



DIRECTOR'S REPORT

_____ to the _____
National Advisory Council on Drug Abuse

_____ May 2021 _____

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Director
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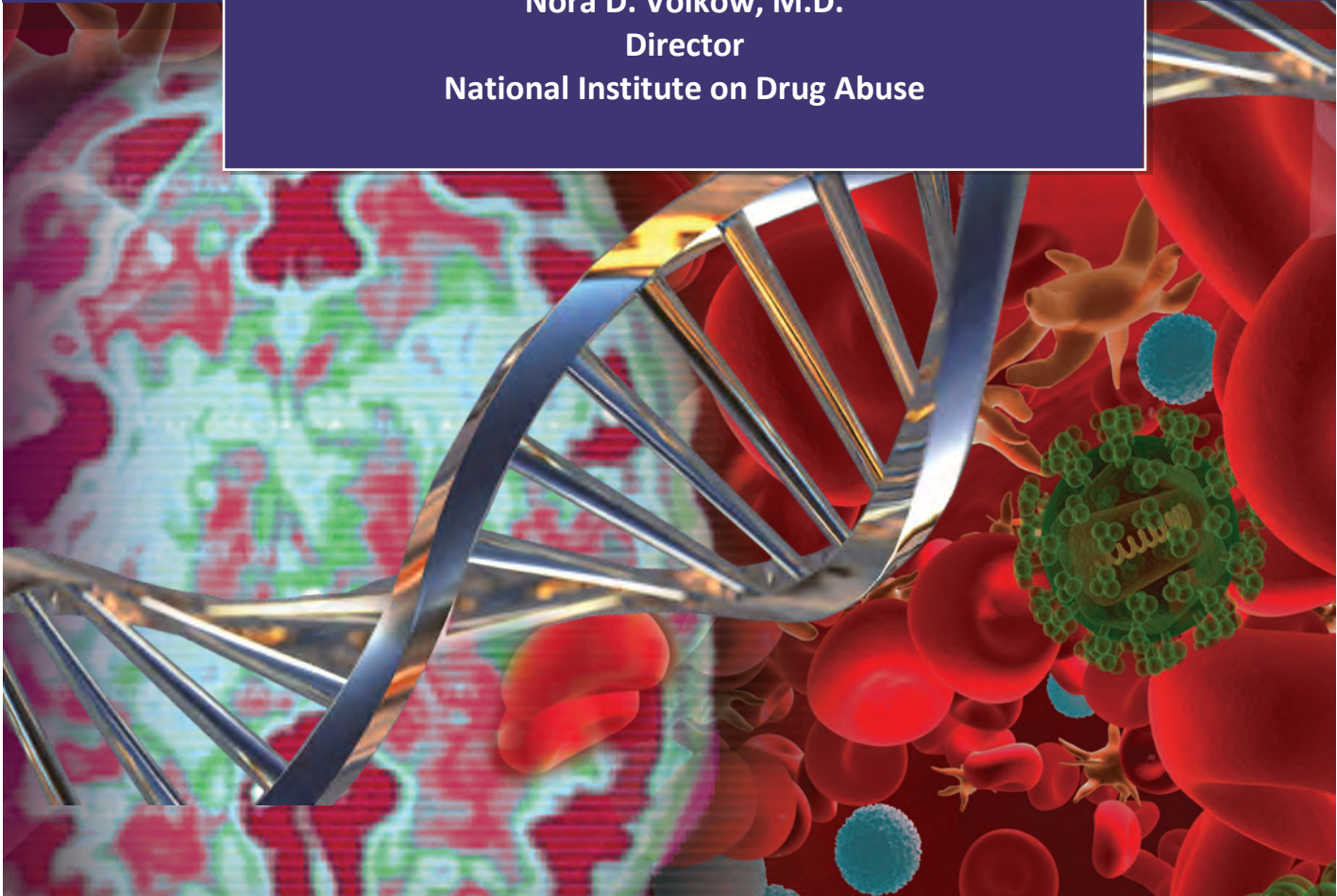


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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Controlling Opioid Receptor Functional Selectivity By Targeting Distinct Subpockets Of The Orthosteric Site Uprety R, Che T, Zaidi SA, Grinnell SG, Varga BR, Faouzi A, Slocum ST, Allaoa A, Varadi A, Nelson M, Bernhard SM, Kulko E, Le Rouzic V, Eans SO, Simons CA, Hunkele A, Subrath J, Pan YX, Javitch JA, McLaughlin JP, Roth BL, Pasternak GW, Katritch V, Majumdar S. *Elife*. 2021; 10:e56519.

Controlling receptor functional selectivity profiles for opioid receptors is a promising approach for discovering safer analgesics; however, the structural determinants conferring functional selectivity are not well understood. Here, we used crystal structures of opioid receptors, including the recently solved active state kappa opioid complex with MP1104, to rationally design novel mixed mu (MOR) and kappa (KOR) opioid receptor agonists with reduced arrestin signaling. Analysis of structure-activity relationships for new MP1104 analogs points to a region between transmembrane 5 (TM5) and extracellular loop (ECL2) as key for modulation of arrestin recruitment to both MOR and KOR. The lead compounds, MP1207 and MP1208, displayed MOR/KOR Gi-partial agonism with diminished arrestin signaling, showed efficient analgesia with attenuated liabilities, including respiratory depression and conditioned place preference and aversion in mice. The findings validate a novel structure-inspired paradigm for achieving beneficial in vivo profiles for analgesia through different mechanisms that include bias, partial agonism, and dual MOR/KOR agonism.

Striatal Dopamine Mediates Hallucination-Like Perception In Mice Schmac K, Bosc M, Ott T, Sturgill JF, Kepecs A. *Science*. 2021; 372(6537): eabf4740.

Hallucinations, a central symptom of psychotic disorders, are attributed to excessive dopamine in the brain. However, the neural circuit mechanisms by which dopamine produces hallucinations remain elusive, largely because hallucinations have been challenging to study in model organisms. We developed a task to quantify hallucination-like perception in mice. Hallucination-like percepts, defined as high-confidence false detections, increased after hallucination-related manipulations in mice and correlated with self-reported hallucinations in humans. Hallucination-like percepts were preceded by elevated striatal dopamine levels, could be induced by optogenetic stimulation of mesostriatal dopamine neurons, and could be reversed by the antipsychotic drug haloperidol. These findings reveal a causal role for dopamine-dependent striatal circuits in hallucination-like perception and open new avenues to develop circuit-based treatments for psychotic disorders.

CB1 Receptor Signaling Modulates Amygdalar Plasticity During Context-Cocaine Memory Reconsolidation To Promote Subsequent Cocaine Seeking Higginbotham JA, Wang R, Richardson BD, Shiina H, Tan SM, Presker MA, Rossi DJ, Fuchs RA. *J Neurosci*. 2021; 41(4): 613-629.

Contextual drug-associated memories precipitate craving and relapse in cocaine users. Such associative memories can be weakened through interference with memory reconsolidation, a process by which memories are maintained following memory retrieval-induced destabilization. We hypothesized that cocaine-memory reconsolidation requires cannabinoid type 1 receptor (CB1R) signaling based on the fundamental role of the endocannabinoid system in synaptic plasticity and emotional memory processing. Using an instrumental model of cocaine relapse, we evaluated

whether systemic CB1R antagonism (AM251; 3 mg/kg, i.p.) during memory reconsolidation altered (1) subsequent drug context-induced cocaine-seeking behavior as well as (2) cellular adaptations and (3) excitatory synaptic physiology in the basolateral amygdala (BLA) in male Sprague Dawley rats. Systemic CB1R antagonism, during, but not after, cocaine-memory reconsolidation reduced drug context-induced cocaine-seeking behavior 3 d, but not three weeks, later. CB1R antagonism also inhibited memory retrieval-associated increases in BLA zinc finger 268 (zif268) and activity regulated cytoskeletal-associated protein (Arc) immediate-early gene (IEG) expression and changes in BLA AMPA receptor (AMPA) and NMDA receptor (NMDAR) subunit phosphorylation that likely contribute to increased receptor membrane trafficking and synaptic plasticity during memory reconsolidation. Furthermore, CB1R antagonism increased memory reconsolidation-associated spontaneous EPSC (sEPSC) frequency in BLA principal neurons during memory reconsolidation. Together, these findings suggest that CB1R signaling modulates cellular and synaptic mechanisms in the BLA that may facilitate cocaine-memory strength by enhancing reconsolidation or synaptic reentry reinforcement, or by inhibiting extinction-memory consolidation. These findings identify the CB1R as a potential therapeutic target for relapse prevention.

Reelin Deficiency Contributes To Long-Term Behavioral Abnormalities Induced By Chronic Adolescent Exposure To Δ 9-Tetrahydrocannabinol In Mice

Iemolo A, Montilla-Perez P, Nguyen J, Risbrough VB, Taffe MA, Teles F. *Neuropharmacology*. 2021; 187: 108495.

Cannabis use is widespread among adolescents and has been associated with long-term negative outcomes on neurocognitive functions. However, the factors that contribute to the long-term detrimental effects of cannabis use remain poorly understood. Here, we studied how Reelin deficiency influences the behavior of mice exposed to cannabis during adolescence. Reelin is a gene implicated in the development of the brain and of psychiatric disorders. To this aim, heterozygous Reeler (HR) mice, that express reduced level of Reelin, were chronically injected during adolescence with high doses (10 mg/kg) of Δ 9-tetrahydrocannabinol (THC), a major psychoactive component of cannabis. Two weeks after the last injection of THC, mice were tested with multiple behavioral assays, including working memory, social interaction, locomotor activity, anxiety-like responses, stress reactivity, and pre-pulse inhibition. Compared to wild-type (WT), HR mice treated with THC showed impaired social behaviors, elevated disinhibitory phenotypes and increased reactivity to aversive situations, in a sex-specific manner. Overall, these findings show that Reelin deficiency influences behavioral abnormalities caused by heavy consumption of THC during adolescence and suggest that elucidating Reelin signaling will improve our understanding of neurobiological mechanisms underlying behavioral traits relevant to the development of psychiatric conditions.

Expansion Sequencing: Spatially Precise In Situ Transcriptomics In Intact Biological Systems

Alon S, Goodwin DR, Sinha A, Wassie AT, Chen F, Daugharthy ER, Bando Y, et al. *Science*. 2021; 371(6528): eaax2656.

