher past-month total drinks (B = 0.46-0.70, all P < 0.001) and more alcohol consequences (B = 0.63-0.89, all P ≤ 0.10) at wave 2 compared with non-users. Cigarette users (B = 0.24, P = 0.038) and dual e-cigarette/cigarette users (B = 0.32, P = 0.038) reported higher past-month total drinks compared with e-cigarette users. There was no

conclusive evidence that non-daily use of e-cigarettes or cigarettes predicted poorer alcohol use outcomes compared with daily use. In the United States between 2013 and 2015, after adjustment for sociodemographic characteristics, cigarette and e-cigarette use were associated with alcohol use 1 year later.

Machine Learning And Natural Language Processing For Geolocation-Centric Monitoring And Characterization Of Opioid-Related Social Media Chatter Sarker A, Gonzalez-Hernandez G, Ruan Y, Perrone J. JAMA Netw Open. 2019; 2(11): e1914672.
Automatic curation of consumer-generated, opioid-related social media big data may enable real-time monitoring of the opioid epidemic in the United States. To develop and validate an automatic text-processing pipeline for geospatial and temporal analysis of opioid-mentioning social media chatter. This cross-sectional, population-based study was conducted from December 1, 2017, to August 31, 2019, and used more than 3 years of publicly available social media posts on Twitter, dated from January 1, 2012, to October 31, 2015, that were geolocated in Pennsylvania. Opioid-mentioning tweets were extracted using prescription and illicit opioid names, including street names and misspellings. Social media posts (tweets) (n = 9006) were manually categorized into 4 classes, and training and evaluation of several machine learning algorithms were performed. Temporal and geospatial patterns were analyzed with the best-performing classifier on unlabeled data. Pearson and Spearman correlations of county- and substate-level abuse-indicating tweet rates with opioid overdose death rates from the Centers for Disease Control and Prevention WONDER database and with 4 metrics from the National Survey on Drug Use and Health for 3 years were calculated. Classifier performances were measured through microaveraged F1 scores (harmonic mean of precision and recall) or accuracies and 95% CIs. A total of 9,006 social media posts were annotated, of which 1,748 (19.4%) were related to abuse; 2,001 (22.2%) were related to information; 4,830 (53.6%) were unrelated; and 427 (4.7%) were not in the English language. Yearly rates of abuse-indicating social media post showed statistically significant correlation with county-level opioid-related overdose death rates (n = 75) for 3 years (Pearson r = 0.451, P < .001; Spearman r = 0.331, P = .004). Abuse-indicating tweet rates showed consistent correlations with 4 NSDUH metrics (n = 13) associated with nonmedical prescription opioid use (Pearson r = 0.683, P = .01; Spearman r = 0.346, P = .25), illicit drug use (Pearson r = 0.850, P < .001; Spearman r = 0.341, P = .25), illicit drug dependence (Pearson r = 0.937, P < .001; Spearman r = 0.495, P = .09), and illicit drug dependence or abuse (Pearson r = 0.935, P < .001; Spearman r = 0.401, P = .17) over the same 3-year period, although the tests lacked power to demonstrate statistical significance. A classification approach involving an ensemble of classifiers produced the best performance in accuracy or microaveraged F1 score (0.726; 95% CI, 0.708-0.743). The correlations obtained in this study suggest that a social media–based approach reliant on supervised machine learning may be suitable for geolocation-centric monitoring of the U.S. opioid epidemic in near real time.

Construction Trade and Extraction Workers: A Population At High Risk For Drug Use In The United States, 2005-2014 Ompad DC, Gershon RR, Sandh S, Acosta P, Palamar JJ. Drug Alcohol Depend. 2019; 205: 107640.
To estimate prevalence of past-month marijuana, cocaine, and nonmedical prescription opioid (NPO) use and determine employment-related correlates of drug use among construction trade/extraction workers (CTEW). We analyzed ten years of data (2005-2014) from 293,492 adults (age≥18) in the National Survey on Drug Use and Health, comparing CTEW and non-CTEW. CTEW were 5.6% (n = 16,610) of the sample. Compared to non-CTEW, CTEW were significantly more likely to report past-month marijuana (12.3% vs. 7.5%), cocaine (1.8% vs. 0.8%), and/or

NPO use (3.4% vs. 2.0%; Ps<.001). Among CTEW, past-week unemployment and working for >3 employers was associated with increased odds of marijuana and NPO use. Missing 1-2 days in the past month because the participant did not want to go into work was associated with increased odds for use of marijuana, cocaine, and NPO use. Missing 3-5 days of work in the past month because sick or injured was associated with double the odds (aOR = 2.00 [95% CI: 1.33-3.02]) of using NPO. Having written drug policies was associated with reduced odds for cocaine use, and workplace tests for drug use during hiring and random drug testing were also associated with lower odds of marijuana use. CTEW are a high-risk population for drug use. Precarious employment is associated with higher prevalence of drug use while some workplace drug policies were associated with lower prevalence. Coupled with reports of high overdose mortality among CTEW, these findings suggest that prevention and harm reduction programming is needed to prevent drug-related morbidity and mortality among CTEW.

A Family-Centered Prevention Ameliorates The Associations Of Low Self-Control During Childhood With Employment Income And Poverty Status In Young African American Adults Brody GH, Yu T, Miller GE, Chen E. J Child Psychol Psychiatry. 2020; 61(4): 425-435. Children with low self-control who grow up in poverty are at elevated risk for living in poverty when they are adults. The purpose of this study was to further understand the intergenerational continuity of poverty by (a) examining the likelihood that children with low levels of self-control at age 11 earn less employment income and are more likely to live in poverty 14 years later, at age 25; and (b) determining, via a preventive intervention, whether enhancing supportive parenting during childhood will ameliorate these associations. Parents and their 11-year-old children from 381 families participated in the Strong African American Families (SAAF) program or a control condition. Teachers assessed children's self-control at 11 years; parents reported their use of supportive parenting when children were 11 and 13 years; emerging adults provided data on cognitive and emotional self-control at 19, 20, and 21 years; and young adults indicated their employment income at 25 years. Significant two-way interactions were detected between children's self-control and prevention condition for employment income (b = -183.18, 95% CI [-363.82, -2.53], p < .05) and poverty status (b = 0.257, 95% CI [0.018, 0.497], p < .05). Low self-control at age 11 forecast less employment income and a greater likelihood of living in poverty among children in the control condition, but not among low self-control SAAF participants. Mediated moderation analyses confirmed that enhanced supportive parenting accounted for SAAF's effects on employment income (indirect effect = 63.057, 95% BCA [19.385, 124.748]) and poverty status (indirect effect = -0.071, 95% BCA [-0.165, -0.016]).This study is unique in using a randomized controlled trial to show that preventive interventions designed to enhance parenting and strengthen families can buffer the long-term economic consequences of low self-control.

TREATMENT RESEARCH

Effects Of A Methamphetamine Vaccine, IXT-v100, On Methamphetamine-Related Behaviors
Keller CM, Spence AL, Stevens MW, Owens SM, Guerin GF, Goeders NE. Psychopharmacology (Berl). 2020; 237(3): 655-667.
Vaccines have been developed as a potential treatment for methamphetamine (meth) use disorder (MUD). Immunization with the meth vaccine IXT-v100 has previously been shown to elicit antibodies with high affinity for meth and thus may be an effective treatment for MUD. These studies were designed to determine the efficacy of IXT-v100 on meth-taking and meth-seeking behaviors in rats. In the acquisition and maintenance study, male and female rats were trained to

self-administer meth (0.06 mg/kg/infusion) over an 8-week period following vaccination. In the last 4 weeks, the dose of meth was increased or decreased each week. To assess meth-seeking behavior, the meth-primed reactivity model was used. Rats were trained to self-administer meth for 5 weeks, followed by a 5-week or 11-week forced abstinence period during which the animals were vaccinated. Rats were then placed back into the self-administration chamber immediately after being injected with meth (1 mg/kg, i.p.) but did not receive meth during the session. Responses were recorded and used as a measure of meth seeking. Results from the acquisition and maintenance study in Wistar rats show that vaccination with IXT-v100 adjuvanted with glucopyranosyl lipid A stable emulsion decreases the percentage of animals that will self-administer a moderate level of meth. In the meth-primed reactivity studies, results from males showed that vaccination significantly attenuates meth-seeking behavior. Together, these results suggest vaccination with IXT-v100 may be effective at decreasing meth-taking and meth-seeking behaviors in humans suffering with MUD.

