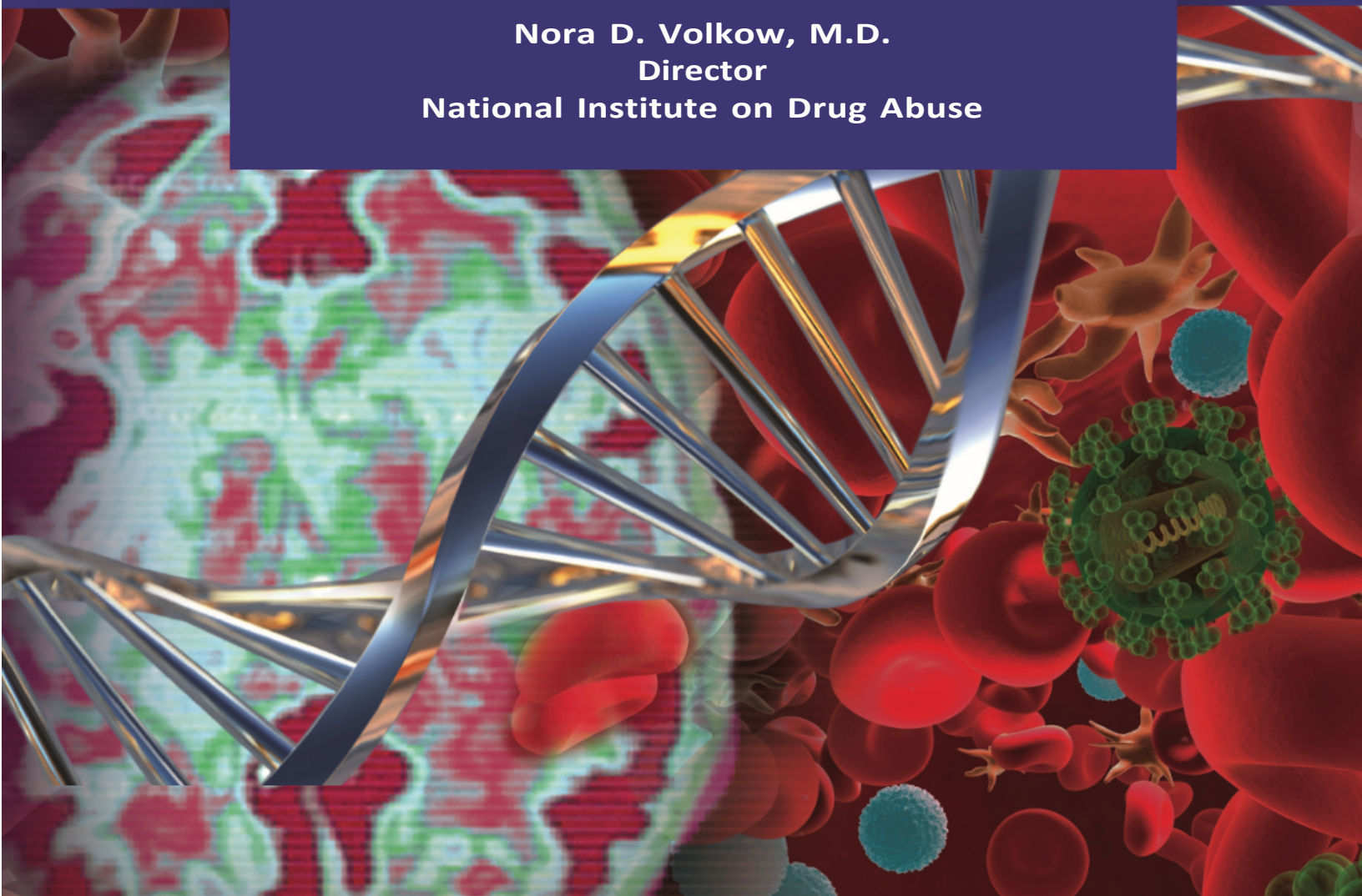# DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

February 6, 2024

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Director
National Institute on Drug Abuse

RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Subsecond Fluctuations In Extracellular Dopamine Encode Reward and Punishment Prediction Errors In Humans Sands LP, Jiang A, Liebenow B, DiMarco E, Laxton AW, Tatter SB, Montague PR, Kishida KT. Science Advances, Dec 1, 2023.
In the mammalian brain, midbrain dopamine neuron activity is hypothesized to encode reward prediction errors that promote learning and guide behavior by causing rapid changes in dopamine levels in target brain regions. This hypothesis (and alternatives regarding dopamine's role in punishment-learning) has limited direct evidence in humans. We report intracranial, subsecond measurements of dopamine release in human striatum measured, while volunteers (i.e., patients undergoing deep brain stimulation surgery) performed a probabilistic reward and punishment learning choice task designed to test whether dopamine release encodes only reward prediction errors or whether dopamine release may also encode adaptive punishment learning signals. Results demonstrate that extracellular dopamine levels can encode both reward and punishment prediction errors within distinct time intervals via independent valence-specific pathways in the human brain.

Mesoaccumbal Glutamate Neurons Drive Reward Via Glutamate Release But Aversion Via Dopamine Co-Release Warlow SM, Singhal SM, Hollon NG, Faget L, Dowlat DS, Zell V, Hunker AC, Zweifel LS, Hnasko TS. Neuron 112, February 2024.
Ventral tegmental area (VTA) projections to the nucleus accumbens (NAc) drive reward-related motivation. Although dopamine neurons are predominant, a substantial glutamatergic projection is also present, and a subset of these co-release both dopamine and glutamate. Optogenetic stimulation of VTA glutamate neurons not only supports self-stimulation but can also induce avoidance behavior, even in the same assay. Here, we parsed the selective contribution of glutamate or dopamine co-release from VTA glutamate neurons to reinforcement and avoidance. We expressed channelrhodopsin-2 (ChR2) in mouse VTA glutamate neurons in combination with CRISPR-Cas9 to disrupt either the gene encoding vesicular glutamate transporter 2 (VGLUT2) or tyrosine hydroxylase (*Th*). Selective disruption of VGLUT2 abolished optogenetic self-stimulation but left real-time place avoidance intact, whereas CRISPR-Cas9 deletion of *Th* preserved self-stimulation but abolished place avoidance. Our results demonstrate that glutamate release from VTA glutamate neurons is positively reinforcing but that dopamine release from VTA glutamate neurons can induce avoidance behavior.