Methods for highly multiplexed RNA imaging are limited in spatial resolution and thus in their ability to localize transcripts to nanoscale and subcellular compartments. We adapt expansion microscopy, which physically expands biological specimens, for long-read untargeted and targeted in situ RNA sequencing. We applied untargeted expansion sequencing (ExSeq) to the mouse brain, which yielded the readout of thousands of genes, including splice variants. Targeted ExSeq yielded nanoscale-resolution maps of RNAs throughout dendrites and spines in the neurons of the mouse hippocampus, revealing patterns across multiple cell types, layer-specific cell types across the

mouse visual cortex, and the organization and position-dependent states of tumor and immune cells in a human metastatic breast cancer biopsy. Thus, ExSeq enables highly multiplexed mapping of RNAs from nanoscale to system scale.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Assessment Of Changes In Alcohol And Marijuana Abstinence, Co-Use, And Use Disorders Among U.S. Young Adults From 2002 to 2018 McCabe SE, Arterberry BJ, Dickinson K, Evans-Polce RJ, Ford JA, Ryan JE, Schepis TS. JAMA Pediatr. 2021; 175(1): 64-72.

Importance: Recent information on the trends in past-year alcohol abstinence and marijuana abstinence, co-use of alcohol and marijuana, alcohol use disorder, and marijuana use disorder among US young adults is limited. Objectives: To assess national changes over time in past-year alcohol and marijuana abstinence, co-use, alcohol use disorder, and marijuana use disorder among US young adults as a function of college status (2002-2018) and identify the covariates associated with abstinence, co-use, and marijuana use disorder in more recent cohorts (2015-2018).

Design, Setting, and Participants: This study examined cross-sectional survey data collected in US households annually between 2002 and 2018 as part of the National Survey on Drug Use and Health. The survey used an independent, multistage area probability sample for all states to produce nationally representative estimates. The sample included 182 722 US young adults aged 18 to 22 years. The weighted screening and weighted full interview response rates were consistently above 80% and 70%, respectively. Main Outcomes and Measures: Measures included past-year abstinence, alcohol use, marijuana use, co-use, alcohol use disorder, marijuana use disorder, prescription drug use, prescription drug misuse, prescription drug use disorder, and other drug use disorders based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Results: The weighted sample comprised 51.1% males. Between 2002 and 2018, there was an annual increase in past-year alcohol abstinence among young adults (college students: 0.54%; 95% CI, 0.44%-0.64%; non-college students: 0.33%; 95% CI, 0.24%-0.43%). There was an annual increase in marijuana use from 2002 to 2018 (college: 0.46%; 95% CI, 0.37%-0.55%; non-college: 0.49%; 95% CI, 0.40%-0.59%) without an increase in marijuana use disorder for all young adults. Past-year alcohol use disorder decreased annually (college: 0.66%; 95% CI, 0.60%-0.74%; non-college: 0.61%; 95% CI, 0.55%-0.69%), while co-use of alcohol and marijuana increased annually between 2002 and 2018 among all young adults (college: 0.60%; 95% CI, 0.51%-0.68%; non-college: 0.56%; 95% CI, 0.48%-0.63%). Young adults who reported co-use of alcohol and marijuana or met criteria for alcohol use disorder and/or marijuana use disorder accounted for 82.9% of young adults with prescription drug use disorder and 85.1% of those with illicit drug use disorder. More than three-fourths of those with both alcohol use disorder and marijuana use disorder reported past-year prescription drug use (78.2%) and illicit drug use (77.7%); 62.2% reported prescription drug misuse. Conclusions and Relevance: The findings of this study suggest that US colleges and communities should create and maintain supportive resources for young adults as the substance use landscape changes, specifically as alcohol abstinence, marijuana use, and co-use increase. Interventions for polysubstance use, alcohol use disorder, and marijuana use disorder may provide valuable opportunities for clinicians to screen for prescription drug misuse.

Cannabis, Vaping, And Respiratory Symptoms In A Probability Sample of U.S. Youth Boyd CJ, McCabe SE, Evans-Polce RJ, Veliz PT. J Adolesc Health. 2021: S1054-139X(21)00047-1.

Purpose: The purpose of this study was to explore the association between respiratory symptoms among U.S. adolescents who were current (past 30-day) users of cigarettes, e-cigarettes, and/or cannabis, as well as lifetime users of cannabis with electronic nicotine delivery systems (ENDS). **Methods:** Wave 4 from a national probability sample (N = 14,798) of adolescents (12–17 years) using Population Assessment of Tobacco and Health Study data was used for this study. Retention rate was 88.4%. **Results:** The odds of indicating “wheezing or whistling” in the chest were roughly two times higher among those who had used cannabis in ENDS (adjusted odds ratio 1.81, 95% confidence interval 1.47–2.22); neither e-cigarettes nor cigarettes had a significant association with all five respiratory symptoms in the fully adjusted models. **Conclusions:** This study provides preliminary evidence that adolescents' cannabis use with ENDS may have negative health consequences. Lifetime cannabis use with ENDS was substantially associated with higher odds of respiratory symptoms.

[Expanding Access To Methadone Treatment In Ohio Through Federally Qualified Health Centers And A Chain Pharmacy: A Geospatial Modeling Analysis](#) Iloglu S, Joudrey PJ, Wang EA, Thornhill TA 4th, Gonsalves G. Drug Alcohol Depend. 2021; 220.

In the United States, methadone provision for opioid use disorder (OUD) occurs at opioid treatment programs (OTPs). Ohio recently enacted a policy to expand methadone administration to Federally Qualified Health Centers (FQHC). Using geospatial analysis, this study compared how the provision of methadone at current OTPs or the proposed expansion to FQHCs and pharmacies meets the urban and rural need for OUD treatment. Over one-third of OUD treatment need was not covered by existing OTPs and coverage decreased with rural classification of zip codes. Most of the gap between supply and need could be mitigated with FQHC methadone provision, which would expand both urban and rural access.

[Changing Course: Supporting A Shift To Environmental Strategies In A State Prevention System](#) Ballard PJ, Pankratz M, Wagoner KG, Cornacchione Ross J, Rhodes SD, Azagba S, Song EY, Wolfson M. Subst Abuse Treat Prev Policy. 2021; 16(1): 7

Background: This study examines how the North Carolina state prevention system responded to a policy shift from individual-level prevention strategies to environmental strategies from the perspective of the organizations implementing the policy shift. **Methods:** We use two data sources. First, we conducted interviews to collect qualitative data from key informants. Second, we used prevention provider agency expenditure data from the year the shift was announced and the following year. **Results:** The interviews allowed us to identify effective features of policy change implementation in complex systems, such as the need for clear communication and guidance about the policy changes. Our interview and expenditure analyses also underscore variation in the level of guidance and oversight provided by implementing agencies to prevention providers. **Conclusions:** Our analyses suggest that more active monitoring and oversight may have facilitated more consistent implementation of the policy shift toward greater use of environmental prevention strategies.

TREATMENT RESEARCH

[Differences In Exposure To Toxic And/or Carcinogenic Volatile Organic Compounds Between Black And White Cigarette Smokers](#) St Helen G, Benowitz NL, Ko J, Jacob P, Gregorich SE, Pérez-Stable EJ, Murphy SE, Hecht SS, Hatsukami DK, Donny EC. J Expo Sci Environ Epidemiol. 2021; 31(2): 211-223.

Objective: It is unclear why Black smokers in the United States have elevated risk of some tobacco-related diseases compared to White smokers. One possible causal mechanism is differential intake of tobacco toxicants, but results across studies are inconsistent. Thus, we examined racial differences in biomarkers of toxic volatile organic compounds (VOCs) present in tobacco smoke. **Method:** We analyzed baseline data collected from 182 Black and 184 White adult smokers who participated in a randomized clinical trial in 2013-2014 at 10 sites across the United States. We examined differences in urinary levels of ten VOC metabolites, total nicotine equivalents (TNE), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), controlling for covariates such as cigarettes per day (CPD), as well as differences in VOCs per TNE to assess the extent to which tobacco exposure, and not metabolic factors, accounted for racial differences. **Results:** Concentration of metabolites of acrolein, acrylonitrile, ethylene oxide, and methylating agents were significantly higher in Blacks compared to Whites when controlled for covariates. Other than the metabolite of methylating agents, VOCs per TNE did not differ between Blacks and Whites. Concentrations of TNE/CPD and VOCs/CPD were significantly higher in Blacks. Menthol did not contribute to racial differences in VOC levels. **Conclusions:** For a given level of CPD, Black smokers likely take in higher levels of acrolein, acrylonitrile, and ethylene oxide than White smokers. Our findings are consistent with Blacks taking in more nicotine and toxicants per cigarette smoked, which may explain their elevated disease risk relative to other racial groups.

Method For Successfully Inducting Individuals Who Use Illicit Fentanyl Onto

Buprenorphine/Naloxone Antoine D, Huhn AS, Strain EC, Turner G, Jardot J, Hammond AS, Dunn KE. Am J Addict. 2021; 30(1): 83-87.

Background and Objectives: Individuals exposed to fentanyl are at risk of precipitated withdrawal using typical buprenorphine/naloxone induction procedures. **Methods:** This case series describes buprenorphine/naloxone inductions of four individuals who tested positive for fentanyl. **Results:** Buprenorphine-precipitated withdrawal was observed in two individuals who completed a conventional buprenorphine/naloxone induction strategy. Two more individuals completed a revised buprenorphine/naloxone induction strategy that did not precipitate withdrawal. **Discussion and Conclusion:** Using multiple 2 mg doses of buprenorphine/naloxone in patients already in mild/moderate withdrawal improved outcomes. **Scientific Significance:** Persons who use illicit fentanyl might be less likely to experience precipitated withdrawal from this revised buprenorphine/naloxone induction strategy.

Activation Of Trace Amine-associated Receptor 1 Selectively Attenuates The Reinforcing Effects Of Morphine

Liu J, Seaman R Jr, Johnson B, Wu R, Vu J, Tian J, Zhang Y, Li JX. Br J Pharmacol. 2021; 178(4): 933-945.

Background and Purpose: Trace amine-associated TA1 receptors play critical roles in regulating dopamine transmission. Previous studies showed that pharmacologically or genetically manipulating the activity of TA1 receptors modulates addiction-like behaviours associated with psychostimulants. However, little is known about whether TA1 receptor modulation would regulate the behavioural effects of opioids. **Experimental Approach:** Effects of the selective TA1 receptor partial agonist RO5263397 on the addiction-related and antinociceptive effects of morphine were systematically assessed in male rats and mice. **Key Results:** RO5263397 attenuated the expression of morphine-induced behavioural sensitization in wildtype but not TA1 receptor knockout mice. RO5263397 shifted the dose-effect curve of morphine self-administration downward and reduced the breakpoint in a progressive ratio schedule of reinforcement but did not affect food self-

administration in rats. RO5263397 decreased the cue- and drug-induced reinstatement of morphine-seeking behaviour in rats. RO5263397 alone did not trigger reinstatement of morphine-seeking behaviour or change locomotor activity in rats with a history of morphine self-administration. However, RO5263397 did not affect the expression of morphine-induced conditioned place preference in mice or rats. RO5263397 did not affect naltrexone-precipitated jumping behaviour or naltrexone-induced conditioned place aversion in morphine-dependent mice. Furthermore, RO5263397 did not affect the analgesic effects of morphine in an acute nociception model in mice and a chronic pain model in rats. Conclusion and Implications: These results indicated that TA1 receptor activation selectively attenuated the reinforcing, but not withdrawal or antinociceptive effects of morphine, suggesting that selective TA1 receptor agonists might be useful to combat opioid addiction, while sparing the analgesic effects.