Kappa Opioid Agonists Reduce Oxycodone Self-Administration In Male Rhesus Monkeys
Zamarripa CA, Naylor JE, Huskinson SL, Townsend EA, Prisinzano TE, Freeman KB. Psychopharmacology (Berl). 2020; 237(5): 1471-1480.
Combinations of mu and kappa opioid receptor (KOR) agonists have been proposed as potential analgesic formulations with reduced abuse liability. The current studies extend previous work by investigating the typical KOR agonist, salvinorin A, and the atypical KOR agonist, nalfurafine, as deterrents of oxycodone self-administration using a progressive ratio (PR) schedule of reinforcement. In separate experiments, adult male rhesus monkeys (N = 4/experiment) were trained under a PR schedule of reinforcement to self-administer cocaine (0.1 mg/kg/injection) and saline on alternating days. Oxycodone (0.01-0.1 mg/kg/injection) alone and combined with salvinorin A (experiment 1; 0.006, 0.012 mg/kg/injection) or nalfurafine (experiment 2; 0.0001-0.00032 mg/kg/injection) were tested within the alternating cocaine and saline baseline. The mechanism of nalfurafine's effects on oxycodone self-administration was investigated via pretreatment with the KOR antagonist, nor-binaltorphimine (nor-BNI; 10 mg/kg; i.m.). All subjects self-administered oxycodone alone above saline levels at sufficiently large doses, and combining salvinorin A or nalfurafine with oxycodone reduced the mean number of injections per session to saline levels (experiment 1) or to levels that were significantly lower than oxycodone alone (experiment 2). The ability of nalfurafine to reduce oxycodone self-administration was reversed by pretreatment with nor-BNI. These results demonstrate that KOR agonists, including the clinically used KOR agonist, nalfurafine, can punish self-administration of a prescription opioid analgesic, oxycodone, in rhesus monkeys and that nalfurafine's punishing effect is KOR-dependent. Combinations of KOR agonists with prescription opioids may have reduced abuse liability.

Craving To Quit: A Randomized Controlled Trial Of Smartphone App-Based Mindfulness Training For Smoking Cessation
Garrison KA, Pal P, O'Malley SS, Pittman BP, Gueorguieva R, Rojiani R, Scheinost D, Dallery J, Brewer JA. Nicotine Tob Res. 2020; 22(3): 324-331.
Mindfulness training may reduce smoking rates and lessen the association between craving and smoking. This trial tested the efficacy of mindfulness training via smartphone app to reduce smoking. Experience sampling (ES) was used to measure real-time craving, smoking, and mindfulness. A researcher-blind, parallel randomized controlled trial compared the efficacy of mobile mindfulness training with experience sampling (MMT-ES; Craving to Quit) versus experience sampling only (ES) to (1) increase 1-week point-prevalence abstinence rates at 6 months, and (2) lessen the association between craving and smoking. A modified intent-to-treat approach was used for treatment starters (MMT-ES n = 143; ES n = 182; 72% female, 81% white,

age 41 ± 12 year). No group difference was found in smoking abstinence at 6 months (overall, 11.1%; MMT-ES, 9.8%; ES, 12.1%; $\chi 2(1) = 0.43$, p = .51). From baseline to 6 months, both groups showed a reduction in cigarettes per day (p < .0001), craving strength (p < .0001) and frequency (p < .0001), and an increase in mindfulness (p < .05). Using ES data, a craving by group interaction was observed (F(1,3785) = 3.71, p = .05) driven by a stronger positive association between craving and cigarettes per day for ES (t = 4.96, p < .0001) versus MMT-ES (t = 2.03, p = .04). Within MMT-ES, the relationship between craving and cigarettes per day decreased as treatment completion increased (F(1,104) = 4.44, p = .04). Although mindfulness training via smartphone app did not lead to reduced smoking rates compared with control, our findings provide preliminary evidence that mindfulness training via smartphone app may help lessen the association between craving and smoking, an effect that may be meaningful to support quitting in the longer term. This is the first reported full-scale randomized controlled trial of any smartphone app for smoking cessation. Findings provide preliminary evidence that smartphone app–based MMT-ES may lessen the association between craving and smoking.Clinicaltrials.gov NCT02134509.

[**Mechanical Turk Data Collection In Addiction Research: Utility, Concerns And Best Practices**](#) Mellis AM, Bickel WK. Addiction. Mar 5, 2020. [Epub ahead of print].
Amazon Mechanical Turk (MTurk) provides a crowdsourcing platform for the engagement of potential research participants with data collection instruments. This review (1) provides an introduction to the mechanics and validity of MTurk research; (2) gives examples of MTurk research; and (3) discusses current limitations and best practices in MTurk research. We review four use cases of MTurk for research relevant to addictions: (1) the development of novel measures, (2) testing interventions, (3) the collection of longitudinal use data to determine the feasibility of longer-term studies of substance use, and (4) the completion of large batteries of assessments to characterize the relationships between measured constructs. We review concerns with the platform, ways of mitigating these and important information to include when presenting findings. MTurk has proved to be a useful source of data for behavioral science more broadly, with specific applications to addiction science. However, it is still not appropriate for all use cases, such as population-level inference. To live up to the potential of highly transparent, reproducible science from MTurk, researchers should clearly report inclusion/exclusion criteria, data quality checks and reasons for excluding collected data, how and when data were collected and both targeted and actual participant compensation. Although online survey research is not a substitute for random sampling or clinical recruitment, the Mechanical Turk community of both participants and researchers has developed multiple tools to promote data quality, fairness and rigor. Overall, Mechanical Turk has provided a useful source of convenience samples despite its limitations and has demonstrated utility in the engagement of relevant groups for addiction science.

[**Pharmacological Characterization Of 17-cyclopropylmethyl-3,14-dihydroxy-4,5-epoxy-6-[(3'-fluoro-4'-pyridyl)acetamido]morphinan (NFP) As A Dual Selective MOR/KOR Ligand With Potential Applications In Treating Opioid Use Disorder**](#) Zheng Y, Obeng S, Reinecke BA, Chen C, Phansalkar PS, Walentiny DM, Gerk PM, Liu-Chen L-Y, Selley DE, Beardsley PM, Zhang Y. Eur J Pharmacol. 2019; 865: 172812.
For thousands of years opioids have been the first-line treatment option for pain management. However, the tolerance and addiction potential of opioids limit their applications in clinic. NFP, a MOR/KOR dual-selective opioid antagonist, was identified as a ligand that significantly antagonized the antinociceptive effects of morphine with lesser withdrawal effects than naloxone at similar doses. To validate the potential application of NFP in opioid addiction treatment, a series of in vitro and in vivo assays were conducted to further characterize its pharmacological profile. In

calcium mobilization assays and MOR internalization studies, NFP showed the apparent capacity to antagonize DAMGO-induced calcium flux and etorphine-induced MOR internalization. In contrast to the opioid agonists DAMGO and morphine, cells pretreated with NFP did not show apparent desensitization and down regulation of the MOR. Though in vitro bidirectional transport studies showed that NFP might be a P-gp substrate, in warm-water tail-withdrawal assays it was able to antagonize the antinociceptive effects of morphine indicating its potential central nervous system activity. Overall, these results suggest that NFP is a promising dual selective opioid antagonist that may have the potential to be used therapeutically in opioid use disorder treatment.

Enhancement Of Opioid Antinociception By Nicotine Barreto de Moura F, Withey SL, Bergman J. J Pharmacol Exp Ther. 2019; 371(3): 624-632.
Nicotine can produce antinociception in preclinical pain models; however, the ability of nicotine to augment the antinociceptive effects of opioid agonists has not been investigated. The present experiments were conducted to determine how nicotine modifies the effects of opioid agonists differing in efficacy. Male squirrel monkeys responded for the delivery of milk under a fixed ratio 10 schedule of reinforcement. During the 30-second timeout period following each milk delivery, the subject's tail was immersed in 35, 50, 52, or 55°C water, and the latency to remove the tail was recorded. Dose-response functions for tail-withdrawal latency and operant performance were determined for fentanyl, oxycodone, buprenorphine, and nalbuphine alone and after treatment with nicotine. Excepting nalbuphine, all opioids produced dose-related disruptions in food-maintained responding and increases in tail-withdrawal latency at each water temperature. Nicotine did not exacerbate the behaviorally disruptive effects of the μ-opioids on operant performance but produced a significant mecamylamine-sensitive enhancement of the antinociceptive potency of each opioid. Failure of arecoline to augment the antinociceptive effects of oxycodone and antagonism by mecamylamine suggests this nicotine-induced augmentation of prescription opioid antinociception was nicotinic acetylcholine receptor (nAChR) mediated. This was reflected in leftward shifts in the antinociceptive dose-response curve of each opioid, ranging from 2- to 7-fold increases in the potency of oxycodone across all water temperatures to an approximately 70-fold leftward shift in the antinociceptive dose-response curve of nalbuphine at the lower and intermediate water temperatures. These results suggest that nicotine may enhance μ-opioid antinociceptive effects without concomitantly exacerbating their behaviorally disruptive effects. SIGNIFICANCE STATEMENT: Prescription opioids remain the most effective pain-management pharmacotherapeutics but are limited by their adverse effects. The present results indicate that nicotine enhances antinociceptive effects of various opioid agonists in nonhuman primates without increasing their disruptive effects on operant performance. These results suggest that nicotine might function as an opioid adjuvant for pain management by enabling decreased clinically effective analgesic doses of prescription opioids without exacerbating their adverse behavioral effects.