Single Nucleus Transcriptomics Of Ventral Midbrain Identifies Glial Activation Associated With Chronic Opioid Use Disorder Wei J, Lambert TY, Valada A, Patel N, Walker K, Lenders J, Schmidt CJ, Iskhakova M, Alazizi A, Mair-Meijers H, Mash DC, Luca F, Pique-Regi R, Bannon MJ, Akbarian S. Nature 14: 5610, Sept 12, 2023.
Dynamic interactions of neurons and glia in the ventral midbrain mediate reward and addiction behavior. We studied gene expression in 212,713 ventral midbrain single nuclei from 95 individuals with history of opioid misuse, and individuals without drug exposure. Chronic exposure to opioids was not associated with change in proportions of glial and neuronal subtypes, however glial transcriptomes were broadly altered, involving 9.5−6.2% of expressed genes within microglia, oligodendrocytes, and astrocytes. Genes associated with activation of the immune response including interferon, NFkB signaling, and cell motility pathways were upregulated, contrasting with

down-regulated expression of synaptic signaling and plasticity genes in ventral midbrain nondopaminergic neurons. Ventral midbrain transcriptomic reprogramming in the context of chronic opioid exposure included 325 genes that previous genome-wide studies had linked to risk of substance use traits in the broader population, thereby pointing to heritable risk architectures in the genomic organization of the brain's reward circuitry.

[The Projection-Specific Signals That Establish Functionally Segregated Dopaminergic Synapses](#) Terauchi A, Yee P, Johnson-Venkatesh EM, Seiglie MP, Kim L, Pitino JC, Kritzer E, Zhang Q, Zhou J, Li Y, Ginty DD, Lee W-CA, Umemori H. Cell 186:3845-3861, August 31, 2023. Dopaminergic projections regulate various brain functions and are implicated in many neuropsychiatric disorders. There are two anatomically and functionally distinct dopaminergic projections connecting the midbrain to striatum: nigrostriatal, which controls movement, and mesolimbic, which regulates motivation. However, how these discrete dopaminergic synaptic connections are established is unknown. Through an unbiased search, we identify that two groups of antagonistic TGF-b family members, bone morphogenetic protein (BMP)6/BMP2 and transforming growth factor (TGF)-b2, regulate dopaminergic synapse development of nigrostriatal and mesolimbic neurons, respectively. Projection-preferential expression of their receptors contributes to specific synapse development. Downstream, Smad1 and Smad2 are specifically activated and required for dopaminergic synapse development and function in nigrostriatal vs. mesolimbic projections. Remarkably, Smad1 mutant mice show motor defects, whereas Smad2 mutant mice show lack of motivation. These results uncover the molecular logic underlying the proper establishment of functionally segregated dopaminergic synapses and may provide strategies to treat relevant, projection-specific disease symptoms by targeting specific BMPs/TGF-b and/or Smads.

[Rules and Mechanisms Governing G Protein Coupling Selectivity Of GPCRs](#) Masuho I, Kise R, Gainza P, VonMoo E, Li X, Tany R, Wakasugi-Masuho H, Correia BE, Martemyanov KA. Cell Reports 42:113173, October 31, 2023.
G protein-coupled receptors (GPCRs) convert extracellular stimuli into intracellular signaling by coupling to heterotrimeric G proteins of four classes:Gi/o, Gq, Gs and G12/13. However, our understanding of the G protein selectivity of GPCRs is incomplete. Here, we quantitatively measure the enzymatic activity of GPCRs in living cells and reveal the G protein selectivity of 124 GPCRs with the exact rank order of their G protein preference. Using this information, we establish a classification of GPCRs by functional selectivity, discover the existence of a G12/13-coupled receptor, G15-coupled receptors, and a variety of subclasses for Gi/o-, Gq-, and Gs-coupled receptors, culminating in development of the predictive algorithm of G protein selectivity. We further identify the structural determinants of G protein selectivity, allowing us to synthesize non-existent GPCRs with de novo G protein selectivity and efficiently identify putative pathogenic variants.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

[The Interaction Of E-Cigarette Use and Mental Health Symptoms On Risk Of Cigarette Smoking Initiation Among Young Adults In The United States](#) Harlow AF, Han DH, Eckel SP, McConnell R, Leventhal AM, Barrington-Trimis JL. Addiction. 2023 Dec; 118(12):2317-2326. Epub 2023 Aug 24. PMID: 37620973.

Background and Aims: It is unknown whether young adults who vape nicotine and have poor mental health have greater risk of smoking initiation than expected based on individual risks of vaping and mental health alone. This study aimed to estimate the joint association of vaping and mental health symptoms with smoking initiation among young adults, and test for additive interaction between vaping and mental health in smoking initiation risk. **Design:** Using five waves of the Population Assessment of Tobacco and Health (wave 1, 2013-2014; wave 2, 2014-2015; wave 3, 2015-2016; wave 4, 2016-2018; wave 5, 2018-2019), we estimated risk differences (RD) for the association of time-varying and time-lagged vaping and internalizing (e.g., anxiety, depressive) and externalizing (e.g., inattention/hyperactivity) mental health symptoms with cigarette smoking initiation at follow-up, over four 1-year intervals. We calculated interaction contrasts (IC) to estimate the excess risk of smoking initiation attributable to the interaction of vaping and mental health symptoms. **Setting:** United States. **Participants:** A total of 6908 cigarette-naïve individuals aged 18-24 years. **Measurements:** Exposures included current (past-30 day) vaping and internalizing and externalizing mental health symptoms (high vs. moderate/low symptoms). The outcome was smoking initiation (ever cigarette use) after 1 year. **Findings:** The per-interval risk of smoking initiation was 7.6% (1039 cases/13 712 person-intervals). Compared with noncurrent vaping and moderate/low mental health symptoms, adjusted RDs for current vaping and high mental health symptoms were 17.2% (95% confidence interval [CI]: 7.2% to 27.3%) for internalizing and 18.7% (95% CI: 8.1% to 29.2%) for externalizing symptoms. The excess risk attributed to interaction of current vaping and high externalizing symptoms was IC = 11.3% (95% CI: 1.3% to 21.2%; P = 0.018), with inconclusive findings for internalizing symptoms (IC = 7.7% [95% CI: -2.2% to 17.7%; P = 0.097]). **Conclusions:** There is possible, but inconclusive, superadditivity between vaping and mental health in risk of smoking initiation among young adults in the United States.