Developing Translational Vaccines Against Heroin And Fentanyl Through Investigation Of Adjuvants And Stability Blake S, Bremer PT, Zhou B, Petrovsky N, Smith LC, Hwang CS, Janda KD. Mol Pharm. 2021; 18(1): 228-235.

The nearly insurmountable adversity that accompanies opioid use disorder (OUD) creates life-altering complications for opioid users. To worsen matters, existing small-molecule drugs continue to inadequately address OUD due to their engagement of the opioid receptor, which can leave the user to deal with side effects and financial hardships from their repeated use. An alternative therapeutic approach utilizes endogenously generated antibodies through active vaccination to reduce the effect of opioids without modulating the opioid receptor. Here, we explore different adjuvants and storage conditions to improve opioid vaccine efficacy and shelf life. Our results revealed that inulin-based formulations (Advax) containing a CpG oligodeoxynucleotide (ODN) acted as effective adjuvants when combined with a heroin conjugate: immunized mice showed excellent recovery from heroin-induced antinociception accompanied by high titer, high opioid affinity serum antibodies similar to the immunopotentiating properties of traditional alum-based adjuvants. Moreover, nonhuman primates vaccinated with a heroin/fentanyl combination vaccine demonstrated potent antibody responses against opioids when formulated with both inulin and alum adjuvants. Finally, storing a freeze-dried opioid vaccine formulation maintained efficacy for up 1 year at room temperature. The results from our studies represent an advance toward a clinically feasible opioid vaccine.

Pharmacological Comparison Of Mitragynine And 7-Hydroxymitragynine: In Vitro Affinity And Efficacy For M-Opioid Receptor And Opioid-Like Behavioral Effects In Rats Obeng S, Wilkerson JL, León F, Reeves ME, Restrepo LF, Gamez-Jimenez LR, Patel A, Pennington AE, Taylor VA, Ho NP, Braun T, Fortner JD, Crowley ML, Williamson MR, Pallares VLC, Mottinelli M, Lopera-Londoño C, McCurdy CR, McMahan LR, Hiranita T. J Pharmacol Exp Ther. 2021; 376(3): 410-427.

Relationships between μ -opioid receptor (MOR) efficacy and effects of mitragynine and 7-hydroxymitragynine are not fully established. We assessed in vitro binding affinity and efficacy and discriminative stimulus effects together with antinociception in rats. The binding affinities of mitragynine and 7-hydroxymitragynine at MOR (K_i values 77.9 and 709 nM, respectively) were higher than their binding affinities at κ -opioid receptor (KOR) or δ -opioid receptor (DOR). [35 S]guanosine 5'-O-[γ -thio]triphosphate stimulation at MOR demonstrated that mitragynine was an antagonist, whereas 7-hydroxymitragynine was a partial agonist ($E_{max} = 41.3\%$). In separate groups of rats discriminating either morphine (3.2 mg/kg) or mitragynine (32 mg/kg), mitragynine

produced a maximum of 72.3% morphine-lever responding, and morphine produced a maximum of 65.4% mitragynine-lever responding. Other MOR agonists produced high percentages of drug-lever responding in the morphine and mitragynine discrimination assays: 7-hydroxymitragynine (99.7% and 98.1%, respectively), fentanyl (99.7% and 80.1%, respectively), buprenorphine (99.8% and 79.4%, respectively), and nalbuphine (99.4% and 98.3%, respectively). In the morphine and mitragynine discrimination assays, the KOR agonist U69,593 produced maximums of 72.3% and 22.3%, respectively, and the DOR agonist SNC 80 produced maximums of 34.3% and 23.0%, respectively. 7-Hydroxymitragynine produced antinociception; mitragynine did not. Naltrexone antagonized all of the effects of morphine and 7-hydroxymitragynine; naltrexone antagonized the discriminative stimulus effects of mitragynine but not its rate-decreasing effects. Mitragynine increased the potency of the morphine discrimination yet decreased morphine antinociception. Here we illustrate striking differences in MOR efficacy, with mitragynine having less than 7-hydroxymitragynine. Significance Statement: At human μ -opioid receptor (MOR) in vitro, mitragynine has low affinity and is an antagonist, whereas 7-hydroxymitragynine has 9-fold higher affinity than mitragynine and is an MOR partial agonist. In rats, intraperitoneal mitragynine exhibits a complex pharmacology including MOR agonism; 7-hydroxymitragynine has higher MOR potency and efficacy than mitragynine. These results are consistent with 7-hydroxymitragynine being a highly selective MOR agonist and with mitragynine having a complex pharmacology that combines low efficacy MOR agonism with activity at nonopioid receptors.

5HT-2C Agonist Lorcaserin Decreases Cannabis Self-administration In Daily Cannabis

Smokers Arout CA, Cooper ZD, Reed SC, Foltin RW, Comer SD, Levin FR, Haney M. *Addict Biol.* 2021e12993.

There are no FDA-approved treatments for cannabis use disorder (CUD). Preclinical research has shown that the 5HT-2C agonist lorcaserin attenuates cue-induced reinstatement of THC seeking and self-administration. The goal of this placebo-controlled, counterbalanced, within-subject human laboratory study was to examine lorcaserin's effects on cannabis intoxication and self-administration. Lorcaserin (10 mg BID) was administered during one of two 13-day inpatient phases and placebo during the other; each phase was separated by ≥ 7 days of washout. Inpatient phases comprised (1) standardized cannabis administration (7.0% THC) at no financial cost (intoxication), counterbalanced with (2) the option to self-administer cannabis following either 0 or 3 days of abstinence. Cognitive task performance, food intake, subjective ratings of drug effects, objective/subjective sleep measures, and tobacco cigarette use were also assessed. Fifteen normal-weight, daily cannabis users (4F, 11M) not seeking treatment for CUD completed the study. Lorcaserin significantly reduced cannabis self-administration following 0 and 3 days of cannabis abstinence and also reduced craving for cannabis during abstinence. Lorcaserin produced small but significant increases in positive cannabis ratings and body weight relative to placebo. Lorcaserin also reduced tobacco cigarette smoking on days of cannabis administration relative to placebo. During abstinence, subjective but not objective measures of sleep quality worsened during lorcaserin maintenance. Overall, lorcaserin's ability to decrease drug taking and cannabis craving in nontreatment-seeking cannabis users supports further investigation of 5HT-2C agonists as potential pharmacotherapies for CUD.

Lorcaserin Treatment For Extended-release Naltrexone Induction And Retention For Opioid Use Disorder Individuals: A Pilot, Placebo-controlled Randomized Trial Levin FR, Mariani JJ,

Pavlicova M, Choi CJ, Basaraba C, Mahony AL, Brooks DJ, Naqvi N, Bisaga A. *Drug Alcohol Depend.* 2021; 219: 108482.

Background: Opioid Use Disorder (OUD) is a significant public health problem associated with severe morbidity and mortality. While effective pharmacotherapies are available, limitations exist with each. Induction onto extended-release naltrexone (XR-NTX) is more difficult than initiation of buprenorphine or methadone, even in inpatient settings, as it is recommended that patients remain abstinent for at least 7 days prior to initiating XR-NTX. The purpose of this trial was to determine if lorcaserin, a 5HT_{2c} agonist, improves outpatient XR-NTX induction rates. **Methods:** An 8-week trial beginning with a brief detoxification period and induction onto XR-NTX. Sixty participants with OUD were enrolled in the trial, with 49 participants at the initiation of detoxification randomized to lorcaserin or placebo for 39 days. Additionally, ancillary medications were provided. The primary outcome was the proportion of participants inducted onto the first XR-NTX injection. Secondary outcomes were withdrawal severity (measured by COWS and SOWS) prior to the first injection and the proportion of participants receiving the second XR-NTX injection. **Results:** The proportion of participants inducted onto the first (lorcaserin: 36 %; placebo: 44 %; $p = .67$) and the second XR-NTX injection (lorcaserin: 27 %; placebo: 31 %; $p = .77$) was not significantly different between treatment arms. Prior to the first injection, withdrawal scores did not significantly differ between treatment arms over time (treatment*time interaction COWS: $p = .11$; SOWS: $p = .39$). **Conclusions:** Lorcaserin failed to improve outpatient XR-NTX induction rates. Although this study is small, the findings do not support the use of lorcaserin in promoting induction onto XR-NTX or in mitigating withdrawal symptoms.

[Endogenous Theta Stimulation During Meditation Predicts Reduced Opioid Dosing Following Treatment With Mindfulness-Oriented Recovery Enhancement](#) Hudak J, Hanley AW, Marchand WR, Nakamura Y, Yabko B, Garland EL. *Neuropsychopharmacology.* 2021; 46(4): 836-843.

Veterans experience chronic pain at greater rates than the rest of society and are more likely to receive long-term opioid therapy (LTOT), which, at high doses, is theorized to induce maladaptive neuroplastic changes that attenuate self-regulatory capacity and exacerbate opioid dose escalation. Mindfulness meditation has been shown to modulate frontal midline theta (FMT) and alpha oscillations that are linked with marked alterations in self-referential processing. These adaptive neural oscillatory changes may promote reduced opioid use and remediate the neural dysfunction occasioned by LTOT. In this study, we used electroencephalography (EEG) to assess the effects of a mindfulness-based, cognitive training intervention for opioid misuse, Mindfulness-Oriented Recovery Enhancement (MORE), on alpha and theta power and FMT coherence during meditation. We then examined whether these neural effects were associated with reduced opioid dosing and changes in self-referential processing. Before and after 8 weeks of MORE or a supportive psychotherapy control, veterans receiving LTOT ($N = 62$) practiced mindfulness meditation while EEG was recorded. Participants treated with MORE demonstrated significantly increased alpha and theta power (with larger theta power effect sizes) as well as increased FMT coherence relative to those in the control condition—neural changes that were associated with altered self-referential processing. Crucially, MORE significantly reduced opioid dose over time, and this dose reduction was partially statistically mediated by changes in frontal theta power. Study results suggest that mindfulness meditation practice may produce endogenous theta stimulation in the prefrontal cortex, thereby enhancing inhibitory control over opioid dose escalation behaviors.