Comparison Of Orexin 1 And Orexin 2 Ligand Binding Modes Using X-ray Crystallography And Computational Analysis Rappas M, Ali AAE, Bennett KA, Brown JD, Bucknell SJ, Congreve M, Cooke RM, Cseke G, de Graaf C, Doré AS, Errey JC, Jazayeri A, Marshall FH, Mason JS, Mould R, Patel JC, Tehan BG, Weir M, Christopher JA. J Med Chem. 2020; 63(4): 1528-1543.
The orexin system, which consists of the two G protein-coupled receptors OX1 and OX2, activated by the neuropeptides OX-A and OX-B, is firmly established as a key regulator of behavioral arousal, sleep, and wakefulness and has been an area of intense research effort over the past two decades. X-ray structures of the receptors in complex with 10 new antagonist ligands from diverse chemotypes are presented, which complement the existing structural information for the system and

highlight the critical importance of lipophilic hotspots and water molecules for these peptidergic GPCR targets. Learnings from the structural information regarding the utility of pharmacophore models and how selectivity between OX1 and OX2 can be achieved are discussed.

Effects Of Methamphetamine Isomers On D-methamphetamine Self-Administration And Food-Maintained Responding In Male Rats Bardo MT, Denehy ED Hammerslag LR, Dwoskin LP, Blough BE, Landavazo A, Bergman J, Kohut SJ. Psychopharmacology (Berl). 2019; 236(12): 3557-3565.

Methamphetamine (METH) abuse is generally attributed to the d-isomer. Self-administration of l-METH has been examined only in rhesus monkeys with a history of cocaine self-administration or drug-naïve rats using high toxic doses. In this study, the ability of l-METH and, for comparison, d-METH to engender self-administration in experimentally naïve rats, as well as to decrease d-METH self-administration and food-maintained responding, was examined. Male Sprague-Dawley rats were used in 3 separate experiments. In experiment 1, the acquisition of l- or d-METH self-administration followed by dose-response determinations was studied. In experiment 2, rats were trained to self-administer d-METH (0.05 mg/kg/infusion) and, then, various doses of l- or d-METH were given acutely prior to the session; the effect of repeated l-METH (30 mg/kg) also was examined. In experiment 3, rats were trained to respond for food reinforcement and, then, various doses of l- or d-METH were given acutely prior to the session; the effect of repeated l-METH (3 mg/kg) also was examined. Reliable acquisition of l- and d-METH self-administration was obtained at unit doses of 0.5 and 0.05 mg/kg/infusion respectively. The dose-response function for l-METH self-administration was flattened and shifted rightward compared with d-METH self-administration, with peak responding for l- and d-METH occurring at unit doses of 0.17 and 0.025 respectively. l-METH also was approximately 10-fold less potent than d-METH in decreasing d-METH self-administration and 2-fold lower in decreasing food-maintained responding. Tolerance did not occur to repeated l-METH pretreatments on either measure. As a potential pharmacotherapeutic, l-METH has less abuse liability than d-METH and its efficacy in decreasing d-METH self-administration and food-maintained responding is sustained with repeated treatment.

HIV/AIDS-RELATED RESEARCH

Neurocognitive Impairment Is Worse In HIV/HCV-Coinfected Individuals With Liver Dysfunction Barokar J, McCutchan A, Deutsch R, Tang B, Cherner M, Bharti AR. J Neurovirol. 2019; 25(6): 792-799.

Infections with HIV and hepatitis C virus (HCV) can individually and jointly contribute to neurocognitive impairment (NCI). Rates of NCI in HIV/HCV-coinfected persons range from 40% to 63% but its correlates have not been described. In this study, we examined HIV/HCV-coinfected adults on antiretroviral therapy (ART) with undetectable HIV RNA in blood (n = 412) who were assessed using a comprehensive neuropsychological test battery. Demographics, host and viral biomarkers, and markers of liver dysfunction were compared between impaired (n = 198) and unimpaired (n = 214) participants using logistic regression. The cohort was predominantly middle-aged men, half of whom (48%) had NCI. The odds of NCI increased by almost two-fold when serum albumin was < 4 g/dL, 1.7-fold when alanine aminotransferase (ALT) levels were > 50 IU/L, and 2.2-fold with every unit increase in log10 AST to Platelet Ratio Index (APRI). These readily available clinical biomarkers of NCI measure hepatic injury and/or dysfunction, suggesting a mechanism for the effects of HCV infection on NCI. They may identify patients at increased risk of NCI who could be prioritized for early initiation of HCV treatment to protect or improve cognition.

[**Methamphetamine Enhances HIV-1 Replication In CD4$^+$T-Cells Via A Novel IL-1β Auto-Regulatory Loop**](#) Lawson KS, Prasad A, Groopman JE. Front. Immunol. 2020 Feb 7; 11: 136.
Methamphetamine (Meth) abuse is a worldwide public health problem and contributes to HIV-1 pathobiology and poor adherence to anti-retroviral therapies. Specifically, Meth is posited to alter molecular mechanisms to provide a more conducive environment for HIV-1 replication and spread. Enhanced expression of inflammatory cytokines, such as Interleukin-1b (IL-1b), has been shown to be important for HIV-1 pathobiology. In addition, microRNAs (miRNAs) play integral roles in fine-tuning the innate immune response. Notably, the effects of Meth abuse on miRNA expression are largely unknown. We studied the effects of Meth on IL-1b and miR-146a, a well-characterized member of the innate immune signaling network. We found that Meth induces miR-146a and triggers an IL-1b auto-regulatory loop to modulate innate immune signaling in CD4+ T-cells. We also found that Meth enhances HIV-1 replication via IL-1 signaling. Our results indicate that Meth activates an IL-1b feedback loop to alter innate immune pathways and favor HIV-1 replication. These observations offer a framework for designing targeted therapies in HIV-infected Meth using hosts.

[**Cannabis Exposure Is Associated With A Lower Likelihood Of Neurocognitive Impairment In People Living With HIV**](#) Watson CW, Paolillo EW, Morgan EE, Umlauf A, Sundermann EE, Ellis RJ, Letendre S, Marcotte TD, Heaton RK, Grant I. J Acquir Immune Defic Syndr. 2020 Jan 1; 83(1): 56-64.
Aging and HIV have adverse effects on the central nervous system, including increased inflammation and neural injury and confer risk of neurocognitive impairment (NCI). Previous research suggests the nonacute neurocognitive effects of cannabis in the general population are adverse or null. However, in the context of aging and HIV, cannabis use may exert beneficial effects due to its anti-inflammatory properties. In the current study, we examined the independent and interactive effects of HIV and cannabis on NCI and the potential moderation of these effects by age. Participants included 679 people living with HIV (PLHIV) and 273 people living without HIV (HIV-) (18-79 years old) who completed neurocognitive, neuromedical, and substance use assessments. NCI was defined as a demographically corrected global deficit score ≥ 0.5. Logistic regression models examined the effects of age, HIV, cannabis (history of cannabis substance use disorder and cannabis use in past year), and their 2-way and 3-way interactions on NCI. In logistic regression models, only a significant interaction of HIV X cannabis was detected (P = 0.02). Among PLHIV, cannabis was associated with a lower proportion of NCI (odds ratio = 0.53, 95% confidence interval = 0.33-0.85) but not among HIV- individuals (P = 0.40). These effects did not vary by age. Findings suggest cannabis exposure is linked to a lower odds of NCI in the context of HIV. A possible mechanism of this result is the anti-inflammatory effect of cannabis, which may be particularly important for PLHIV. Further investigations are needed to refine the effects of dose, timing, and cannabis compound on this relationship, which could inform guidelines for cannabis use among populations vulnerable to cognitive decline.

[**Immune Status And Associated Mortality After Cancer Treatment Among Individuals With HIV In The Antiretroviral Therapy Era**](#) Calkins KL, Chander G, Joshu CE, Visvanathan K, Fojo AT, Lesko CR, Moore RD, Lau B. JAMA Oncol. 2019.
Immunologic decline associated with cancer treatment in people with HIV is not well characterized. Quantifying excess mortality associated with cancer treatment–related immunosuppression may help inform cancer treatment guidelines for persons with HIV. To estimate the association between cancer treatment and CD4 count and HIV RNA level in persons with HIV and between posttreatment CD4 count and HIV RNA trajectories and all-cause mortality.