[**Association Between Opioid Dose Reduction Rates and Overdose Among Patients Prescribed Long-Term Opioid Therapy**](#) Glanz JM, Xu S, Narwaney KJ, McClure DL, Rinehart DJ, Ford MA, Nguyen AP, Binswanger IA. Subst Abus. 2023 Jul; 44(3):209-219. Epub 2023 Sep 13. PMID: 37702046.

Background: Tapering long-term opioid therapy is an increasingly common practice, yet rapid opioid dose reductions may increase the risk of overdose. The objective of this study was to compare overdose risk following opioid dose reduction rates of ≤10%, 11% to 20%, 21% to 30%, and >30% per month to stable dosing. **Methods:** Researchers conducted a retrospective cohort study in three health systems in Colorado and Wisconsin. Participants were patients ≥18 years of age prescribed long-term opioid therapy between January 1, 2006, and June 30, 2019. Five opioid dosing patterns and drug overdoses (fatal and nonfatal) were identified using electronic health records, pharmacy records, and the National Death Index. Cox proportional hazard regression was conducted on a propensity score-weighted cohort to estimate adjusted hazard ratios (aHRs) for follow-up periods of 1, 3, 6, 9, and 12 months after a dose reduction. **Results:** In a cohort of 17,540 patients receiving long-term opioid therapy, 42.7% of patients experienced a dose reduction. Relative to stable dosing, a dose reduction rate of >30% was associated with an increased risk of overdose and the aHR estimates decreased as the follow-up increased; the aHRs for the 1-, 6- and 12-month follow-ups were 5.33 (95% CI, 1.98-14.34), 1.81 (95% CI, 1.08-3.03), and 1.49 (95% CI, 0.97-2.27), respectively. The slower tapering rates were not associated with overdose risk. **Conclusions:** Patients receiving long-term opioid therapy exposed to dose reduction rates of >30% per month had increased overdose risk relative to patients exposed to stable dosing. Results support the use of slow dose reductions to minimize the risk of overdose.

Comparing Organization-Focused and State-Focused Financing Strategies on Provider-Level Reach of a Youth Substance Use Treatment Model: A Mixed-Method Study Dopp AR, Hunter SB, Godley MD, González I, Bongard M, Han B, Cantor J, Hindmarch G, Lindquist K, Wright B, Schlang D, Passetti LL, Wright KL, Kilmer B, Aarons GA, Purtle J. Implementation Science 2023 Oct 12; 18(1):50.

Background: Financial barriers in substance use disorder service systems have limited the widespread adoption—i.e., provider-level reach—of evidence-based practices (EBPs) for youth substance use disorders. Reach is essential to maximizing the population-level impact of EBPs. One promising, but rarely studied, type of implementation strategy for overcoming barriers to EBP reach is financing strategies, which direct financial resources in various ways to support implementation. Researchers evaluated financing strategies for the Adolescent Community Reinforcement Approach (A-CRA) EBP by comparing two U.S. federal grant mechanisms, organization-focused and state-focused grants, on organization-level A-CRA reach outcomes. **Methods:** A-CRA implementation took place through organization-focused and state-focused grantee cohorts from 2006 to 2021. Researchers used a quasi-experimental, mixed-method design to compare reach between treatment organizations funded by organization-focused versus state-focused grants (164 organizations, 35 states). Using administrative training records, researchers calculated reach as the per-organization proportion of trained individuals who received certification in A-CRA clinical delivery and/or supervision by the end of grant funding. Researchers tested differences in certification rate by grant type using multivariable linear regression models that controlled for key covariates (e.g., time), and tested threats to internal validity from our quasi-experimental design through a series of sensitivity analyses. They also drew on interviews and surveys collected from the treatment organizations and (when relevant) interviews with state administrators to identify factors that influenced reach. **Results:** The overall certification rates were 27 percentage points lower in state-focused versus organization-focused grants (p = .01). Sensitivity analyses suggested these findings were not explained by confounding temporal trends nor by organizational or state characteristics. They did not identify significant quantitative moderators of reach outcomes, but qualitative findings suggested certain facilitating factors were more influential for organization-focused grants (e.g., strategic planning) and certain barrier factors were more impactful for state-focused grants (e.g., states finding it difficult to execute grant activities). **Discussion:** As the first published comparison of EBP reach outcomes between financing strategies, these findings can help guide state and federal policy related to financing strategies for implementing EBPs that reduce youth substance use. Future work should explore contextual conditions under which different financing strategies can support the widespread implementation of EBPs for substance use disorder treatment.

Lessons Learned From Housing First, Rapid Rehousing Trials With Youth Experiencing Homelessness Slesnick N, Brakenhoff B, Bunger A, Chavez L, Cuthbertson C, Famelia R, Feng X, Fitzpatrick M, Ford J, Hatsu I, Holowacz E, Jaderlund S, Kelleher K, Luthy E, Mallory A, Martin J, Pizzulo A, Stone-Sabali S, Yilmazer T, Wu Q, Zhang J. Addict Sci Clin Pract. 2023 Sept; 18(1): 58

Background: Youth, 18 to 24 years, experiencing homelessness (YEH) are recognized as having developmental challenges dissimilar to older adults. Yet, research on efforts to end homelessness and prevent or intervene in drug use and mental health problems among youth have lagged behind that of adults. The Housing First (HF) Model, which underlies Permanent Supportive Housing (PSH) and Rapid Re-Housing (RRH), has become preferred over treatment-first models. **Methods and results:** We provide an overview of PSH and RRH studies to date and summarize our current understanding of their utility for use with YEH. Finally, we review our team's current and past

randomized trials testing RRH with YEH, providing lessons learned and recommendations. **Conclusion:** Current research efforts to guide best practices are hampered by a lack of fidelity to HF principles, lack of randomized design, and lack of focus on youth. Lessons learned and recommendations from our work are offered to facilitate the future work of those who seek to end homelessness and address drug use and mental health problems among youth.