[Effects Of A Parenting-Focused Mindfulness Intervention On Adolescent Substance Use And Psychopathology: A Randomized Controlled Trial](#) Chaplin TM, Mauro KL, Curby TW, Niehaus C, Fischer S, Turpyn CC, Martelli AM, Miller AB, Leichtweis RN, Baer R, Sinha R. Res Child Adolesc Psychopathol. 2021. Online ahead of print.

Substance use and psychopathology symptoms increase in adolescence. One key risk factor for these is high parent stress. Mindfulness interventions reduce stress in adults and may be useful to reduce parent stress and prevent substance use (SU) and psychopathology in adolescents. This study tested the feasibility and effects of a mindfulness intervention for parents on adolescent SU and psychopathology symptoms. Ninety-six mothers of 11-17 year olds were randomly assigned to a mindfulness intervention for parents (the Parenting Mindfully [PM] intervention) or a brief parent education [PE] control group. At pre-intervention, post-intervention, 6-month follow-up, and 1-year follow-up, adolescents reported on SU and mothers and adolescents reported on adolescent externalizing and internalizing symptoms. Primary intent to treat analyses found that the PM intervention prevented increases in adolescent SU over time, relative to the PE control group. The PM intervention also prevented increases in mother-reported externalizing symptoms over time relative to the PE control group. However, PM did not have a significant effect on internalizing symptoms. PM had an indirect effect on adolescent-reported externalizing symptoms through greater mother mindfulness levels at post-intervention, suggesting mother mindfulness as a potential intervention mechanism. Notably, while mothers reported high satisfaction with PM, intervention attendance was low (31% of mothers attended zero sessions). Secondary analyses with mothers who attended $\geq 50\%$ of the interventions ($n = 48$) found significant PM effects on externalizing symptoms, but not SU. Overall, findings support mindfulness training for parents as a promising intervention and future studies should work to promote accessibility for stressed parents. Clinical Trials Identifier: NCT02038231; Date of Registration: January 13, 2014.

HIV/AIDS RELATED RESEARCH

[GPR18 Drives FAAH Inhibition-Induced Neuroprotection Against HIV-1 Tat-Induced Neurodegeneration](#) Hermes DJ, Yadav-Samudrala BJ, Xu C, Paniccia JE, Meeker RB, Armstrong ML, Reisdorph N, Cravatt BF, Mackie K, Lichtman AH, Ignatowska-Jankowska BM, Lysle DT, Fitting S. Exp. Neurol. 2021; 341: 113699.

Human immunodeficiency virus type 1 (HIV-1) is known to provoke microglial immune responses which likely play a paramount role in the development of chronic neuroinflammatory conditions and neuronal damage related to HIV-1 associated neurocognitive disorders (HAND). In particular, HIV-1 Tat protein is a proinflammatory neurotoxin which predisposes neurons to synaptodendritic injury. Drugs targeting the degradative enzymes of endogenous cannabinoids have shown promise in reducing inflammation with minimal side effects in rodent models. Considering that markers of neuroinflammation can predict the extent of neuronal injury in HAND patients, we evaluated the neurotoxic effect of HIV-1 Tat-exposed microglia following blockade of fatty acid amid hydrolyze (FAAH), a catabolic enzyme responsible for degradation of endocannabinoids, e.g. anandamide (AEA). In the present study, cultured murine microglia were incubated with Tat and/or a FAAH inhibitor (PF3845). After 24 h, cells were imaged for morphological analysis and microglial conditioned media (MCM) was collected. Frontal cortex neuron cultures (DIV 7-11) were then exposed to MCM, and neurotoxicity was assessed via live cell calcium imaging and staining of actin positive dendritic structures. Results demonstrate a strong attenuation of microglial

responses to Tat by PF3845 pretreatment, which is indicated by 1) microglial changes in morphology to a less proinflammatory phenotype using fractal analysis, 2) a decrease in release of neurotoxic cytokines/chemokines (MCP-1/CCL2) and matrix metalloproteinases (MMPs; MMP-9) using ELISA/multiplex assays, and 3) enhanced production of endocannabinoids (AEA) using LC/MS/MS. Additionally, PF3845's effects on Tat induced microglial-mediated neurotoxicity, decreased dysregulation of neuronal intracellular calcium and prevented the loss of actin-positive staining and punctate structure in frontal cortex neuron cultures. Interestingly, these observed neuroprotective effects appeared to be independent of cannabinoid receptor activity (CB1R & CB2R). We found that a purported GPR18 antagonist, CID-85469571, blocked the neuroprotective effects of PF3845 in all experiments. Collectively, these experiments increase understanding of the role of FAAH inhibition and Tat in mediating microglial neurotoxicity in the HAND condition.

Impact Of HIV-Infection On Human Somatosensory Processing, Spontaneous Cortical Activity, And Cortical Thickness: A Multimodal Neuroimaging Approach

Casagrande CC, Lew BJ, Taylor BK, Schantell M, O'Neill J, May PE, Swindells S, Wilson TW. Hum Brain Mapp. 2021 Mar 18. Epub ahead of print.

HIV-infection has been associated with widespread alterations in brain structure and function, although few studies have examined whether such aberrations are co-localized and the degree to which clinical and cognitive metrics are related. We examine this question in the somatosensory system using high-resolution structural MRI (sMRI) and magnetoencephalographic (MEG) imaging of neural oscillatory activity. Forty-four participants with HIV (PWH) and 55 demographically-matched uninfected controls completed a paired-pulse somatosensory stimulation paradigm during MEG and underwent 3T sMRI. MEG data were transformed into the time-frequency domain; significant sensor level responses were imaged using a beamformer. Virtual sensor time series were derived from the peak responses. These data were used to compute response amplitude, sensory gating metrics, and spontaneous cortical activity power. The T1-weighted sMRI data were processed using morphological methods to derive cortical thickness values across the brain. From these, the cortical thickness of the tissue coinciding with the peak response was estimated. Our findings indicated both PWH and control exhibit somatosensory gating, and that spontaneous cortical activity was significantly stronger in PWH within the left postcentral gyrus. Interestingly, within the same tissue, PWH also had significantly reduced cortical thickness relative to controls. Follow-up analyses indicated that the reduction in cortical thickness was significantly correlated with CD4 nadir and mediated the relationship between HIV and spontaneous cortical activity within the left postcentral gyrus. These data indicate that PWH have abnormally strong spontaneous cortical activity in the left postcentral gyrus and such elevated activity is driven by locally reduced cortical gray matter thickness.

Cannabis Use Is Associated With Reduced Risk Of Exposure To Fentanyl Among People On Opioid Agonist Therapy During A Community-wide Overdose Crisis

Socias ME, Choi J, Lake S, Wood E, Valleriani J, Hayashi K, Kerr T, Milloy MJ. Drug Alcohol Depend. 2021; 219: 108420. Background: The ongoing opioid overdose crisis is driven largely by exposure to illicitly-manufactured fentanyl. Preliminary observational and experimental research suggests that cannabis could potentially play a role in reducing use of prescription opioids among individuals with chronic pain. However, there is limited data on the effects of cannabis on illicit opioid consumption, particularly fentanyl, especially among individuals on opioid agonist therapy (OAT). We sought to assess the longitudinal association between cannabis use and exposure to fentanyl among people on

OAT. Methods: Data were drawn from two community-recruited prospective cohorts of people who use drugs in Vancouver, Canada. We used generalized linear mixed-effects modeling, adjusted by relevant confounders, to investigate the relationship between cannabis use and recent fentanyl exposure (both assessed by urine drug testing) among participants on OAT between 2016 and 2018. Results: Among the 819 participants on OAT who contributed 1989 observations over the study period, fentanyl exposure was common. At the baseline interview, fentanyl was detected in a majority of participants (431, 53 %), with lower prevalence among individuals with urine drug tests positive for tetrahydrocannabinol (47 vs. 56 %, $p = 0.028$). Overall study interviews, cannabis use was independently associated with reduced likelihood of being recently exposed to fentanyl (Adjusted Prevalence Ratio = 0.91, 95 % Confidence Interval: 0.83 - 0.99). Conclusions: Participants on OAT using cannabis had significantly lower risk of being exposed to fentanyl. Our findings reinforce the need for experimental trials to investigate the potential benefits and risks of controlled cannabinoid administration for people on OAT.

Biomarkers Of Endothelial Dysfunction In Cocaine Overdose And Overdose-related Cardiovascular Events Manini AF, Gibson CL, Miller ML, Richardson LD, Vargas-Torres CC, Vedanthan R, Hurd YL. *Addict Biol.* 2021; 26(2): e12901.

Overdose of stimulant drugs has been associated with increased risk of adverse cardiovascular events (ACVE), some of which may be ascribed to endothelial dysfunction. The aims of this study were to evaluate biomarkers of endothelial dysfunction in emergency department (ED) patients with acute cocaine overdose and to assess the association between in-hospital ACVE in ED patients with any acute drug overdose. This was a prospective consecutive cohort study over 9 months (2015-2016) at two urban, tertiary-care hospital EDs. Consecutive adults (≥ 18 years) presenting with suspected acute drug overdose were eligible and separated into three groups: cocaine ($n = 47$), other drugs ($n = 128$), and controls ($n = 11$). Data were obtained from medical records and linked to waste serum specimens, sent as part of routine clinical care, for biomarker analysis. Serum specimens were collected and analyzed using enzyme-linked immunosorbent assay kit for three biomarkers of endothelial dysfunction: (a) endothelin-1 (ET-1), (b) regulated upon activation normal T cell expressed and secreted (RANTES), and (c) soluble intercellular adhesion molecule-1 (siCAM-1). Mean siCAM was elevated for cocaine compared with controls and other drugs ($p < .01$); however, mean RANTES and ET-1 levels were not significantly different for any drug exposure groups. Receiver operating characteristics curve analysis for prediction of in-hospital ACVE revealed excellent performance of siCAM-1 (area under curve, 0.86; $p < .001$) but lack of predictive utility for either RANTES or ET-1. These results suggest that serum siCAM-1 is a viable biomarker for acute cocaine overdose and that endothelial dysfunction may be an important surrogate for adverse cardiovascular events following any drug overdose.

Cardiovascular Risk Factors And Illicit Drug Use May Have A More Profound Effect On Coronary Atherosclerosis Progression In People Living With HIV Kolossváry M, Fishman EK, Gerstenblith G, Bluemke DA, Mandler RN, Celentano D, Kickler TS, Bazr S, Chen S, Lai S, Lai H. *Eur Radiol.* 2021; 31(5): 2756-2767.