This observational cohort study included 196 adults with HIV who had an incident first cancer and available cancer treatment data while in the care of The Johns Hopkins HIV Clinic from January 1, 1997, through March 1, 2016. The study hypothesized that chemotherapy and/or radiotherapy in people with HIV would increase HIV RNA levels owing to treatment tolerability issues and would be associated with a larger initial decline in CD4 count and slower CD4 recovery compared with surgery or other treatment. An additional hypothesis was that these CD4 count declines would be associated with higher mortality independent of baseline CD4 count, antiretroviral therapy use, and risk due to the underlying cancer. Data were analyzed from December 1, 2017, through April 1, 2018. Initial cancer treatment category (chemotherapy and/or radiotherapy vs. surgery or other treatment). Post-cancer treatment longitudinal CD4 count, longitudinal HIV RNA level, and all-cause mortality. Among the 196 participants (135 [68.9%] male; median age, 50 [interquartile range, 43-55] years), chemotherapy and/or radiotherapy decreased initial CD4 count by 203 cells/μL (95% CI, 92-306 cells/μL) among those with a baseline CD4 count of greater than 500 cells/μL. The decline for those with a baseline CD4 count of no greater than 350 cells/μL was 45 cells/μL (interaction estimate, 158 cells/μL; 95% CI, 31-276 cells/μL). Chemotherapy and/or radiotherapy had no detrimental association with HIV RNA levels. After initial cancer treatment, every 100 cells/μL decrease in CD4 count resulted in a 27% increase in mortality (hazard ratio, 1.27; 95% CI, 1.08-1.53), adjusting for HIV RNA level. No significant increase in mortality was associated with a unit increase in log10 HIV RNA after adjusting for CD4 count (hazard ratio, 1.24; 95% CI, 0.94-1.65). In this study, chemotherapy and/or radiotherapy was associated with significantly reduced initial CD4 count in adults with HIV compared with surgery or other treatment. Lower CD4 count after cancer treatment was associated with an increased hazard of mortality. Further research is necessary on the immunosuppressive effects of cancer treatment in adults with HIV and whether health care professionals must consider the balance of cancer treatment efficacy against the potential cost of further immunosuppression. Monitoring of immune status may also be helpful given the decrease in CD4 count after treatment and the already immunocompromised state of patients with HIV.

[Hepatitis C-Positive Donor Liver Transplantation For Hepatitis C Seronegative Recipients](#)
Ting P-S, Hamilton JP, Gurakar A, Urrunaga NH, Ma M, Glorioso J, King E, Toman LP, Wesson R, Garonzik-Wang J, Ottmann S, Philosophe B, Sulkowski M, Cameron AM, Durand CM, Chen P-H. Transpl Infect Dis. 2019; 21(6): e13194.
The opioid crisis has led to an increase in hepatitis C virus-positive donors in the past decade. Whereas historically hepatitis C seropositive organs were routinely discarded, the advent of direct-acting antiviral agents has notably expanded the utilization of organs from donors with hepatitis C. There has been growing experience with liver transplantation (LT) from hepatitis C seropositive donors to hepatitis C seropositive recipients. However, data remain limited on LT from hepatitis C seropositive or hepatitis C ribonucleic acid positive donors to hepatitis C seronegative recipients. We performed a retrospective study of 26 hepatitis C seronegative recipients who received hepatitis C seropositive donor livers followed by preemptive antiviral therapy with direct-acting antiviral treatment at the Johns Hopkins Hospital Comprehensive Transplant Center from January 1, 2017, to August 31, 2019. Twenty-five of the 26 recipients are alive with proper graft function; 20 of them received livers from hepatitis C nucleic acid testing positive donors. All 12 recipients who completed their direct-acting antiviral courses and have reached sufficient follow-up for sustained virologic response have achieved sustained virologic response. Nine of our recipients have either completed direct-acting antiviral treatment without sufficient follow-up time for sustained virologic response or are undergoing direct-acting antiviral treatment. One patient is awaiting antiviral treatment initiation pending insurance approval. Of note, 11 of 12 patients with sustained virologic

response received a hepatitis C nucleic acid testing positive donor liver. Hepatitis C seronegative patients who receive a hepatitis C seropositive or hepatitis C nucleic acid testing positive liver allograft can enjoy good short-term outcomes with hepatitis C cure following direct-acting antiviral treatment.

Ending The HIV Epidemic In The USA: An Economic Modelling Study In Six Cities

Nosyk B, Zang X, Krebs E, Enns B, Min JE, Behrends CN, Del Rio C, Dombrowski JC, Feaster DJ, Golden M, Marshall BDL, Mehta SH, Metsch LR, Pandya A, Schackman BR, Shoptaw S, Strathdee SA. Localized HIV Modeling Group. Lancet HIV. 2020 Mar 5. pii: S2352-3018(20)30033-3. [Epub ahead of print].

The HIV epidemic in the USA is a collection of diverse local microepidemics. We aimed to identify optimal combination implementation strategies of evidence-based interventions to reach 90% reduction of incidence in 10 years, in six US cities that comprise 24·1% of people living with HIV in the USA. In this economic modelling study, we used a dynamic HIV transmission model calibrated with the best available evidence on epidemiological and structural conditions for six US cities: Atlanta (GA), Baltimore (MD), Los Angeles (CA), Miami (FL), New York City (NY), and Seattle (WA). We assessed 23 040 combinations of 16 evidence-based interventions (i.e., HIV prevention, testing, treatment, engagement, and re-engagement) to identify combination strategies providing the greatest health benefit while remaining cost-effective. Main outcomes included averted HIV infections, quality-adjusted life-years (QALYs), total cost (in 2018 US$), and incremental cost-effectiveness ratio (ICER; from the health-care sector perspective, 3% annual discount rate). Interventions were implemented at previously documented and ideal (90% coverage or adoption) scale-up, and sustained from 2020 to 2030, with outcomes evaluated until 2040. Optimal combination strategies providing health benefit and cost-effectiveness contained between nine (Seattle) and 13 (Miami) individual interventions. If implemented at previously documented scale-up, these strategies could reduce incidence by between 30·7% (95% credible interval 19·1-43·7; Seattle) and 50·1% (41·5-58·0; New York City) by 2030, at ICERs ranging from cost-saving in Atlanta, Baltimore, and Miami, to $95 416 per QALY in Seattle. Incidence reductions reached between 39·5% (26·3-53·8) in Seattle and 83·6% (70·8-87·0) in Baltimore at ideal implementation. Total costs of implementing strategies across the cities at previously documented scale-up reached $559 million per year in 2024; however, costs were offset by long-term reductions in new infections and delayed disease progression, with Atlanta, Baltimore, and Miami projecting cost savings over the 20-year study period. Evidence-based interventions can deliver substantial public health and economic value; however, complementary strategies to overcome social and structural barriers to HIV care will be required to reach national targets of the ending the HIV epidemic initiative by 2030.

Correlates Of Transactional Sex Among A Rural Population Of People Who Inject Drugs

Allen ST, White RH, O'Rourke A, Ahmad NJ, Hazelett T, Kilkenny ME, Sherman SG. AIDS & Behavior. 2020 Mar; 24(3): 775-781.

In the United States, high rates of HIV infection among persons who engage in transactional sex are partially driven by substance use. Little is known about transactional sex among rural populations of people who inject drugs (PWID). Using data from a 2018 survey of 420 rural PWID in West Virginia, we used logistic regression to identify correlates of recent transactional sex (past 6 months). Most study participants were male (61.2%), white (83.6%), and reported having injected heroin (81.0%) in the past 6 months. Nearly one-fifth (18.3%) reported engaging in recent transactional sex. Independent correlates of transactional sex were: being female [adjusted odds ratio (aOR) 3.90; 95% CI 2.12-7.16]; being a sexual minority (aOR 3.07; 95% CI 1.60-5.87); being

single (aOR 3.22; 95% CI 1.73-6.01); receptive syringe sharing (aOR 3.13; 95% CI 1.73-5.66); and number of injections per day (aOR 1.08; 95% CI 1.01-1.15). Rural PWID who engage in transactional sex are characterized by multiple vulnerabilities that increase their HIV risk.

[Altered Monocyte Phenotype And Dysregulated Innate Cytokine Responses Among People Living With HIV And Opioid-Use Disorder](#) Underwood ML, Nguyen T, Uebelhoer LS, Kunkel LE, Korthuis PT, Lancioni CL. AIDS. 2020 Feb 1; 34(2): 177-188.