TREATMENT RESEARCH

Fentanyl-Induced Respiratory Depression In Rodents Is Inhibited By Bioabsorbable, Subcutaneous Naltrexone Implants At 3.5 Months Benner JD, Cohen SM, Hollenbaugh JA, Fishman, M. Addict Biol. 2023; 28(12): e13350.

The aim of this study is to determine if extended-release, bioabsorbable, subcutaneous naltrexone (NTX) implants inhibit respiratory depression after an IV injection of fentanyl. Bioabsorbable implants fabricated from two different release-controlling polymers, poly-D-L-lactide (PDLLA) and polycaprolactone (PCL), alone (placebo) or containing NTX, were subcutaneously implanted in Sprague Dawley rats. After 3.5 months of implantation, the rodents were administered an IV bolus of fentanyl through the tail vein. The placebo implant rats received a dose of 4 micrograms (mcg) - (10 mcg/kg/dose), while the NTX implanted animals received a dose of 8 mcg (20 mcg/kg/dose). The minimum active dose of fentanyl that caused a $> 50 \pm 2\%$ depression in the respiration rate in the placebo implanted rodents was 4 mcg. The respiration rate of the placebo implanted rats dropped from 208 ± 14 breaths/minute at predose, to 84 ± 12 breaths/minute ($p = 0.0003$) at 2 min. In contrast, all NTX implanted animals easily tolerated twice the dose of 8 mcg of fentanyl without any significant reduction in respiration rate. The mean respiration rate = increased from 164 ± 22 breaths/minute at predose to 178 ± 17 breaths/minute ($p = 0.24$) at 2 min. The mean plasma concentrations of NTX, 3.5 months after implantation, ranged from 7.4 (± 1.1) ng/mL to 80.3 (± 37.5) ng/mL. Bioabsorbable implants containing NTX effectively blocked fentanyl-induced respiratory depression in rodents as compared with placebo implants, 3.5 months after implantation.

Cannabidiol and Mitragynine Exhibit Differential Interactive Effects In The Attenuation Of Paclitaxel-Induced Mechanical Allodynia, Acute Antinociception, and Schedule-Controlled Responding In Mice Ortiz YT, Bilbrey JA, Felix JS, Kienegger EA, Mottinelli M, Mukhopadhyay S, McCurdy CR, McMahon LR, Wilkerson JL. Pharmacol Rep. 2023; 75(4): 937-950.

Background: For many chemotherapy patients, peripheral neuropathy is a debilitating side effect. Mitragyna speciosa (kratom) contains the alkaloid mitragynine (MG), which produces analgesia in multiple preclinical pain models. In humans, anecdotal reports suggest cannabidiol (CBD) may enhance kratom-related analgesia. We examined the interactive activity of MG and CBD in a mouse chemotherapy-induced peripheral neuropathy (CIPN) model. We also examined MG + CBD in acute antinociception and schedule-controlled responding assays, as well as examined underlying receptor mechanisms. Methods: Male and female C57BL/6J mice received a cycle of intraperitoneal (ip) paclitaxel injections (cumulative dose 32 mg/kg). The von Frey assay was utilized to assess CIPN allodynia. In paclitaxel-naïve mice, schedule-controlled responding for food was conducted under a fixed ratio (FR)-10, and hot plate antinociception was examined. **Results:** MG dose-relatedly attenuated CIPN allodynia (ED50 102.96 mg/kg, ip), reduced schedule-controlled responding (ED50 46.04 mg/kg, ip), and produced antinociception (ED50 68.83 mg/kg, ip). CBD attenuated allodynia (ED50 85.14 mg/kg, ip) but did not decrease schedule-controlled responding or produce antinociception. Isobolographic analysis revealed 1:1, 3:1 MG + CBD mixture ratios

additively attenuated CIPN allodynia. All combinations decreased schedule-controlled responding and produced antinociception. WAY-100635 (serotonin 5-HT1A receptor antagonist) pretreatment (0.01 mg/kg, ip) antagonized CBD anti-allodynia. Naltrexone (an opioid receptor antagonist) pretreatment (0.032 mg/kg, ip) antagonized MG anti-allodynia and acute antinociception but produced no change in MG-induced decreased schedule-controlled behavior. Yohimbine (α2 receptor antagonist) pretreatment (3.2 mg/kg, ip) antagonized MG anti-allodynia and produced no change in MG-induced acute antinociception or decreased schedule-controlled behavior. **Conclusions:** Although more optimization is needed, these data suggest CBD combined with MG may be useful as a novel CIPN therapeutic.

[Impairment Of Endothelial Function By Aerosol From Marijuana Leaf Vaporizers](#)
Liu J, Nabavizadeh P, Rao P, Derakhshandeh R, Han DD, Guo R, Murphy MB, Cheng J, Schick SF, Springer ML. J Am Heart Assoc. 2023; 12(23): e032969.
Background: Marijuana leaf vaporizers, which heat plant material and sublimate Δ-9-tetrahydrocannabinol without combustion, are popular alternatives to smoking cannabis that are generally perceived to be less harmful. We have shown that smoke from tobacco and marijuana, as well as aerosol from e-cigarettes and heated tobacco products, impair vascular endothelial function in rats measured as arterial flow-mediated dilation (FMD). **Methods And Results:** We exposed 8 rats per group to aerosol generated by 2 vaporizer systems (Volcano and handheld Yocan) using marijuana with varying Δ-9-tetrahydrocannabinol levels, in a single pulsatile exposure session of 2 s/min over 5 minutes, and measured changes in FMD. To model secondhand exposure, we exposed rats for 1 minute to diluted aerosol approximating release of uninhaled Volcano aerosol into typical residential rooms. Exposure to aerosol from marijuana with and without cannabinoids impaired FMD by ≈50%. FMD was similarly impaired by aerosols from Yocan (237 °C), and from Volcano at both its standard temperature (185 °C) and the minimum sublimation temperature of Δ-9-tetrahydrocannabinol (157 °C), although the low-temperature aerosol condition did not effectively deliver Δ-9-tetrahydrocannabinol to the circulation. Modeled secondhand exposure based on diluted Volcano aerosol also impaired FMD. FMD was not affected in rats exposed to clean air or water vapor passed through the Volcano system. **Conclusions:** Acute direct exposure and modeled secondhand exposure to marijuana leaf vaporizer aerosol, regardless of cannabinoid concentration or aerosol generation temperature, impair endothelial function in rats comparably to marijuana smoke. Our findings indicate that use of leaf vaporizers is unlikely to reduce the vascular risk burden of smoking marijuana.