Objectives: To assess whether HIV infection directly or indirectly promotes coronary artery disease (CAD) volume progression in a longitudinal study of African Americans. Methods: We randomly selected 300 individuals with subclinical CAD (210 male; age: 48.0 ± 7.2 years; 226 HIV infected, 174 cocaine users) from 1429 cardiovascularly asymptomatic participants of a prospective epidemiological study between May 2004 and August 2015. Individuals underwent coronary CT

angiography at two time points (mean follow-up: 4.0 ± 2.3 years). We quantified noncalcified (NCP: -100-350HU), low-attenuation noncalcified (LA-NCP: -100-30HU), and calcified (CP: ≥ 351 HU) plaque volumes. Linear mixed models were used to assess the effects of HIV infection, atherosclerotic cardiovascular disease (ASCVD) risk, and years of cocaine use on plaque volumes. Results: There was no significant difference in annual progression rates between HIV-infected and HIV-uninfected regarding NCP (8.7 [IQR: 3.0-19.4] mm³/year vs. 4.9 [IQR: 1.5-18.3] mm³/year, $p = 0.14$), LA-NCP (0.2 [IQR: 0.0-1.6] mm³/year vs. 0.2 [IQR: 0.0-0.9] mm³/year, $p = 0.07$) or CP volumes (0.3 [IQR: 0.0-3.4] mm³/year vs. 0.1 [IQR: 0.0-3.2] mm³/year, $p = 0.30$). Multivariately, HIV infection was not associated with NCP (-6.9mm³, CI: [-32.8-19.0], $p = 0.60$), LA-NCP (-0.1mm³, CI: [-2.6-2.4], $p = 0.92$), or CP volumes (-0.3mm³, CI: [-9.3-8.6], $p = 0.96$). However, each percentage of ASCVD and each year of cocaine use significantly increased total, NCP, and CP volumes among HIV-infected individuals, but not among HIV-uninfected. Importantly, none of the HIV-associated medications had any effect on plaque volumes ($p > 0.05$ for all). Conclusions: The more profound adverse effect of risk factors in HIV-infected individuals may explain the accelerated progression of CAD in these people, as HIV infection was not independently associated with any coronary plaque volume. Key points: • Human immunodeficiency virus-infected individuals may have similar subclinical coronary artery disease, as the infection is not independently associated with coronary plaque volumes. • However, cardiovascular risk factors and illicit drug use may have a more profound effect on atherosclerosis progression in those with human immunodeficiency virus infection, which may explain the accelerated progression of CAD in these people. • Nevertheless, through rigorous prevention and abstinence from illicit drugs, these individuals may experience similar cardiovascular outcomes as -uninfected individuals.

[Heroin Use Is Associated With Liver Fibrosis In The Miami Adult Studies On HIV \(MASH\) Cohort](#) Baum MK, Tamargo JA, Ehman RL, Sherman KE, Chen J, Liu Q, Mandler RN, Teeman C, Martinez SS, Campa A. Drug Alcohol Depend. 2021; 220: 108531.

Background: People who use opioids and people living with HIV (PLWH) are at increased risk for liver-related morbidity and mortality. Although animal models suggest that chronic opioid use may cause liver damage, research in humans is limited. We aimed to determine whether opioid use, particularly heroin, was associated with liver fibrosis. Methods: Cross-sectional analysis of 679 participants (295 HIV/HCV uninfected, 218 HIV mono-infected, 87 HCV mono-infected, 79 HIV/HCV coinfecting) from the Miami Adult Studies on HIV (MASH) cohort. Liver fibrosis was assessed via magnetic resonance elastography (MRE) on a 3 T Siemens MAGNETOM Prisma scanner. Results: A total of 120 (17.7 %) participants used opioids. Liver fibrosis was present in 99 (14.6 %) participants and advanced liver fibrosis in 31 (4.6 %). Heroin use (N = 46, 6.8 %) was associated with HCV-seropositivity, smoking, misuse of prescription opioids, and polysubstance use. The use of heroin, but not misuse of prescription opioids, was significantly associated with liver fibrosis (OR = 2.77, 95 % CI: 1.18-6.50) compared to heroin non-users, after adjustment for confounders including excessive alcohol consumption, polysubstance use and HIV and HCV infections. Both HIV and HCV infections were associated with liver fibrosis, whether virally suppressed/undetectable or viremic. Conclusions: Heroin use was independently associated with increased risk for liver fibrosis irrespective of the use of other substances and HIV or HCV infections. Both HIV and HCV were associated with higher risk for liver fibrosis, even among those with suppressed or undetectable viral loads. The exact mechanisms for opioid-induced liver fibrosis remain to be fully elucidated.

Connecting The Dots: A Comparison Of Network Analysis And Exploratory Factor Analysis To Examine Psychosocial Syndemic Indicators Among HIV-Negative Sexual Minority Men

Lee JS, Bainter SA, Carrico AW, Glynn TR, Rogers BG, Albright C, O'Cleirigh C, Mayer KH, Safren SA. J Behav Med. 2020; 43(6): 1026-1040.

Syndemics, or comorbid and mutually reinforcing psychosocial problems, are associated with increased HIV risk among men who have sex with men (MSM). Although the dynamic interplay among syndemic indicators is theorized to be crucial for increasing risk of HIV acquisition, novel approaches are needed to understand how these syndemic problems interrelate. This study examined the associations between nine self-reported syndemic indicators in 194 MSM at high risk of HIV acquisition. We compared exploratory factor analyses (EFA) to a network analysis. In the present study, network analysis consisted of edges representing bidirectional partial polychoric correlations between nodes, which represent psychosocial syndemic indicators. EFA yielded a 1-factor solution including suicidal ideation (SI), injection drug use (IDU), depression, social anxiety, intimate partner violence, substance use, and sexual compulsivity, and excluded heavy drinking and childhood sexual abuse. Network analysis yielded a pattern of interconnectedness with the most central nodes being SI, IDU, substance use, and depression. Statistically significant relationships (absolute edge weights) were found between SI and depression, social anxiety, and IDU, and IDU and substance use. These results suggest that depression and substance use, especially more severe presentations of these conditions such as SI and IDU, are prominent interconnected components of the HIV syndemic among MSM at high risk for HIV acquisition. SI, IDU, substance use, and depression may indeed be prudent targets of intervention. Future research on the inclusion of these syndemic indicators in analytical models involving interaction terms may be warranted.

Medication Adherence And Rate Of Nicotine Metabolism Are Associated With Response To Treatment With Varenicline Among Smokers With HIV

Bauer AM, Hosie Quinn M, Lubitz SF, Flitter A, Ashare RL, Leone FT, Gross R, Hitsman B, Schnoll R. Addict Behav. 2021;112: 106638. People living with HIV/AIDS (PLWHA) who smoke have shown lower cessation rates within placebo-controlled randomized trials of varenicline. Adherence and rate of nicotine metabolism may be associated with quit rates in such clinical trials. This secondary analysis of a randomized placebo-controlled trial of varenicline for smoking among PLWHA examined the relationship between varenicline adherence, nicotine metabolism and end-of-treatment smoking cessation. Combining varenicline and placebo arms, greater adherence and faster nicotine metabolism were related to higher quit rates. Increasing varenicline adherence and ensuring that fast nicotine metabolizers receive varenicline may increase quit rates for PLWHA.

Self-efficacy As A Mediator Of Patient Navigation Interventions To Engage Persons Living With HIV And Substance Use

Traynor SM, Metsch LR, Gooden L, Stitzer M, Matheson T, Tross S, Carrico AW, Jain MK, Del Rio C, Feaster DJ. Drug Alcohol Depend. 2021; 221: 108567.

Background: People living with HIV who report substance use (PLWH-SU) face many barriers to care, resulting in an increased risk for poor health outcomes and the potential for ongoing disease transmission. This study evaluates the mechanisms by which Patient Navigation (PN) and Contingency Management (CM) interventions may work to address barriers to care and improve HIV outcomes in this population. Methods: Mediation analysis was conducted using data from a randomized, multi-site trial testing PN interventions to improve HIV care outcomes among 801 hospitalized PLWH-SU. Direct and indirect effects of PN and PN + CM were evaluated through five potential mediators-psychosocial conditions, healthcare avoidance, financial hardship, system

barriers, and self-efficacy for HIV treatment adherence-on engagement in HIV care and viral suppression. Results: The PN + CM intervention had an indirect effect on improving engagement in HIV care at 6 months by increasing self-efficacy for HIV treatment adherence ($\beta = 0.042$, 95% CI = 0.008, 0.086). PN + CM also led to increases in viral suppression at 6 months ($\beta = 0.090$, 95% CI = 0.023, 0.168) and 12 months ($\beta = 0.069$, 95% CI = 0.009, 0.129) via increases in self-efficacy, although the direct effects were not significant. No mediating effects were observed for PN alone. Conclusion: PN + CM interventions for PLWH-SU can increase an individual's self-efficacy for HIV treatment adherence, which in turn improves engagement in care at 6 months and may contribute to viral suppression over 12 months. Building self-efficacy may be a key factor in the success of such interventions and should be considered as a primary goal of PN + CM in practice.

Prevalence And Medication Treatment Of Opioid Use Disorder Among Primary Care Patients With Hepatitis C and HIV

Tsui JI, Akosile MA, Lapham GT, Boudreau DM, Johnson EA, Bobb JF, Binswanger IA, Yarborough BJH, Glass JE, Rossom RC, Murphy MT, Cunningham CO, Arnsten JH, Thakral M, Saxon AJ, Merrill JO, Samet JH, Bart GB, Horigian VE, Bradley KA. *J Gen Intern Med.* 2021; 36(4): 930-937.