BACKGROUND: Opioid-use disorders (OUD) and hepatitis C or B co-infection (HEP) are common among people living with HIV (PLHIV). The impact of OUD on innate and adaptive immunity among PLHIV with and without HEP is unknown. OBJECTIVES: To investigate the impact of OUD on monocyte and T-cell phenotypes, cytokine responses to lipopolysaccharide (LPS) and phytohemagglutinin (PHA), and plasma inflammatory markers, among PLHIV with and without HEP. METHODS: Cross-sectional study enrolling PLHIV receiving ART, with and without OUD. Flow cytometry determined monocyte and T-cell phenotypes; LPS and PHA-induced cytokine production was assessed following LPS and PHA stimulation by multiplex cytokine array; plasma IL-6, soluble CD163, and soluble CD14 were measured by ELISA. RESULTS: Twenty-two PLHIV with OUD and 37 PLHIV without OUD were included. PLHIV with OUD exhibited higher frequencies of intermediate (CD14CD16) and nonclassical (CD14CD16) monocytes when compared with PLHIV without OUD (P=0.0025; P=0.0001, respectively), regardless of HEP co-infection. Soluble CD163 and monocyte cell surface CD163 expression was increased among PLHIV with OUD and HEP, specifically. Regardless of HEP co-infection, PLHIV with OUD exhibited reduced production of IL-10, IL-8, IL-6, IL-1alpha, and TNF-alpha in response to LPS when compared with PLHIV without OUD; PHA-induced production of IL-10, IL-1alpha, IL-1beta, IL-6, and TNF-alpha were also reduced among individuals with OUD. CONCLUSION: OUD among PLHIV are associated with altered monocyte phenotypes and a dysregulated innate cytokine response. Defining underlying mechanisms of opioid-associated innate immune dysregulation among PLHIV should be prioritized to identify optimal OUD treatment strategies.

CLINICAL TRIALS NETWORK RESEARCH

[Documented Opioid Use Disorder And Its Treatment In Primary Care Patients Across Six U.S. Health Systems](#) Boudreau DM, Lapham G, Johnson EA, Bobb JF, Matthews AG, McCormack J, Liu D, Campbell CI, Rossom RC, Binswanger IA, Yarborough BJ, Arnsten JH, Cunningham CO, Glass JE, Murphy MT, Zare M, Hechter RC, Ahmedani B, Braciszewski JM, Horigian VE, Szapocznik J, Samet JH, Saxon AJ, Schwartz RP, Bradley KA. J Subst Abuse Treat. 2020 Mar; 112S: 41-48.

BACKGROUND: The United States is in the middle of an opioid overdose epidemic, and experts are calling for improved detection of opioid use disorders (OUDs) and treatment with buprenorphine or extended release (XR) injectable naltrexone, which can be prescribed in general medical settings. To better understand the magnitude of opportunities for treatment among primary care (PC) patients, we estimated the prevalence of documented OUD and medication treatment of OUD among PC patients. METHODS: This cross-sectional study included patients with ≥2 visits to PC clinics across 6 healthcare delivery systems who were ≥16 years of age during the study period (fiscal years 2014-2016). Diagnoses, prescriptions, and healthcare utilization were ascertained from electronic health records and insurance claims (5 systems that also offer health insurance). Documented OUDs were defined as ≥1 International Classification of Diseases code for OUDs (active or remission), and OUD treatment was defined as ≥1 prescription(s) for

buprenorphine formulations indicated for OUD or naltrexone XR, during the 3-year study period. The prevalence of documented OUD and treatment (95% confidence intervals) across health systems were estimated, and characteristics of patients by treatment status were compared. Prevalence of OUD and OUD treatment were adjusted for age, gender, and race/ethnicity. Combined results were also adjusted for site. RESULT: Among 1,403,327 eligible PC patients, 54-62% were female and mean age ranged from 46 to 51 years across health systems. The 3-year prevalence of documented OUD ranged from 0.7-1.4% across the health systems. Among patients with documented OUD, the prevalence of medication treatment (primarily buprenorphine) varied across health systems: 3%, 12%, 16%, 20%, 22%, and 36%. CONCLUSION: The prevalence of documented OUD and OUD treatment among PC patients varied widely across health systems. The majority of PC patients with OUD did not have evidence of treatment with buprenorphine or naltrexone XR, highlighting opportunities for improved identification and treatment in medical settings. These results can inform initiatives aimed at improving treatment of OUD in PC. Future research should focus on why there is such variation and how much of the variation can be addressed by improving access to medication treatment.

[Service Utilization And Chronic Condition Outcomes Among Primary Care Patients With Substance Use Disorders And Co-Occurring Chronic Conditions](#) Stephens KA, West II, Hallgren KA, Mollis B, Ma K, Donovan DM, Stuvek B, Baldwin LM. J Subst Abuse Treat. 2020 Mar; 112S: 49-55.

BACKGROUND: Patients with a substance use disorder (SUD) often present with co-occurring chronic conditions in primary care. Despite the high co-occurrence of chronic medical conditions and SUD, little is known about whether chronic condition outcomes or related service utilization in primary care varies between patients with versus without documented SUDs. This study examined whether having an SUD influenced the use of primary care services and common chronic condition outcomes for patients with diabetes, hypertension, and obesity. METHODS: A longitudinal cohort observational study examined electronic health record data from 21 primary care clinics in Washington and Idaho to examine differences in service utilization and clinical outcomes for diabetes, hypertension, and obesity in patients with and without a documented SUD diagnosis. Differences between patients with and without documented SUD diagnoses were compared over a three-year window for clinical outcome measures, including hemoglobin A1c, systolic and diastolic blood pressure, and body mass index, as well as service outcome measures, including number of encounters with primary care and co-located behavioral health providers, and orders for prescription opioids. Adult patients (N = 10,175) diagnosed with diabetes, hypertension, or obesity before the end of 2014, and who had ≥2 visits across a three-year window including at least one visit in 2014 (baseline) and at least one visit occurring 12 months or longer after the 2014 visit (follow-up) were examined. RESULTS: Patients with SUD diagnoses and co-occurring chronic conditions were seen by providers more frequently than patients without SUD diagnoses (p's < 0.05), and patients with SUD diagnoses were more likely to be prescribed opioid medications. Chronic condition outcomes were no different for patients with versus without SUD diagnoses. DISCUSSION: Despite the higher visit rates to providers in primary care, a majority of patients with SUD diagnoses and chronic medical conditions in primary care did not get seen by co-located behavioral health providers, who can potentially provide and support evidence-informed care for both SUD and chronic conditions. Patients with chronic medical conditions also were more likely to get prescribed opioids if they had an SUD diagnosis. Care pathway innovations for SUDs that include greater utilization of evidence-informed co-treatment of SUDs and chronic conditions within primary care settings may be necessary for improving care overall for patients with comorbid SUDs and chronic conditions.

Implementation Of Emergency Department-Initiated Buprenorphine For Opioid Use Disorder In A Rural Southern State Bogan C, Jennings L, Haynes L, Barth K, Moreland A, Oros M, Goldsby S, Lane S, Funcell C, Brady K. J Subst Abuse Treat. 2020 Mar; 112S: 73-78.

AIM: The National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN), an entity aimed at bridging researchers and community-based substance abuse treatment providers to develop new treatment approaches, has taken an interest in the dissemination of findings from a randomized clinical trial by D'Onofrio demonstrating that initiating buprenorphine in the emergency department (ED) enhances linkage to treatment [JAMA 2015; 313 (16): 1636-1644]. In the Southern Consortium Node of the CTN, the authors have taken an implementation science approach to expand on the D'Onofrio study by implementing an ED-based buprenorphine initiation program in three diverse South Carolina EDs utilizing a predominantly peer recovery coach model. The aim of this pilot program was to foundationally integrate universal screening, brief interventions and referral to treatment (SBIRT) in hospital EDs to identify patients with at-risk substance use. Through brief interventions, patient navigators assessed readiness to change and motivation for treatment of patients. Patients willing to engage in treatment were referred to appropriate community resources. Patients identified to have opioid use disorder (OUD) and willing to engage in treatment were eligible for ED-initiated buprenorphine and peer recovery coaches assisted in arranging next day follow-up with a community treatment program or other local provider for ongoing treatment. METHOD: Hospital partner sites included a large academic medical center, a large private hospital, and a small community hospital. Prior to implementing this quality improvement initiative, the authors completed an ED workflow analysis at each site, developed internal planning committees including identification of a "hospital champion," facilitated electronic health record modifications, educated more than 200 ED nurses and providers, and identified a network of local community "fast-track" providers able to accept patients for next-day appointments. RESULTS: Within 14 months, all three sites were fully operationalized and project staff in 3 ED sites screened 6523 patients for substance misuse with 33.0% screened positive for at-risk substance use. Positive screening results were as follows by substance: 907 alcohol, 100 cocaine, 40 methamphetamine, 7 amphetamines, 96 marijuana, 12 benzodiazepines, 3 Ecstasy/MDMA/ Molly, 10 other/unknown substance, 274 heroin, 90 prescription opioids, 32 other/unknown opioid, 254 undetermined polysubstance use without opioids, and 331 polysubstance use with opioids. Of the 727 positive screened patients for non-medical opioid use, 70.0% were determined potentially eligible to receive buprenorphine initiation. Two-hundred thirty-one patients were initiated with one dose of 8 mg sublingual buprenorphine or 8-2 mg sublingual buprenorphine/naloxone; 76.6% of those initiated arrived to next-day appointments for continued medications for opioid use disorder (MOUD); and 59.9% of those patients were retained in treatment at 30 days. Of referred patients, payor at time of ED visit were as follows: 71.1% uninsured, 21.4% state Medicaid, 1.6% Medicare, and 5.9% private health insurance. CONCLUSION: With adequate resources and institutional support, implementation of evidence-based quality improvement initiatives focused on OUDs are feasible and enhance linkage to evidence-based treatment in a rural Southern state. Lessons learned from this implementation study can be used to guide future CTN studies focused on ED settings. PROJECT SUPPORT: Financially supported by South Carolina Department of Health and Human Services with consultation and guidance from Mosaic Group and South Carolina Department of Alcohol and Other Drug Services.