[Effects Of Hyperdirect Pathway Theta Burst Transcranial Magnetic Stimulation On Inhibitory Control, Craving, and Smoking In Adults With Nicotine Dependence: A Double-Blind, Randomized Crossover Trial](#) Upton S, Brown AA, Ithman M, Newman-Norlund R, Sahlem G, Prisciandaro JJ, McClure EA, Froeliger B. Biol Psychiatry Cogn Neurosci Neuroimaging. 2023; 8(11): 1156-1165.
Background: Nicotine dependence is associated with dysregulated hyperdirect pathway (HDP)-mediated inhibitory control (IC). However, there are currently no evidence-based treatments that have been shown to target the HDP to improve IC and reduce cigarette cravings and smoking. **Methods:** Following a baseline nonstimulation control session, this study (N = 37; female: n = 17) used a double-blind, randomized crossover design to examine the behavioral and neural effects of intermittent theta burst stimulation (iTBS) and continuous TBS (cTBS) to the right inferior frontal gyrus (rIFG)-a key cortical node of the HDP. Associations between treatment effects were also explored. **Results:** At baseline, HDP IC task-state functional connectivity was positively associated

with IC task performance, which confirmed the association between HDP circuit function and IC. Compared with iTBS, rIFG cTBS improved IC task performance. Compared with the baseline nonstimulation control session, both TBS conditions reduced cigarette craving and smoking; however, although craving and smoking were lower for cTBS, no differences were found between the two active conditions. In addition, although HDP IC task-state functional connectivity was greater following cTBS than iTBS, there was no significant difference between conditions. Finally, cTBS-induced improvement in IC task performance was associated with reduced craving, and cTBS-induced reduction in craving was associated with reduced smoking. **Conclusions:** These findings warrant further investigation into the effects of rIFG cTBS for increasing IC and reducing craving and smoking among individuals with nicotine dependence. Future sham-controlled cTBS studies may help further elucidate the mechanisms by which rIFG cTBS mediates IC and smoking behavior.

[Tryptophan Substitution In CJ-15,208 (cyclo[Phe-D-Pro-Phe-Trp]) Introduces Δ-Opioid Receptor Antagonism, Preventing Antinociceptive Tolerance and Stress-Induced Reinstatement Of Extinguished Cocaine-Conditioned Place Preference](#) Scherrer KH, Eans SO, Medina JM, Senadheera SN, Khaliq T, Murray TF, McLaughlin JP, Aldrich JV. Pharmaceuticals (Basel). 2023; 16(9).
The macrocyclic tetrapeptide CJ-15,208 (cyclo[Phe-D-Pro-Phe-Trp]) and its D-Trp isomer exhibit kappa opioid receptor (KOR) antagonism, which prevents stress-induced reinstatement of extinguished cocaine-conditioned place preference. Here, we evaluated the effects of substitution of Trp and D-Trp on the peptides' opioid activity, antinociceptive tolerance, and the ability to prevent relapse to extinguished drug-CPP. Six analogs were synthesized using a combination of solid-phase peptide synthesis and cyclization in solution. The analogs were evaluated in vitro for opioid receptor affinity in radioligand competition binding assays, efficacy in the [35S]GTPγS assay, metabolic stability in mouse liver microsomes, and for opioid activity and selectivity in vivo in the mouse 55 °C warm-water tail-withdrawal assay. Potential liabilities of locomotor impairment, respiratory depression, acute tolerance, and conditioned place preference (CPP) were also assessed in vivo, and the ameliorating effect of analogs on the reinstatement of extinguished cocaine-place preference was assessed. Substitutions of other D-amino acids for D-Trp did not affect (or in one case increased) KOR affinity, while two of the three substitutions of an L-amino acid for Trp decreased KOR affinity. In contrast, all but one substitution increased mu opioid receptor (MOR) affinity in vitro. The metabolic stabilities of the analogs were similar to those of their respective parent peptides, with analogs containing a D-amino acid being much more rapidly metabolized than those containing an L-amino acid in this position. In vivo, CJ-15,208 analogs demonstrated antinociception, although potencies varied over an 80-fold range and the mediating opioid receptors differed by substitution. KOR antagonism was lost for all but the D-benzothienylalanine analog, and the 2'-naphthylalanine analog instead demonstrated significant delta opioid receptor (DOR) antagonism. Introduction of DOR antagonism coincided with reduced acute opioid antinociceptive tolerance and prevented stress-induced reinstatement of extinguished cocaine-CPP.

[Self-Adjuvanting TLR7/8 Agonist and Fentanyl Hapten Co-Conjugate Achieves Enhanced Protection Against Fentanyl Challenge](#) Powers N, Massena C, Crouse B, Smith M, Hicks L, Evans JT, Miller S, Pravetoni M, Burkhart D. Bioconjug Chem. 2023; 34(10): 1811-1821.
Currently approved pharmacotherapies for opioid use disorders (OUDs) and overdose reversal agents are insufficient to slow the spread of OUDs due to the proliferation of fentanyl. This is evident in the 31% rise in drug overdose deaths from 2019 to 2022, with rates increasing from 21.6

to 28.3 overdoses per 100,000 deaths. Vaccines are a potential alternative or adjunct therapy for the treatment of several substance use disorders (nicotine, cocaine) but have shown limited clinical success due to suboptimal antibody titers. In this study, we demonstrate that coconjugation of a Toll-like receptor 7/8 (TLR7/8) agonist (UM-3006) alongside a fentanyl-based hapten (F1) on the surface of the carrier protein cross-reactive material 197 (CRM) significantly increased generation of high-affinity fentanyl-specific antibodies. This demonstrated enhanced protection against fentanyl challenges relative to an unconjugated (admix) adjuvant control in mice. Inclusion of aluminum hydroxide (alum) adjuvant further increased titers and enhanced protection, as determined by analysis of fentanyl concentration in serum and brain tissue. Collectively, our findings present a promising approach to enhance the efficacy of antiopioid vaccines, underscoring the need for extensive exploration of TLR7/8 agonist conjugates as a compelling strategy to combat opioid use disorders.