Background: Hepatitis C and HIV are associated with opioid use disorders (OUD) and injection drug use. Medications for OUD can prevent the spread of HCV and HIV. Objective: To describe the prevalence of documented OUD, as well as receipt of office-based medication treatment, among primary care patients with HCV or HIV. Design: Retrospective observational cohort study using electronic health record and insurance data. Participants: Adults ≥ 18 years with ≥ 2 visits to primary care during the study (2014-2016) at 6 healthcare systems across five states (CO, CA, OR, WA, and MN). Main measures: The primary outcome was the diagnosis of OUD; the secondary outcome was OUD treatment with buprenorphine or oral/injectable naltrexone. Prevalence of OUD and OUD treatment was calculated across four groups: HCV only; HIV only; HCV and HIV; and neither HCV nor HIV. In addition, adjusted odds ratios (AOR) of OUD treatment associated with HCV and HIV (separately) were estimated, adjusting for age, gender, race/ethnicity, and site. Key results: The sample included 1,368,604 persons, of whom 10,042 had HCV, 5821 HIV, and 422 both. The prevalence of diagnosed OUD varied across groups: 11.9% (95% CI: 11.3%, 12.5%) for those with HCV; 1.6% (1.3%, 2.0%) for those with HIV; 8.8% (6.2%, 11.9%) for those with both; and 0.92% (0.91%, 0.94%) among those with neither. Among those with diagnosed OUD, the prevalence of OUD medication treatment was 20.9%, 16.0%, 10.8%, and 22.3%, for those with HCV, HIV, both, and neither, respectively. HCV was not associated with OUD treatment (AOR = 1.03; 0.88, 1.21), whereas patients with HIV had a lower probability of OUD treatment (AOR = 0.43; 0.26, 0.72). Conclusions: Among patients receiving primary care, those diagnosed with HCV and HIV were more likely to have documented OUD than those without. Patients with HIV were less likely to have documented medication treatment for OUD.

CLINICAL TRIALS NETWORK RESEARCH

Emergency Department Patients With Untreated Opioid Use Disorder: A Comparison Of Those Seeking Versus Not Seeking Referral To Substance Use Treatment

Coupet E Jr, D'Onofrio G, Chawarski M, Edelman EJ, O'Connor PG, Owens P, Martel S, Fiellin DA, Cowan E, Richardson L, Huntley K, Whiteside LK, Lyons MS, Rothman RE, Pantaloni M, Hawk K. *Drug Alcohol Depend.* 2021; 219: 108428.

Background: Little is known regarding the sociodemographic and clinical characteristics of emergency department (ED) patients with untreated opioid use disorder (OUD) and the relationship of those characteristics with whether they were seeking a referral to substance use treatment at the time of their ED visit. Methods: Using data collected from 2/2017-1/2019 from participants enrolled in Project ED Health (CTN-0069), we conducted a cross-sectional analysis of patients with untreated moderate to severe OUD presenting to one of four EDs in Baltimore, New York City, Cincinnati, or Seattle. Sociodemographic and clinical correlates, and International Classification of Diseases Tenth Revision (ICD-10) diagnosis codes related to opioid withdrawal, injection-related infection, other substance use, overdose, and OUD of those seeking and not seeking a referral to substance use treatment on presentation were compared using univariate analyses. Results: Among 394 study participants, 15.2 % (60/394) came to the ED seeking a referral to substance use treatment. No differences in age, gender, education, health insurance status or housing stability were detected between those seeking and not seeking referral to substance use treatment. Those seeking a referral to substance use treatment were less likely to have urine toxicology testing positive for amphetamine [17 % (10/60) vs 31 % (104/334), $p = 0.023$] and methamphetamine [23 % (14/60) vs 40 % (132/334), $p = 0.017$] compared to those not seeking a referral. Conclusion: Most patients with untreated OUD seen in the EDs were not seeking a referral to substance use treatment. Active identification, treatment initiation, and coding may improve ED efforts to address untreated OUD.

Early Implementation Of Screening For Substance Use In Rural Primary Care: A Rapid Analytic Qualitative Study

Moore SK, Saunders EC, Hichborn E, McLeman B, Meier A, Young R, Nesin N, Farkas S, Hamilton L, Marsch LA, Gardner T, McNeely J. *Subst Abus.* 2020 Dec 2: 1-14. Epub ahead of print.

Few primary care patients are screened for substance use. As part of a phased feasibility study examining the implementation of electronic health record-integrated screening with the Tobacco, Alcohol, and Prescription Medication Screening (TAPS) Tool and clinical decision support (CDS) in rural primary care clinics, focus groups were conducted to identify early indicators of success and challenges to screening implementation. Method: Focus groups ($n = 6$) were conducted with medical assistants (MAs: $n = 3$: 19 participants) and primary care providers (PCPs: $n = 3$: 13 participants) approximately one month following screening implementation in three Federally Qualified Health Centers in Maine. Rapid analysis and matrix analysis using Proctor's Taxonomy of Implementation Outcomes were used to explore implementation outcomes. Results: There was consensus that screening is being used, but use of the CDS was lower, in part due to limited positive screens. Fidelity was high among MAs, though discomfort with the CDS surfaced among PCPs, impacting adoption and fidelity. The TAPS Tool's content, credibility and ease of workflow integration were favorably assessed. Challenges include screening solely at annual visits and self-administered screening for certain patients. Conclusions: Results reveal indicators of implementation success and strategies to address challenges to screening for substance use in primary care.

Increased Morbidity and Mortality In Hypertensive Patients With Substance Use Disorders: Electronic Health Record Findings

Winhusen T, Theobald J, Kaelber DC, Lewis D. *J Stud Alcohol Drugs.* 2020; 81(4): 471-478.

Objective: Substance use disorder (SUD) management by medical providers may be important for patients with comorbid health conditions exacerbated by SUD. This study evaluated potential associations of SUD with morbidity and mortality in a large sample of hypertensive patients.

Method: Analysis of a limited data set was obtained through IBM Watson Health Explorys, a platform integrating data from electronic health records. Matched controls were defined for each of five SUDs: tobacco use disorder (TUD), alcohol use disorder (AUD), cocaine use disorder (COUD), opioid use disorder (OUD), and cannabis use disorder (CUD) using Mahalanobis distance within propensity score calipers. All patients were from The MetroHealth System (Cleveland, OH) and had diagnosed hypertension. SUD group participants had diagnosed abuse/dependence for the substance of interest. Controls for each SUD group had no diagnosis code related to the substance of interest and were selected to match the SUD patients on several factors. Total sample sizes for each SUD-control comparison ranged from 3,176 (CUD) to 49,696 (TUD); proportions of female patients ranged from 31.7% (AUD) to 51.2% (TUD). Outcomes were diagnosis (yes/no) of the following: cerebrovascular accident, myocardial infarction, renal failure, and all-cause mortality. Results: Logistic regressions revealed that SUD was significantly associated with cerebrovascular accident (odds ratios [ORs]: TUD = 2.23; AUD = 1.68; COUD = 2.53; OUD = 1.87; CUD = 2.20), renal failure (ORs: TUD = 1.46; COUD = 2.09; OUD = 1.77), myocardial infarction (ORs: TUD = 2.96; AUD = 1.92; COUD = 3.00), and mortality (ORs: TUD = 1.34; AUD = 1.60; COUD = 1.83; OUD = 1.35; CUD = 1.39). Conclusions: Among patients with hypertension, those with SUDs appear to have significantly greater risk for morbidity and mortality, suggesting the importance of managing SUD in hypertensive patients.

Variants Of Opioid Genes And Response To Treatment Of Opioid Use Disorder With Buprenorphine-naloxone Versus Extended-release Naltrexone In Caucasians

Randesi M, Rotrosen J, Nunes EV, Lee JD, Novo P, Levran O, Ott J, Pavlicova M, Scodes J, Kreek MJ. *Am J Drug Alcohol Abuse*. 2020; 46(6): 761-768.

Background: Sublingual buprenorphine-naloxone (BUP-NX), an FDA-approved treatment for opioid use disorder (OUD), combines buprenorphine (a partial mu/kappa agonist) with naloxone (a mu/ kappa antagonist). Extended-release injection naltrexone (XR-NTX; a mu receptor antagonist and kappa receptor partial agonist) is also an FDA-approved treatment for OUD. However, while some patients respond well to these medications, many others leave treatment and relapse. Objectives: Determine whether gene variants in the opioid gene system are associated with better or worse treatment response. Methods: In a 24-week, multisite, randomized, comparative effectiveness trial of daily, sublingual self-administration of BUP-NX versus monthly injection of XR-NTX conducted in the National Drug Abuse Clinical Trials Network, DNA was collected and four opioid gene variants were evaluated: (1) mu opioid receptor 118A>G; (2) 68-bp repeat in prodynorphin; (3) prodynorphin SNP rs910080; and (4) kappa opioid receptor SNP rs6473797. In non-Hispanic Caucasians ($N = 334$), two outcomes measures were assessed: received first dose (yes/no) and received last dose (yes/no). Separate logistic regressions were used to model each outcome measure as a function of treatment (XR-NTX vs BUP-NX), each gene variant, and their interaction. Results: There were no significant main effects of gene variant on receiving first dose or last dose. There were also no significant gene variant by treatment interactions. Conclusions: The outcome of treatment of OUD with medications is likely a complex function of multiple factors, including environmental, psychosocial, and possibly genetic, such that major effects of genetic variants may be unlikely.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

ABCD Analyses Of Prenatal Exposure To Cannabis: Associations Between Prenatal Cannabis Exposure And Childhood Outcomes: Results From The ABCD Study

Paul SE, Hatoum AS, Fine JD, Johnson EC, Hansen I, Karcher NR, Moreau AL, Bondy E, Qu Y, Carter EB, Rogers CE, Agrawal A, Barch DM, Bogdan R. JAMA Psychiatry. 2021; 78(1): 64-76.

Importance: In light of increasing cannabis use among pregnant women, the US Surgeon General recently issued an advisory against the use of marijuana during pregnancy. Objective: To evaluate whether cannabis use during pregnancy is associated with adverse outcomes among offspring.

Design, setting, and participants: In this cross-sectional study, data were obtained from the baseline session of the ongoing longitudinal Adolescent Brain and Cognitive Development Study, which recruited 11 875 children aged 9 to 11 years, as well as a parent or caregiver, from 22 sites across the United States between June 1, 2016, and October 15, 2018. Exposure: Prenatal cannabis

exposure prior to and after maternal knowledge of pregnancy. Main outcomes and measures:

Symptoms of psychopathology in children (i.e., psychotic-like experiences [PLEs] and internalizing, externalizing, attention, thought, and social problems), cognition, sleep, birth weight, gestational age at birth, body mass index, and brain structure (i.e., total intracranial volume, white matter volume, and gray matter volume). Covariates included familial (e.g., income and familial psychopathology), pregnancy (e.g., prenatal exposure to alcohol and tobacco), and child (e.g., substance use) variables. Results: Among 11 489 children (5997 boys [52.2%]; mean [SD] age, 9.9 [0.6] years) with nonmissing prenatal cannabis exposure data, 655 (5.7%) were exposed to cannabis prenatally. Relative to no exposure, cannabis exposure only before (413 [3.6%]) and after (242 [2.1%]) maternal knowledge of pregnancy were associated with greater offspring psychopathology characteristics (i.e., PLEs and internalizing, externalizing, attention, thought and, social problems), sleep problems, and body mass index, as well as lower cognition and gray matter volume (all $|\beta| > 0.02$; all false discovery rate [FDR]-corrected $P < .03$). Only exposure after knowledge of pregnancy was associated with lower birth weight as well as total intracranial volume and white matter volumes relative to no exposure and exposure only before knowledge (all $|\beta| > 0.02$; all FDR-corrected $P < .04$). When including potentially confounding covariates, exposure after maternal knowledge of pregnancy remained associated with greater PLEs and externalizing, attention, thought, and social problems (all $\beta > 0.02$; FDR-corrected $P < .02$). Exposure only prior to maternal knowledge of pregnancy did not differ from no exposure on any outcomes when considering potentially confounding variables (all $|\beta| < 0.02$; FDR-corrected $P > .70$). Conclusions and relevance: This study suggests that prenatal cannabis exposure and its correlated factors are associated with greater risk for psychopathology during middle childhood. Cannabis use during pregnancy should be discouraged.