Comparison Of Timeline Follow-Back Self-Report And Oral Fluid Testing To Detect Substance Use In Adult Primary Care Patients Nordeck CD, Gryczynski J, O'Grady KE, Polak K, Svikis DS, McNeely J, Wu LT, Schwartz RP. Drug Alcohol Depend. 2020 Apr 1; 209: 107939. [Epub 2020 Feb 22].

BACKGROUND: Timeline Follow-back (TLFB) interviews using self-report are often used to assess substance use. Oral fluid testing (OFT) offers an objective measure of substance use. There are limited data on the agreement between TLFB and OFT. METHODS: In this secondary analysis from a multisite study in five primary care sites, self-reported TLFB and OFT data collected under confidential conditions were compared to assess concordance (N=1799). OFT samples were analyzed for marijuana, heroin, cocaine, and non-medical use of prescription opioids. Demographic differences in discordance relative to TLFB and OFT concordant results for marijuana, the only substance with an adequate sample size in this analysis, were examined using multinomial logistic regression. RESULTS: Overall concordance rates between TLFB and OFT were 94.9% or higher for each substance, driven by large subgroups with no use. Among participants with discordant use, marijuana was the only substance with lower detection on OFT than self-report (27.6% OFT-positive only vs. 32.2% TLFB-positive only), whereas cocaine (65.6% vs 8.6%), prescription opioids (90.4% vs 6.0%), and heroin (40.7% vs 26.0%) all had higher detection via OFT than TLFB. Participants who reported marijuana use but had a negative OFT were more likely to be younger, Hispanic, and White compared to those with TLFB and OFT concordant positive results. CONCLUSIONS: TLFB and OFT show disparate detection of different substances. Researchers should consider the implications of using either self-report or oral fluid testing in isolation, depending on the substance and collection setting. Triangulating multiple sources of information may improve detection of drug use.

[A Systematic Scoping Review Of Research On Black Participants In The National Drug Abuse Treatment Clinical Trials Network](#) Montgomery L, Burlew AK, Haeny AM, Jones CA. Psychol Addict Behav. 2020 Feb; 34(1): 117-127. [Epub 2019 Jun 27].

Black individuals experience a disproportionate burden of substance-related disabilities and premature death relative to other racial/ethnic groups, highlighting the need for additional research. The National Drug Abuse Treatment Clinical Trials Network (CTN), a research platform for multisite behavioral, pharmacological, and integrated trials designed to evaluate the effectiveness of substance use treatments in community settings with diversified patient populations, provides a wealth of research knowledge on substance use. Although CTN trials have enrolled over 5,000 Black individuals since its inception in 2000, there has been no synthesis of the findings, discussion of the implications, or suggestions for future research for Black individuals. Members of the Minority Interest Group of the CTN conducted a scoping review of published research on Black participants in CTN trials. Studies were included if the sample was more than 75% Black and/or specific findings pertaining to Black participants were reported. The review yielded 50 articles, with studies that mostly focused on baseline characteristics, followed by substance use treatment outcomes, HIV/risky sex behaviors, retention, comorbid conditions and measurement issues. This review highlighted the importance of several issues that are critical to understanding and treating substance misuse among Black people, such as the characteristics of Black people entering treatment, measurement equivalence, and engaging/retaining adolescents and young adults in treatment. There is still a continued need to identify the most effective treatments for Black individuals who use substances. The CTN offers several untapped opportunities to further advance research on Black individuals who use substances (e.g., secondary analyses of publicly available data).

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

[Sleep Duration, Brain Structure, And Psychiatric And Cognitive Problems In Children](#) Cheng W, Rolls E, Gong W, Du J, Zhang J, Zhang X-Y, Li F, Feng J Molecular Psychiatry. 2020 Feb 3. [Epub ahead of print].

Low sleep duration in adults is correlated with psychiatric and cognitive problems. We performed for the first time a large-scale analysis of sleep duration in children, and how this relates to psychiatric problems including depression, to cognition, and to brain structure. Structural MRI was analyzed in relation to sleep duration, and psychiatric and cognitive measures in 11,067 9-11-year-old children from the Adolescent Brain Cognitive Development (ABCD) Study, using a linear mixed model, mediation analysis, and structural equation methods in a longitudinal analysis. Dimensional psychopathology (including depression, anxiety, impulsive behavior) in the children was negatively correlated with sleep duration. Dimensional psychopathology in the parents was also correlated with short sleep duration in their children. The brain areas in which higher volume was correlated with longer sleep duration included the orbitofrontal cortex, prefrontal and temporal cortex, precuneus, and supramarginal gyrus. Longitudinal data analysis showed that the psychiatric problems, especially the depressive problems, were significantly associated with short sleep duration 1 year later. Further, mediation analysis showed that depressive problems significantly mediate the effect of these brain regions on sleep. Higher cognitive scores were associated with higher volume of the prefrontal cortex, temporal cortex, and medial orbitofrontal cortex. Public health implications are that psychopathology in the parents should be considered in relation to sleep problems in children. Moreover, we show that brain structure is associated with sleep problems in children, and that this is related to whether or not the child has depressive problems.

[Prevalence And Family-Related Factors Associated With Suicidal Ideation, Suicide Attempts, And Self-Injury In Children Aged 9 To 10 Years](#) DeVille DC, Whalen D, Breslin FJ, Morris AS, Khalsa SS, Paulus MP, Barch, DM. JAMA Network Open 3 (2), e1920956 2020 Feb 5.

Importance: Although suicide is a leading cause of death for children in the United States, and the rate of suicide in childhood has steadily increased, little is known about suicidal ideation and behaviors in children. Objective: To assess the overall prevalence of suicidal ideation, suicide attempts, and nonsuicidal self-injury, as well as family-related factors associated with suicidality and self-injury among preadolescent children. Design, setting, and participants: Cross-sectional study using retrospective analysis of the baseline sample from the Adolescent Brain Cognitive Development (ABCD) study. This multicenter investigation used an epidemiologically informed school-based recruitment strategy, with consideration of the demographic composition of the 21 ABCD sites and the United States as a whole. The sample included children aged 9 to 10 years and their caregivers. Main outcomes and measures: Lifetime suicidal ideation, suicide attempts, and nonsuicidal self-injury as reported by children and their caregivers in a computerized version of the Kiddie Schedule for Affective Disorders and Schizophrenia. Results: A total of 11 814 children aged 9 to 10 years (47.8% girls; 52.0% white) and their caregivers were included. After poststratification sociodemographic weighting, the approximate prevalence rates were 6.4% (95% CI, 5.7%-7.3%) for lifetime history of passive suicidal ideation; 4.4% (95% CI, 3.9%-5.0%) for nonspecific active suicidal ideation; 2.4% (95% CI, 2.1%-2.7%) for active ideation with method, intent, or plan; 1.3% (95% CI, 1.0%-1.6%) for suicide attempts; and 9.1% (95% CI, 8.1-10.3) for nonsuicidal self-injury. After covarying by sex, family history, internalizing and externalizing problems, and relevant psychosocial variables, high family conflict was significantly associated with suicidal ideation (odds ratio [OR], 1.12; 95% CI, 1.07-1.16) and nonsuicidal self-injury (OR, 1.09; 95% CI, 1.05-1.14), and low parental monitoring was significantly associated with ideation

(OR, 0.97; 95% CI, 0.95-0.98), attempts (OR, 0.91; 95% CI, 0.86-0.97), and nonsuicidal self-injury (OR, 0.95; 95% CI, 0.93-0.98); these findings were consistent after internal replication. Most of children's reports of suicidality and self-injury were either unknown or not reported by their caregivers. Conclusions and relevance: This study demonstrates the association of family factors, including high family conflict and low parental monitoring, with suicidality and self-injury in children. Future research and ongoing prevention and intervention efforts may benefit from the examination of family factors.

[Risk And Protective Factors For Childhood Suicidality: A US Population-Based Study](#) Janiri D, Doucet GE, Pompili M, Sani G, Luna B, Brent DA, Frangou S Lancet Psychiatry. 2020 March 12. [Epub ahead of print].