Distinct Neural Networks Predict Cocaine Versus Cannabis Treatment Outcomes Lichenstein SD, Kohler R, Ye F, Potenza MN, Kiluk B, Yip SW. Mol Psychiatry. 2023; 28(8): 3365-3372. Treatment outcomes for individuals with substance use disorders (SUDs) are variable and more individualized approaches may be needed. Cross-validated, machine-learning methods are well-suited for probing neural mechanisms of treatment outcomes. Our prior work applied one such approach, connectome-based predictive modeling (CPM), to identify dissociable and substance-specific neural networks of cocaine and opioid abstinence. In Study 1, we aimed to replicate and extend prior work by testing the predictive ability of the cocaine network in an independent sample of 43 participants from a trial of cognitive-behavioral therapy for SUD, and evaluating its ability to predict cannabis abstinence. In Study 2, CPM was applied to identify an independent cannabis abstinence network. Additional participants were identified for a combined sample of 33 with cannabis-use disorder. Participants underwent fMRI scanning before and after treatment. Additional samples of 53 individuals with co-occurring cocaine and opioid-use disorders and 38 comparison subjects were used to assess substance specificity and network strength relative to participants without SUDs. Results demonstrated a second external replication of the cocaine network predicting future cocaine abstinence, however it did not generalize to cannabis abstinence. An independent CPM identified a novel cannabis abstinence network, which was (i) anatomically distinct from the cocaine network, (ii) specific for predicting cannabis abstinence, and for which (iii) network strength was significantly stronger in treatment responders relative to control participants. Results provide further evidence for substance specificity of neural predictors of abstinence and provide insight into neural mechanisms of successful cannabis treatment, thereby identifying novel treatment targets. Clinical trials registration: "Computer-based training in cognitive-behavioral therapy web-based (Man VS Machine)," registration number: NCT01442597. "Maximizing the Efficacy of Cognitive Behavior Therapy and Contingency Management", registration number: NCT00350649. "Computer-Based Training in Cognitive Behavior Therapy (CBT4CBT)", registration number: NCT01406899.

Methamphetamine Use and Utilization Of Medications For Opioid Use Disorder Among Rural People Who Use Drugs Tsui JI, Whitney BM, Korthuis PT, Chan B, Pho MT, Jenkins WD, Young AM, Cooper HLF, Friedmann PD, Stopka TJ, de Gijsel D, Miller WC, Go VF, Westergaard R, Brown R, Seal DW, Zule WA, Feinberg J, Smith GS, Mixson LS, Fredericksen R, Crane HM, Delaney JA. Rural Opioid Initiative Consortium. Drug Alcohol Depend. 2023; 250: 110911. **Background:** Methamphetamine use is common among persons with opioid use disorder. This study evaluated associations between methamphetamine use and treatment with agonist medications

for opioid use disorder (MOUD, specifically buprenorphine, and/or methadone) in U.S. rural communities. **Methods:** The Rural Opioid Initiative (ROI) is a consortium spanning 10 states and 65 rural counties that included persons who reported past 30-day use of opioids and/or injection drug use between 1/2018 and 3/2020. Analyses were restricted to participants who had ever used opioids and had data on past 30-day methamphetamine use. Multivariable models examined the relationship between methamphetamine use and utilization of agonist MOUD. **Results:** Among 2899 participants, 2179 (75.2%) also reported recent methamphetamine use. Persons with methamphetamine use compared to those without were younger, more likely to have injected drugs, be unhoused, criminal justice involved, and less likely to have health insurance. Adjusted for age, sex, race, and study site, recent methamphetamine use was associated with lower relative odds of past 30-day methadone treatment (aOR=0.66; 95% CI: 0.45-0.99) and fewer methadone treatment days (aIRR=0.76; 0.57-0.99), but not past 30-day buprenorphine receipt (aOR=0.90; 0.67-1.20), buprenorphine treatment days in past 6 months: aIRR=0.88; 0.69-1.12) or perceived inability to access buprenorphine (aOR=1.12; 0.87-1.44) or methadone (aOR=1.06; 0.76-1.48). **Conclusion:** Methamphetamine use is common among persons who use opioids in rural U.S. areas and negatively associated with current treatment and retention on methadone but not buprenorphine. Future studies should examine reasons for this disparity and reduce barriers to methadone for persons who use opioids and methamphetamine.

Daily Opioid and Stimulant Co-use and Nonfatal Overdoses In The Context Of Social Disadvantage: Findings On Marginalized Populations Jones AA, Schneider KE, Tobin KE, O'Sullivan D, Latkin CA. J Subst Use Addict Treat. 2023; 151: 208986.

Objective: Opioids and stimulants are increasingly implicated in overdose deaths, particularly among minoritized groups. We examined daily opioid and cocaine co-use, nonfatal overdoses, and naloxone carrying among minoritized people who inject drugs (PWID). **Methods:** The study derived data from 499 PWID in Baltimore City, MD, recruited using street-based outreach between 2016 and 2019. Participants reported overdoses; sociodemographic characteristics; and use of nonmedical prescription opioids, heroin, cocaine, and naloxone. **Results:** Among the participants, the mean age was 46, 34 % were female, 64% self-identified as Black, and 53 % experienced recent homelessness. Black PWID, compared to White PWID, were as likely to use opioids and cocaine daily but were 61 % less likely to have naloxone. After controlling for sociodemographic characteristics, women (aOR: 1.88, 95% CI: 1.14, 3.11), persons experiencing homelessness (aOR:3.07, 95% CI: 1.79, 5.24), and those who experienced a recent overdose (aOR:2.14, 95%CI: 1.29, 3.58) were significantly more likely to use opioids and any form of cocaine every day. In a subanalysis of only female PWID, females engaged in sex work (aOR:2.27, 95% CI: 1.02, 5.07) and females experiencing recent homelessness (aOR:5.82, 95%CI: 2.50, 13.52) were significantly more likely to use opioids and cocaine daily. Furthermore, females (aOR:1.69, 95% CI:1.03, 2.77), persons experiencing homelessness (aOR:1.94, 95% CI:1.16, 3.24), and those with higher educational attainment (aOR:2.06, 95%CI:1.09, 3.91) were more likely to often/always carry naloxone, while Black PWID were less likely to have naloxone (aOR:0.39, 95%CI:0.22, 0.69). **Conclusions:** These findings highlight the need for targeted naloxone distribution and other harm-reduction interventions among minoritized groups in urban areas.