Rates Of Incidental Findings In Brain Magnetic Resonance Imaging In Children

Li Y, Thompson WK, Reuter C, et al. JAMA Neurol. 2021 Mar 22. Online ahead of print.

Importance: Incidental findings (IFs) are unexpected abnormalities discovered during imaging and can range from normal anatomic variants to findings requiring urgent medical intervention. In the case of brain magnetic resonance imaging (MRI), reliable data about the prevalence and significance of IFs in the general population are limited, making it difficult to anticipate, communicate, and manage these findings. Objectives: To determine the overall prevalence of IFs in brain MRI in the nonclinical pediatric population as well as the rates of specific findings and findings for which clinical referral is recommended. Design, setting, and participants: This cohort

study was based on the April 2019 release of baseline data from 11 810 children aged 9 to 10 years who were enrolled and completed baseline neuroimaging in the Adolescent Brain Cognitive Development (ABCD) study, the largest US population-based longitudinal observational study of brain development and child health, between September 1, 2016, and November 15, 2018. Participants were enrolled at 21 sites across the US designed to mirror the demographic characteristics of the US population. Baseline structural MRIs were centrally reviewed for IFs by board-certified neuroradiologists and findings were described and categorized (category 1, no abnormal findings; 2, no referral recommended; 3, consider referral; and 4, consider immediate referral). Children were enrolled through a broad school-based recruitment process in which all children of eligible age at selected schools were invited to participate. Exclusion criteria were severe sensory, intellectual, medical, or neurologic disorders that would preclude or interfere with study participation. During the enrollment process, demographic data were monitored to ensure that the study met targets for sex, socioeconomic, ethnic, and racial diversity. Data were analyzed from March 15, 2018, to November 20, 2020. Main outcomes and measures: Percentage of children with IFs in each category and prevalence of specific IFs. Results: A total of 11 679 children (52.1% boys, mean [SD] age, 9.9 [0.62] years) had interpretable baseline structural MRI results. Of these, 2464 participants (21.1%) had IFs, including 2013 children (17.2%) assigned to category 2, 431 (3.7%) assigned to category 3, and 20 (0.2%) assigned to category 4. Overall rates of IFs did not differ significantly between singleton and twin gestations or between monozygotic and dizygotic twins, but heritability analysis showed heritability for the presence or absence of IFs ($h^2 = 0.260$; 95% CI, 0.135-0.387). Conclusions and relevance: Incidental findings in brain MRI and findings with potential clinical significance are both common in the general pediatric population. By assessing IFs and concurrent developmental and health measures and following these findings over the longitudinal study course, the ABCD study has the potential to determine the significance of many common IFs.

INTRAMURAL RESEARCH

[Evolving Schema Representations In Orbitofrontal Ensembles During Learning](#) Zhou J, Jia C, Montesinos-Cartagena M, Gardner MPH, Zong W, Schoenbaum G. *Nature*. 2021; 590 (7847): 606-611.

How do we learn about what to learn about? Specifically, how do the neural elements in our brain generalize what has been learned in one situation to recognize the common structure of-and speed learning in-other, similar situations? We know this happens because we become better at solving new problems-learning and deploying schemas-through experience. However, we have little insight into this process. Here we show that using prior knowledge to facilitate learning is accompanied by the evolution of a neural schema in the orbitofrontal cortex. Single units were recorded from rats deploying a schema to learn a succession of odour-sequence problems. With learning, orbitofrontal cortex ensembles converged onto a low-dimensional neural code across both problems and subjects; this neural code represented the common structure of the problems and its evolution accelerated across their learning. These results demonstrate the formation and use of a schema in a prefrontal brain region to support a complex cognitive operation. Our results not only reveal a role for the orbitofrontal cortex in learning but also have implications for using ensemble analyses to tap into complex cognitive functions.

Past Experience Shapes The Neural Circuits Recruited For Future Learning Sharpe MJ, Batchelor HM, Mueller LE, Gardner MPH, Schoenbaum G. Nat Neurosci. 2021; 24(3): 391-400.

Experimental research controls for past experience, yet prior experience influences how we learn. Here, we tested whether we could recruit a neural population that usually encodes rewards to encode aversive events. Specifically, we found that GABAergic neurons in the lateral hypothalamus (LH) were not involved in learning about fear in naïve rats. However, if these rats had prior experience with rewards, LH GABAergic neurons became important for learning about fear. Interestingly, inhibition of these neurons paradoxically enhanced learning about neutral sensory information, regardless of prior experience, suggesting that LH GABAergic neurons normally oppose learning about irrelevant information. These experiments suggest that prior experience shapes the neural circuits recruited for future learning in a highly specific manner, reopening the neural boundaries we have drawn for learning of particular types of information from work in naïve subjects.

Ketogenic Diet Reduces Alcohol Withdrawal Symptoms In Humans And Alcohol Intake In Rodents Wiers CE, Vendruscolo LF, van der Veen J-W, Manza P, Shokri-Kojori E, Kroll D, Feldman D, McPherson K, Biesecker E, Zhang R, Herman K, Elvig SK, Vendruscolo JCM, Turner SA, Yang S, Schwandt ML, Tomasi D, Cervenka MC, Fink-Jensen A, Benveniste H, Diazgrandos N, Wang G-J, Koob GF, Volkow ND. Science Advances. 7(15): eabf6780.

Individuals with alcohol use disorder (AUD) show elevated brain metabolism of acetate at the expense of glucose. We hypothesized that a shift in energy substrates during withdrawal may contribute to withdrawal severity and neurotoxicity in AUD, and that a ketogenic diet (KD) may mitigate these effects. We found that inpatients with AUD randomized to receive a KD (n=19) required fewer benzodiazepines during the first week of detoxification, in comparison to those receiving a standard American (SA) diet (n=14). Over a 3-week treatment, KD compared to SA showed lower “wanting” and increased dorsal anterior cingulate cortex (dACC) reactivity to alcohol cues, and altered dACC bioenergetics (i.e., elevated ketones and glutamate, lower neuroinflammatory markers). In a rat model of alcohol dependence, a history of KD significantly reduced alcohol consumption. We provide clinical and preclinical evidence for beneficial effects of KD on managing alcohol withdrawal and on reducing alcohol drinking in AUD.

A Target-Agnostic Screen Identifies Approved Drugs To Stabilize The Endoplasmic Reticulum Resident 2 Proteome Henderson MJ, Trychta KA, Yang S-M, Bäck S, Yasgar A, Wires ES, Danchik C, Yan X, Yano H, Shi L, Wu K-J, Wang AQ, Zahoranszky-Kohalmly G, Hu X, Xu X, Maloney D, Zakharov AV, Rai G, Urano F, Airavaara M, Gavrilova O, Jadhav A, Wang Y, Simeonov A, Harvey BK. Cell Reports. 35(4): 109040.

Endoplasmic reticulum (ER) dysregulation is associated with human pathologies including neurodegenerative, cardiovascular, muscular, and diabetic conditions. Maintenance of ER calcium is critical for functions of the ER and its depletion can lead to loss of ER resident proteins, in a process termed exodosis. Therapeutic compounds capable of attenuating the redistribution of ER proteins under pathological conditions may slow or stop disease progression. To identify such compounds, we performed a quantitative high-throughput screen (qHTS) using the SERCaMP assay, which monitors secretion of ER resident proteins triggered by calcium depletion. Five clinically used drugs (dextromethorphan, bromocriptine, dantrolene, verapamil, and diltiazem) were identified in the screen and characterized using a battery of assays to measure effects on ER calcium, ER stress, and exodosis. Bromocriptine elicited protective effects in cell-based models of

Wolfram syndrome, myopathy, and ischemia as well as *in vivo* models of stroke and diabetes. Bromocriptine reduced exodosis through a non-canonical mechanism as novel bromocriptine analogs exhibited reduced dopamine receptor activity while retaining similar efficacy in stabilizing the ER resident proteome and improving outcomes in models of stroke and diabetes. This study describes a new strategic approach to identify small molecule drugs capable of improving ER proteostasis in human disease conditions.

Sigma-1 Receptor Chaperones Rescue Nucleocytoplasmic Transport Deficit Seen In Cellular And Drosophila ALS/FTD Models Lee PT, Liévens JC, Wang SM, Chuang JY, Khalil B, Wu HE, Chang WC, Maurice T, Su TP. Nat Commun. 2020; 11(1): 5580.

In a subgroup of patients with amyotrophic lateral sclerosis (ALS)/Frontotemporal dementia (FTD), the (G4C2)-RNA repeat expansion from C9orf72 chromosome binds to the Ran-activating protein (RanGAP) at the nuclear pore, resulting in nucleocytoplasmic transport deficit and accumulation of Ran in the cytosol. Here, we found that the sigma-1 receptor (Sig-1R), a molecular chaperone, reverses the pathological effects of (G4C2)-RNA repeats in cell lines and in *Drosophila*. The Sig-1R colocalizes with RanGAP and nuclear pore proteins (Nups) and stabilizes the latter. Interestingly, Sig-1Rs directly bind (G4C2)-RNA repeats. Overexpression of Sig-1Rs rescues, whereas the Sig-1R knockout exacerbates, the (G4C2)-RNA repeats-induced aberrant cytoplasmic accumulation of Ran. In *Drosophila*, Sig-1R (but not the Sig-1R-E102Q mutant) overexpression reverses eye necrosis, climbing deficit, and firing discharge caused by (G4C2)-RNA repeats. These results on a molecular chaperone at the nuclear pore suggest that Sig-1Rs may benefit patients with C9orf72 ALS/FTD by chaperoning the nuclear pore assembly and sponging away deleterious (G4C2)-RNA repeats.

GRANTEE HONORS AND AWARDS

Grantee Awards

Anne Andrews, Ph.D., University California Los Angeles, was awarded the International Union of Pure and Applied Chemistry Distinguished Women in Chemistry/Chemical Engineering Award for her basic and translational research at the nexus of neuroscience and nanoscience. She was also inducted into the American Institute for Medical and Biological Engineering College of Fellows.