Background: Childhood suicidal ideation and behaviours are poorly understood. We examined correlates of suicidality in a U.S. population-based sample of children participating in the Adolescent Brain and Cognitive Development (ABCD) study. The ABCD study aims to examine trajectories of mental health from childhood to adulthood and collects information on multiple domains, including mental and physical wellbeing, brain imaging, behavioural and cognitive characteristics, and social and family environment. We sought to identify and rank risk and protective factors for childhood suicidal thoughts and behaviours across these multiple domains and evaluate their association with self-agreement and caregiver agreement in reporting suicidality. Methods: The ABCD sample comprises a cohort of 11 875 children aged 9–10 years. The sociodemographic factors on which the sample was recruited were age, sex, race, socioeconomic status, and urbanicity. Participants were enrolled at 22 sites, the catchment area of which encompassed over 20% of the entire U.S. population in this age group. Multistage sampling was used to ensure both local randomisation and representativeness of sociodemographic variation of the ABCD sample. The data used in this study were accessed from the ABCD Study Curated Annual Release 2.0. Suicidal thoughts and behaviours (suicidality) in each child were evaluated through independent child and caregiver reports based on the computerized Kiddie Schedule for Affective Disorders and Schizophrenia for DSM-5 (KSADS-5). We used bootstrapped logistic regression to quantify the association between suicidal ideation and behaviours, with measures of mental and physical wellbeing, behaviour, cognition, and social and family environment in participants from the ABCD study. Findings: Our study sample comprised 7994 unrelated children (mean age 9·9 years [SD 0·5]; 4234 [53%] male participants) with complete data on child-reported and caregiver-reported suicidal ideas and behaviours. Overall, 673 (8·4%) children reported any past or current suicidal ideation, 75 (0·9%) had any past or current suicidal plans, and 107 (1·3%) had any past or current suicidal attempts. According to caregivers, 650 (8·1%) of the children reported any past or current suicidal ideation, 46 (0·6%) reported any past or current suicidal plans, and 39 (0·5%) reported past or current suicidal attempts. However, inter-informant agreement was low (Cohen's κ range 0·0–0·2). Regardless of informant, child psychopathology (odds ratio [OR] 1·7–4·8, 95% CI 1·5–7·4) and child-reported family conflict (OR 1·4–1·8, 95% CI 1·1–2·5) were the most robust risk factors for suicidality. The risk of child-reported suicidality increased with higher weekend screen use time (OR 1·3, 95% CI 1·2–1·7) and reduced with greater parental supervision and positive school involvement (for both OR 0·8, 95% CI 0·7–0·9). Additionally, caregiver-reported suicidality was positively associated with caregiver educational level (OR 1·3, 95% CI 1·1–1·5) and male sex in children (1·5, 1·1–2·0), and inversely associated with the number of household cohabitants (0·8, 0·7–1·0). Interpretation: We identified risk and protective factors that show robust and generalisable associations with childhood suicidality. These factors provide actionable targets for optimising prevention and intervention strategies, support the need to identify

and treat psychopathology in school-age children, and underscore the importance of school and family interventions for childhood suicidality.

INTRAMURAL RESEARCH

Causal Evidence Supporting The Proposal That Dopamine Transients Function As Temporal Difference Prediction Errors Maes EJP, Sharpe MJ, Usypchuk AA, Lozzi M, Chang CY, Gardner MPH, Schoenbaum G, Iordanova MD. Nature Neuroscience 2020; 23(2): 176–178. Reward-evoked dopamine transients are well established as prediction errors. However, the central tenet of temporal difference accounts—that similar transients evoked by reward-predictive cues also function as errors—remains untested. In the present communication we addressed this by showing that optogenetically shunting dopamine activity at the start of a reward-predicting cue prevents second-order conditioning without affecting blocking. These results indicate that cue-evoked transients function as temporal-difference prediction errors rather than reward predictions.

Abstinence-Dependent Dissociable Central Amygdala Microcircuits Control Drug Craving Venniro M, Russell TI, Ramsey LA, Richie CT, Lesscher HMB, Giovanetti SM, Messing RO, Shaham Y. Proc Natl Acad Sci USA. 2020 Apr 7; 117(14): 8126-8134.
We recently reported that social choice–induced voluntary abstinence prevents incubation of methamphetamine craving in rats. This inhibitory effect was associated with activation of protein kinase-Cδ (PKCδ)-expressing neurons in central amygdala lateral division (CeL). In contrast, incubation of craving after forced abstinence was associated with activation of CeL-expressing somatostatin (SOM) neurons. Here we determined the causal role of CeL PKCδ and SOM in incubation using short-hairpin RNAs against PKCδ or SOM that we developed and validated. We injected two groups with shPKCδ or shCtrlPKCδ into CeL and trained them to lever press for social interaction (6 d) and then for methamphetamine infusions (12 d). We injected two other groups with shSOM or shCtrlSOM into CeL and trained them to lever press for methamphetamine infusions (12 d). We then assessed relapse to methamphetamine seeking after 1 and 15 abstinence days. Between tests, the rats underwent either social choice–induced abstinence (shPKCδ groups) or homecage forced abstinence (shSOM groups). After test day 15, we assessed PKCδ and SOM, Fos, and double-labeled expression in CeL and central amygdala medial division (CeM). shPKCδ CeL injections decreased Fos in CeL PKCδ-expressing neurons, increased Fos in CeM output neurons, and reversed the inhibitory effect of social choice–induced abstinence on incubated drug seeking on day 15. In contrast, shSOM CeL injections decreased Fos in CeL SOM-expressing neurons, decreased Fos in CeM output neurons, and decreased incubated drug seeking after 15 forced abstinence days. Our results identify dissociable central amygdala mechanisms of abstinence-dependent expression or inhibition of incubation of craving.

In A Rat Model Of Opioid Maintenance, The G-Protein-Biased MOR Agonist TRV130 Decreases Relapse To Oxycodone Seeking And Taking And Prevents Oxycodone-Induced Brain Hypoxia Bossert JM, Kiyatkin E, Korah H, Hoots JK, Afzal A, Perekopskiy D, Thomas S, Fredriksson I, Blough BE, Negus SS, Epstein DH, Shaham Y. Biological Psychiatry. 2020 Feb 24. pii: S0006-3223(20)30103-7.
Maintenance treatment with opioid agonists (buprenorphine, methadone) is effective for opioid addiction but does not eliminate opioid use in all patients. Here, we modeled maintenance treatment in rats that self-administered the prescription opioid oxycodone. The maintenance medication was either buprenorphine or the G-protein-biased mu opioid receptor (MOR) agonist TRV130. We then tested prevention of oxycodone seeking and taking during abstinence using a modified context-induced-reinstatement procedure, a rat relapse model.

[Intrinsic Differences In Insular Circuits Moderate The Negative Association Between Nicotine Dependence And Cingulate-Striatal Connectivity Strength](#) Keeley RJ, Hsu L-M, Brynildsen JK, Lu H, Yang Y, Stein EA. Neuropsychopharmacol. 2020 May; 45(6): 1042-1049.

The development of brain-based biomarkers to assess nicotine dependence severity and treatment efficacy are essential to improve the current marginally effective treatment outcomes. Cross-sectional resting state functional connectivity (rsFC) studies in humans identified a circuit between the dorsal anterior cingulate cortex and the ventral striatum that negatively correlated with increased nicotine dependence severity but was unaffected by acute nicotine administration, suggesting a trait marker of addiction. However, whether this trait circuit dysregulation is predispositional to or resultant from nicotine dependence is unclear. Using a rat model of nicotine dependence with longitudinal fMRI measurements, we assessed the relationship between ACC-striatal rsFC and nicotine dependence severity. Data-driven modularity-based parcellation of the rat medial prefrontal cortex (mPFC) combined with seed-based connectivity analysis with the striatum recapitulated the cingulate-striatum relationship observed in humans. Furthermore, the relationship between cingulate-striatal brain circuits and nicotine dependence severity as indexed by the intensity of precipitated withdrawal, was fully statistically moderated by a predispositional insular-frontal cortical functional circuit. These data suggest that the identified trans-species ACC-striatal circuit relationship with nicotine dependence severity is dysregulated following chronic nicotine administration-induced dependence and may be biased by individual differences in predispositional insula-based striatal-frontal circuits, highlighting the circuit's potential as a biomarker of dependence severity.

[Distinct Inactive Conformations Of The Dopamine D2 And D3 Receptors Correspond To Different Extents Of Inverse Agonism](#) Lane JR, Abramyan AM, Adhikari P, Keen AC, Lee K-H, Sanchez J, Verma RK, Lim HD, Yano H, Javitch JA, Shi L. eLife 9, e52189.