HIV RESEARCH

[**Joint Effects Of Substance Use Disorders and Recent Substance Use On HIV Viral Non-suppression Among People Engaged In HIV Care In An Urban Clinic, 2014-2019**](#) Lesko CR, Falade-Nwulia OO, Pytell JD, Hutton HE, Fojo AT, Keruly JC, Moore RD, Chander G. Addiction. 2023; 118(11): 2193-2202.
Aims: To estimate the joint effects of substance use disorder (SUD) and recent substance use on human immunodeficiency virus (HIV) non-suppression. **Design:** Retrospective clinical cohort study with repeated observations within individuals. **Setting:** Baltimore, Maryland, United States. **Participants:** 1881 patients contributed 10 794 observations. MEASUREMENTS: The primary independent variable was the combination of history of SUD and recent substance use. History of SUD was defined as any prior International Classification of Diseases 9/10 code for cocaine or opioid disorder. Recent substance use was defined as the self-report of cocaine or non-prescribed opioid use on the National Institute on Drug Abuse-modified Alcohol, Smoking and Substance Involvement Screening Test or clinician-documented cocaine or opioid use abstracted from the medical record. The outcome was viral non-suppression, defined as HIV RNA >200 copies/mL on the first viral load measurement within 1 year subsequent to each observation of substance use. We adjusted for birth sex, Black race, age, HIV acquisition risk factors, years in care and CD4 cell count. In secondary analyses, we also adjusted for depressive, anxiety and panic symptoms, cannabis use and cannabis use disorder. **Findings:** On their first observation, 31% of patients had a history of an SUD and 18% had recent substance use. Relative to no history of SUD and no recent substance use, the 1-year fully adjusted risk difference (RD) for viral non-suppression associated with cocaine and opioid use disorder and recent substance use was 7.7% (95% CI = 5.3%-10.0%), the RD was 5.5% (95% CI = 1.2%-9.7%) for history of cocaine use disorder without recent substance use, and the RD was 4.6% (95% CI = 2.7%-6.5%) for recent substance use without a SUD. **Conclusions:** Substance use and substance use disorders appear to be highly prevalent among, and independently associated with, viral non-suppression among people with HIV.

[**Comparing Factors Associated With Increased Stimulant Use In Relation To HIV Status Using A Machine Learning and Prediction Modeling Approach**](#) Blair CS, Javanbakht M, Comulada WS, Bolan R, Shoptaw S, Gorbach PM, Needleman J. Prev Sci. 2023; 24(6): 1102-1114. Stimulant use is an important driver of HIV/STI transmission among men who have sex with men (MSM). Evaluating factors associated with increased stimulant use is critical to inform HIV prevention programming efforts. This study seeks to use machine learning variable selection techniques to determine characteristics associated with increased stimulant use and whether these factors differ by HIV status. Data from a longitudinal cohort of predominantly Black/Latinx MSM in Los Angeles, CA was used. Every 6 months from 8/2014-12/2020, participants underwent STI testing and completed surveys evaluating the following: demographics, substance use, sexual risk behaviors, and last partnership characteristics. Least absolute shrinkage and selection operator (lasso) was used to select variables and create predictive models for an interval increase in self-reported stimulant use across study visits. Mixed-effects logistic regression was then used to describe associations between selected variables and the same outcome. Models were also stratified based on HIV status to evaluate differences in predictors associated with increased stimulant use. Among 2095 study visits from 467 MSM, increased stimulant use was reported at 20.9% (n = 438) visits. Increased stimulant use was positively associated with unstable housing (adjusted [a]OR 1.81; 95% CI 1.27-2.57), STI diagnosis (1.59; 1.14-2.21), transactional sex (2.30; 1.60-3.30), and last partner stimulant use (2.21; 1.62-3.00). Among MSM living with HIV, increased stimulant use

was associated with binge drinking, vaping/cigarette use (aOR 1.99; 95% CI 1.36-2.92), and regular use of poppers (2.28; 1.38-3.76). Among HIV-negative MSM, increased stimulant use was associated with participating in group sex while intoxicated (aOR 1.81; 95% CI 1.04-3.18), transactional sex (2.53; 1.40-2.55), and last partner injection drug use (1.96; 1.02-3.74). Our findings demonstrate that lasso can be a useful tool for variable selection and creation of predictive models. These results indicate that risk behaviors associated with increased stimulant use may differ based on HIV status and suggest that co-substance use and partnership contexts should be considered in the development of HIV prevention/treatment interventions.

[HIV-1 Infection Of Genetically Engineered iPSC-Derived Central Nervous System-Engrafted Microglia In A Humanized Mouse Model](#)
Min AK, Javidfar B, Missall R, Doanman D, Durens M, Graziani M, Mordelt A, Marro SG, de Witte L, Chen BK, Swartz TH, Akbarian S. J. Virology 30 Nov 2023.

Our mouse model is a powerful tool for investigating the genetic mechanisms governing central nervous system (CNS) human immunodeficiency virus type-1 (HIV-1) infection and latency in the CNS at a single-cell level. A major advantage of our model is that it uses induced pluripotent stem cell-derived microglia, which enables human genetics, including gene function and therapeutic gene manipulation, to be explored *in vivo*, which is more challenging to study with current hematopoietic stem cell-based models for neuroHIV. Our transgenic tracing of xenografted human cells will provide a quantitative medium to develop new molecular and epigenetic strategies for reducing the HIV-1 latent reservoir and to test the impact of therapeutic inflammation-targeting drug interventions on CNS HIV-1 latency.

[Activation Of Toll-Like Receptor 3 Inhibits HIV Infection Of Human iPSC-Derived Microglia](#)
Wang P, Liu JB, Wang X, Meng FZ, Xiao QH, Liu L, Zhu J, Hu WH, Ho WZ. J. Med Virol. 21 October 2023.