Effie Apostolou, Ph.D., Weill Cornell Medicine, received the 2021 Emerging Leader Award from the Mark Foundation for Cancer Research for promising early-career projects aimed at addressing unmet needs in cancer research.

Michael R. Bruchas, Ph.D., University of Washington, was awarded the 2021 John J. Abel Award in Pharmacology in recognition of his innovative research and technology advances in the study of G-protein coupled receptor biology and neuromodulatory signaling.

Elissa Chesler, Ph.D., The Jackson Laboratory, has been appointed to The Ann Watson Symington Chair in Addiction Research, one of two newly established endowed chairs at the Jackson Laboratory.

Gregory T. Collins, Ph.D., University of Texas Health Science Center, was awarded the 2021 J.H. Woods Early Career Award in Behavioral Pharmacology in recognition of his innovative and multi-tiered approach to understanding how individual differences, including behavioral and drug histories, impact drug-taking and drug-seeking behaviors. In addition to developing a strong research program, Gregory has an exemplary service record and has shown dedication in his roles as a teacher and mentor of younger scientists.

Amy Janes, Ph.D., Harvard Medical School, was elected the 2021-2022 President-Elect of The College on Problems of Drug Dependence.

Shawn Lockery, Ph.D., University of Oregon, was named Senior Fellow of the National Academy of Inventors for his achievements as an entrepreneur.

Klaus Miczek, Ph.D., Tufts University, was awarded the 2021 MED Associates Brady-Schuster Award by Division 28 of the American Psychological Association.

Lishomwa (Lish) Ndhlovu, M.D., Ph.D., Weill Cornell Medicine, was elected as a Fellow into the American Academy of Microbiology.

Marina Picciotto, Ph.D., Yale School of Medicine, was awarded the Andrew Carnegie Prize in Mind and Brain Science, which recognizes trailblazers in the brain and behavioral sciences, for her work in addiction, memory, and reward behaviors.

Tariq Rana, Ph.D., University California San Diego, has been inducted into the National Academy of Inventors.

Gregory Scherrer, Ph.D., University of North Carolina, has received the 2021 McKnight Endowment Fund for Neuroscience Award for Study of Brain Disorders and the 2021 Brain Research Foundation Scientific Innovations Award. Gregory's studies aim to elucidate the molecular mechanisms by which opioids alter activity in neural circuits to cause opioid addiction and analgesia.

David Stewart, Ph.D., Cold Spring Harbor Laboratories (CSHL), was Elected Fellow of American Association for the Advancement of Science for his outstanding leadership as CSHL's executive director of the Meetings and Courses Program.

William Stoops, Ph.D., University of Kentucky, was awarded the American Psychological Association (APA) 2020 Presidential Citation for his brilliant research, multi-dimensional leadership at APA, and his positive, enthusiastic demeanor.

Talia H. Swartz, M.D., Ph.D., Mount Sinai School of Medicine, was elected as a Fellow in the Infectious Diseases Society of America. This is the Infectious Diseases profession's highest honor given to those who have demonstrated that they are true leaders in the field.

Jill R. Turner, Ph.D., University of Kentucky, was awarded the American Society for Pharmacology and Experimental Therapeutics Division for Neuropharmacology Early Career Award in recognition of her highly impactful research in the field of neuropharmacology, extensive and effective mentoring, and service to the profession and public outreach.

CTN Western States Node

The Western States Node would like to congratulate **Keith Humphreys, Ph.D.**, for his recent appointment as Deputy Editor-in-Chief of *Addiction*, the most widely cited and internationally read journal in the field. This is an honor and tribute to Keith's leadership in international research on alcohol and drug use disorders.

CTN Pacific Northwest Node

The Pacific Northwest Node would like to offer its congratulations to **Andrew Saxon, M.D.**, who is one of six recipients of the [2021 Nyswander/Dole "Marie" Award](#). Named after Vincent Dole, M.D., and Marie Nyswander, M.D., who founded methadone maintenance treatment in the 1960s, the award is the preminent recognition in the field of opioid use disorder treatment. Recipients are nominated by their peers, with a committee then selecting just a handful of national honorees. An awards program to honor all six was held virtually on April 13, 2021, as part of the [American Association for the Treatment of Opioid Dependence's annual conference](#).

STAFF HONORS AND AWARDS

Brandon Harvey, Ph.D., Intramural Research Program (IRP), was appointed to the NIH Occupational Safety and Health Management Committee.

Kathleen Trycya, Ph.D., a postdoctoral fellow in the IRP laboratory of Brandon Harvey, Ph.D., received the 2021 NIDA Women in Science, Promising Postdoctoral Fellow Award.

Emily Wires, Ph.D., a postdoctoral fellow in the IRP laboratory of Brandon Harvey, Ph.D., received the 2021 NIDA Women in Science, Research Recognition Award.

2021 NIDA IRP Fellows Award for Research Excellence Awardees

- Harsh Deshpande
- Ewa Galaj
- Evan Hart
- Therese Ku
- Brenton Laing
- Renata Marchette
- Adrienne McGinn
- Jorge Miranda Barrientos
- David Reiner

STAFF CHANGES

New Staff

Sheba Dunston, Ed.D., M.P.H., CHES, joined the Division of Epidemiology, Services and Prevention Research in January 2021 as a Health Scientist Administrator in the Epidemiology Research Branch. Her program areas in the Epidemiology Research Branch will include building the HIV/AIDS program as well as helping to coordinate the health disparities and equity portfolio. Sheba has served as a Scientific Review Officer with NIH's Center for Scientific Review, as well as a Program Director with the National Cancer Institute's Center to Reduce Cancer Health Disparities. Prior to working at NIH, she served as a Behavioral Scientist with the National Center for Health Statistics at the Centers for Disease Control and Prevention. In this role, she facilitated the full planning and execution of question design and survey evaluation studies to test, develop and improve federal survey questions, including surveys on opioid use, teen alcohol and marijuana use, and substance use/ impaired driving. Sheba has several years of experience in health disparities research, health education, and social and behavioral sciences research and practice. She received an Ed.D. in Health Education, from Columbia University. Her dissertation focused on HIV prevention among African American women. Prior to attending Columbia, she earned an M.P.H. from Drexel University, with a focus on community health, and a B.S. in Biology from Syracuse University.

Rachel Evans joined NIDA in March 2021 as a Senior Press Officer in the Communications Branch, Office of Science Policy and Communications. Previously, Rachel served the NIH National Cancer Institute (NCI) as a public affairs specialist/press officer. She is a self-described "strategic storyteller" who enjoys translating complex content into clear communication, especially through the news media. At NCI, Rachel oversaw coverage of many major press stories, including clinical trials on immunotherapy for children with cancer and patients with breast cancer, comparative oncology (using clinical trials in pet dogs to inform human research), and cancer treatments being studied to treat COVID-19. Prior to joining NIH, Rachel served in her home state of Minnesota as a content manager at the Minnesota Department of Human Services and as a communications specialist at the Minnesota Department of Health. Rachel graduated from the University of Minnesota Twin Cities with a bachelor's degree in Journalism and Gender, Women, and Sexuality Studies, and a master's degree in Health Communication.

Jessica McKlveen, Ph.D., has joined the Division of Extramural Research as a Scientific Program Manager for the HEALthy Brain and Child Development Study. Jessica received her Ph.D. in Neuroscience from the University of Cincinnati where she studied stress neurobiology. During her postdoctoral fellowship, Jessica conducted research on binge-like alcohol effects on neurocircuitry at University of North Carolina, Chapel Hill. Jessica then worked as a Science Officer for Ripple Science Communications and most recently as a Scientific Review Officer at the National Center for Complementary and Integrative Health.

Khurrham Shaikh joined NIDA's Office of Management's Office of Acquisitions as a Supervisory Contract Specialist on March 14, 2021. Khurrham comes to NIDA from a position with the National Heart, Lung, and Blood Institute (NHLBI).

Jeremy Tran joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on April 11, 2021. Jeremy comes to NIDA from a position with the Department of Defense.

Staff Departures

Ivan Navarro, Ph.D., Division of Extramural Research (DER), has accepted a Scientific Review Officer position with the National Institute on Minority Health and Health Disparities. Ivan joined NIDA in January 2017 from NHLBI where he was a Program Analyst. He has been a valuable member of the Scientific Review Branch, played an instrumental role in the peer review of submissions for Medication Development Funding Opportunity Announcements, restarted the NIDA-L study section, and created a record by managing multiple expedited review meetings for medication development applications every couple of weeks. He is passionate about helping under-represented minority investigators succeed through the NIH peer review process and has conducted grantsmanship sessions at several scientific conferences and forums.

Tracy Waldeck, Ph.D., DER, has accepted a position with NIMH to lead their Division of Extramural Activities. Tracy has been an integral member of the DER and NIDA leadership teams since May 2018. She was instrumental to the success of several trans-NIH and trans-NIDA initiatives, especially the recent fast track COVID-related projects. Her deep understanding and knowledge of NIH policy, processes, and peer review made her an integral member of the DER team and an asset to the entire Institute.

Jordi Bonaventura, Ph.D., IRP, received a tenure-track Assistant Professor position at the University of Barcelona. (M. Michaelides Lab)

Retirements

Steven Grant, Ph.D., of NIDA's Division of Neuroscience and Behavior (DNB), retired from Federal Service on February 27, 2021. Steve was with program staff for more than 22 years, including 11 years as the Chief of the Clinical Neuroscience Branch within the Division of Clinical Neuroscience and Behavior Research. During his tenure at NIDA, Steve's program portfolio spanned the cognitive neuroscience of addiction – including neuroeconomics, decision-making, sleep, and metacognition – and development and application of neuroimaging technology. Most recently, Steve served as a Science Officer for the Adolescent Brain and Cognitive Development (ABCD) project and was the DNB coordinator for identifying and facilitating the bi-directional translation of the animal and human research supported within the division. He was also significantly involved with the NIH BRAIN Initiative, Blueprint, and Helping to End Addiction Long-termSM Initiative programs, and played an instrumental role in advancing NIDA priorities at external societies such as American College of Neuropsychopharmacology (ACNP).

Sung Kim, Ph.D., retired from Federal service in February 2021, after more than 26 years of service. Sung was instrumental in the development and production of new and improved drug products for the treatment of Substance Use Disorders (SUDs). He played a core role within

DTMC as a chemistry formulation and drug-form production subject matter expert. Prior to joining NIDA, Sung worked at the Food and Drug Administration and NCI.



National Institute
on Drug Abuse