By analyzing and simulating inactive conformations of the highly homologous dopamine D2 and D3 receptors (D2R and D3R), we find that eticlopride binds D2R in a pose very similar to that in the D3R/eticlopride structure but incompatible with the D2R/risperidone structure. In addition, risperidone occupies a sub-pocket near the Na^+ binding site, whereas eticlopride does not. Based on these findings and our experimental results, we propose that the divergent receptor conformations stabilized by Na^+-sensitive eticlopride and Na^+-insensitive risperidone correspond to different degrees of inverse agonism. Moreover, our simulations reveal that the extracellular loops are highly dynamic, with spontaneous transitions of extracellular loop 2 from the helical conformation in the D2R/risperidone structure to an extended conformation similar to that in the D3R/eticlopride structure. Our results reveal previously unappreciated diversity and dynamics in the inactive conformations of D2R. These findings are critical for rational drug discovery, as limiting a virtual screen to a single conformation will miss relevant ligands.

GRANTEE HONORS AND AWARDS

Daniela Salvemini, Ph.D.*,* Saint Louis University School of Medicine, was awarded the 2020 Pharmacia-American Society for Pharmacology and Experimental Therapeutics (ASPET) Award for Experimental Therapeutics for her outstanding contributions toward understanding the molecular and cellular basis of neuropathic pain.

Linda A. Dykstra, M.A., Ph.D.*,* University of North Carolina, was awarded the 2020 P.B. Dews Lifetime Achievement Award for research in Behavioral Pharmacology.

Erin S. Calipari, Ph.D., Vanderbilt University, was awarded the ASPET 2020 Division for Neuropharmacology Early Career Award. She is being recognized for her innovative and collaborative approaches to research and mentoring. She was invited to present an award lecture entitled "Divergent molecular adaptations in the striatum control of the transition to addiction in males and females."

Tracy Smith, Ph.D.*,* Medical University of South Carolina, was awarded the 2020 Society for Research on Nicotine and Tobacco Jarvik-Russell Early Career Award, named after Murray Jarvik-Russell, which recognizes scientists early in their careers who have made extraordinary contributions to the field of nicotine and tobacco research.

Published in February 2020, a **special issue of *Psychology of Addictive Behaviors*** honors the life and work of **Nancy M. Petry, Ph.D.**, who passed away in July 2018. Nancy was highly engaged with the NIDA Clinical Trials Network as part of two large multisite studies testing contingency management (CM) as a treatment for stimulant use (one in drug free clinics [**CTN-0006**] and the other in methadone clinics [**CTN-0007**]). The articles in the issue span the multiple areas of addiction research to which Dr. Petry made key contributions, including her work on CM, demographic predictors of outcomes, reinforcer pathology and decision making, gambling, and behavior analysis and behavioral pharmacology.

STAFF HONORS AND AWARDS

On April 2, 2020, the U.S. Food and Drug Administration accepted the Investigational New Drug (IND) application filed by Marco Pravetoni, Ph.D. (University of Minnesota), and Sandra Comer, Ph.D. (Columbia University), to start studies in humans of an anti-opioid vaccine. This will allow the investigators to start the first study in humans of an anti-opioid vaccine. **Marta DeSantis, Ph.D.**, Division of Therapeutics and Medical Consequences, was integral in guiding the investigators through the IND preparation and submission.

STAFF CHANGES

New Appointments

Michele Rankin, Ph.D., has joined the Office of Science Policy and Communications (OSPC) as Senior Advisor to the OSPC Director, Jack Stein, Ph.D., where she will help manage NIDA's role in NIH's Helping to End Addiction Long-term[SM] Initiative (NIH HEAL Initiative[SM]), along with other strategic program activities. Michele previously served as NIDA's Research Training Director in the Division of Extramural Research, where she oversaw the strategic growth of the program in both scope and complexity during her tenure.

New Staff

Anne Rancourt, M.P.S., has joined NIDA as the Institute's new communications director and Chief of the Public Information and Liaison Branch, OSPC. Anne comes to us from the National Institute of Allergy and Infectious Diseases, where she oversaw communications on HIV. She previously held communications roles at NIH in the Office of the Director and at the National Heart, Lung and Blood Institute (NHLBI), and has worked as a journalist at *The Washington Post*. She has a B.A. from Georgetown University and a master's degree in strategic public relations from George Washington University.

Sindhu Kizhakke Madathil, Ph.D., joined the Scientific Review Branch, Office of Extramural Policy and Review, Division of Extramural Research, as a Scientific Review Officer. Sindhu is a neuroscientist with more than 20 years of research experience. Previously, she was a Senior Research Scientist at Walter Reed Army Institute of Research, where she managed a neurotrauma research program focused on post-traumatic neuroplasticity, nanoparticle-mediated delivery of therapeutics, and hydrogel mediated point-of-injury care for traumatic brain injury. Sindhu has a Ph.D. in Neuroscience from the Indian Institute of Chemical Biology and conducted her postdoctoral studies at the University of Kentucky Spinal Cord and Brain Injury Research Center. Her postdoctoral research focused on developing mouse models for traumatic brain injury and spinal cord injury.

Nathaniel (Natty) Davis, M.B.A., joined NIDA on February 2, 2020, as the Budget Officer and Chief of the Financial Management Branch. Prior to coming to NIDA, Natty served as the Budget Officer at the National Institute on Minority Health and Health Disparities, and previously he was a senior budget analyst at NHLBI. Prior to joining NIH in 2015, Natty held several positions within the Department of the Army as an active-duty officer and as a civilian budget analyst. He is also currently a member of the Army Reserves, where he serves as a Financial Management Officer in the Office of the Joint Chiefs of Staff.

Arun Mathur joined the NIDA Office of Management's Office of Acquisitions on February 2, 2020, as a Contract Specialist. Arun comes to NIDA from a position with NHLBI.

Nichole Wise joined the NIDA Office of Management's Management Analysis Branch as a Management Analyst on March 15, 2020. Nichole comes to NIDA from a position in the private sector.

Erin Dwyer joined the NIDA Office of Management's Office of Acquisitions on March 15, 2020, as a Contract Specialist. Erin comes to NIDA from a position with the National Institute of Standards and Technology.

Julia Berzhanskaya, Ph.D., joined NIDA's Office of Translational Initiatives and Program Innovations as a Health Scientist Administrator on March 29, 2020. Julia comes to NIDA from a position with the NIH Office of the Director.

Evan Herrmann, Ph.D., joined the NIDA Division of Therapeutics and Medical Consequences' Clinical Research Grants Branch as a Health Scientist Administrator on April 12, 2020.

Marlene Milgrim joined the NIDA Office of Management's Office of Acquisitions as a Contract Specialist on April 12, 2020. Marlene comes to NIDA from a position in the private sector.

Sheila Pirooznia, Ph.D., joined the Division of Extramural Research's Scientific Review Branch as a Health Scientist Administrator on April 26, 2020. Sheila comes to NIDA from a position with the National Institute on Aging.

Staff Departures

Jaqueline Lloyd, Ph.D., a Health Scientist Administrator in NIDA's Prevention Research Branch, left NIDA on March 15, 2020 for a position in the NIH Office of the Director.

Irina Sazonova, Ph.D., a Health Scientist Administrator in NIDA's Office of Translational Initiatives and Program Innovations, left NIDA February 15, 2020, for a position with the National Institute on Aging.

Stacy Novelli, a Budget Analyst in NIDA's Financial Management Branch, left NIDA on February 29, 2020, for a position with the NIH Office of the Director.

Renu Simon left the NIDA Office of Management's Office of Acquisitions on April 10, 2020.

Jagdeep Kathuria left the NIDA Office of Management's Information and Resource Management Branch on April 25, 2020.

Marcus Brown left the NIDA Office of Management's Administrative Management and Analysis Branch on May 9, 2020.

Retirements

Camilla Holland, NIDA Committee Management Official, retired on April 3, 2020, after nearly 50 years of government service. For the more than 28 years of that service, Camilla has been a key member of NIDA's Division of Extramural Research/Office of Extramural Policy and Review. Having deep expertise in committee management policy and the Federal Advisory Committee Act, Camilla has been an invaluable resource to the institute.

IN MEMORIAM

We are saddened by the passing of two outstanding scientists and contributors to the addiction field.

Ron Duman, Ph.D., Professor of Psychiatry and Professor of Neuroscience, Yale University, passed away on February 1, 2020, at the age of 65. Ron made seminal contributions that advanced our understanding of the neurobiological mechanisms underlying the effects of stress on the brain and the mechanism of action of antidepressants. He was known for proposing the neurotropic hypothesis of antidepressant response. He was also the first to identify mTOR signaling and dendritic spine dynamics in prefrontal cortex as a mechanism of action of ketamine.

Eric Simon, Ph.D., Professor Emeritus of New York University Medical Center, passed away on March 30, 2020, at the age of 95. Eric was a major contributor to the field of opioid pharmacology. His laboratory was one of the first to provide evidence for the existence of opioid receptors in the brain, and he coined the term "endorphin." He continued to study the pharmacology of opioids and their mode of action until his retirement at the age of 90.