As a key immune cell in the brain, microglia are essential for protecting the central nervous system (CNS) from viral infections, including HIV. Microglia possess functional Toll-like receptor 3 (TLR3), a key viral sensor for activating interferon (IFN) signaling pathway-mediated antiviral immunity. We, therefore, studied the effect of poly (I:C), a synthetic ligand of TLR3, on the activation of the intracellular innate immunity against HIV in human iPSC-derived microglia (iMg). We found that poly (I:C) treatment of iMg effectively inhibits HIV infection/replication at both mRNA and protein levels. Investigations of the mechanisms revealed that TLR3 activation of iMg by poly (I:C) induced the expression of both type I and type III IFNs. Compared with untreated cells, the poly (I:C)-treated iMg expressed significantly higher levels of IFN-stimulated genes (ISGs) with known anti-HIV activities (ISG15, MxB, Viperin, MxA, and OAS-1). In addition, TLR3 activation elicited the expression of the HIV entry coreceptor CCR5 ligands (CC chemokines) in iMg. Furthermore, the transcriptional profile analysis showed that poly (I:C)-treated cells had the upregulated IFN signaling genes (ISG15, ISG20, IFITM1, IFITM2, IFITM3, IFITM10, APOBEC3A, OAS-2, MxA, and MxB) and the increased CC chemokine signaling genes (CCL1, CCL2, CCL3, CCL4, and CCL15). These observations indicate that TLR3 is a potential therapy target for activating the intracellular innate immunity against HIV infection/replication in human microglial cells. Therefore, further studies with animal models and clinical specimens are necessary to determine the role of TLR3 activation-driven antiviral response in the control and elimination of HIV in infected host cells.

Amphetamine Use and Its Associations With Antiretroviral Adherence and Viral Load Among Sexual Minority Men and Transgender Women Living With HIV Brousseau NM, Kalichman SC, Watson RJ, Eaton LA. AIDS Care. 2023; 35(10): 1472-1479.

Substance use has complex associations to HIV disease progression. The current study tested the associations between several substances and HIV viral load while accounting for confounders relevant to HIV disease progression and substance use. Young sexual minority men and transgender women living with HIV (LWH) in Georgia (N = 385) completed measures and biological tests for HIV viral load and substance use. Multivariable regression models tested the role of specific drugs (i.e., alcohol, cannabis/THC, cocaine, and combined amphetamine and methamphetamine) directly on viral load and indirectly through antiretroviral (ART) adherence. ART adherence and HIV care self-efficacy were consistently associated with greater HIV suppression. Alcohol and cocaine were not associated with ART adherence or viral load. Cannabis was negatively associated with ART adherence (B = -.053, p = .037) but not viral load. Amphetamine/methamphetamine demonstrated significant direct effects on higher viral load (B = .708, p = .010) while indirectly influencing viral load through a negative association with ART adherence. Our findings support previous research demonstrating amphetamine/methamphetamine use impacts viral load both directly and indirectly through ART adherence. Interventions addressing amphetamine/methamphetamine use by young sexual minority men and transgender women LWH are urgently needed, and future research should focus on determining the mechanisms by which formulations of amphetamine impact HIV replication. Trial registration: ClinicalTrials.gov identifier: NCT03665532.

Comparing Factors Associated With Increased Stimulant Use In Relation To HIV Status Using A Machine Learning And Prediction Modeling Approach Blair CS, Javanbakht M, Comulada WS, Bolan R, Shoptaw S, Gorbach PM, Needleman J. Prev Sci. 2023; 24(6): 1102-1114.

Stimulant use is an important driver of HIV/STI transmission among men who have sex with men (MSM). Evaluating factors associated with increased stimulant use is critical to inform HIV prevention programming efforts. This study seeks to use machine learning variable selection techniques to determine characteristics associated with increased stimulant use and whether these factors differ by HIV status. Data from a longitudinal cohort of predominantly Black/Latinx MSM in Los Angeles, CA was used. Every 6 months from 8/2014-12/2020, participants underwent STI testing and completed surveys evaluating the following: demographics, substance use, sexual risk behaviors, and last partnership characteristics. Least absolute shrinkage and selection operator (lasso) was used to select variables and create predictive models for an interval increase in self-reported stimulant use across study visits. Mixed-effects logistic regression was then used to describe associations between selected variables and the same outcome. Models were also stratified based on HIV status to evaluate differences in predictors associated with increased stimulant use. Among 2095 study visits from 467 MSM, increased stimulant use was reported at 20.9% (n = 438) visits. Increased stimulant use was positively associated with unstable housing (adjusted [a]OR 1.81; 95% CI 1.27-2.57), STI diagnosis (1.59; 1.14-2.21), transactional sex (2.30; 1.60-3.30), and last partner stimulant use (2.21; 1.62-3.00). Among MSM living with HIV, increased stimulant use was associated with binge drinking, vaping/cigarette use (aOR 1.99; 95% CI 1.36-2.92), and regular use of poppers (2.28; 1.38-3.76). Among HIV-negative MSM, increased stimulant use was associated with participating in group sex while intoxicated (aOR 1.81; 95% CI 1.04-3.18), transactional sex (2.53; 1.40-2.55), and last partner injection drug use (1.96; 1.02-3.74). Our findings demonstrate that lasso can be a useful tool for variable selection and creation of predictive models. These results indicate that risk behaviors associated with increased stimulant use may differ

based on HIV status and suggest that co-substance use and partnership contexts should be considered in the development of HIV prevention/treatment interventions.

[Lessons Learned From Housing First, Rapid Rehousing Trials With Youth Experiencing Homelessness](#) Slesnick N, Brakenhoff B, Bunger A, Chavez L, Cuthbertson C, Famelia R, Feng X, Fitzpatrick M, Ford J, Hatsu I, Holowacz E, Jaderlund S, Kelleher K, Luthy E, Mallory A, Martin J, Pizzulo A, Stone-Sabali S, Yilmazer T, Wu Q, Zhang J. Addict Sci Clin Pract. 2023 Sept; 18(1): 58
Background: Youth, 18 to 24 years, experiencing homelessness (YEH) are recognized as having developmental challenges dissimilar to older adults. Yet, research on efforts to end homelessness and prevent or intervene in drug use and mental health problems among youth have lagged behind that of adults. The Housing First (HF) Model which underlies Permanent Supportive Housing (PSH) and Rapid Re-Housing (RRH) has become preferred over treatment-first models. **Methods and results:** We provide an overview of PSH and RRH studies to date and summarize our current understanding of their utility for use with YEH. Finally, we review our team's current and past randomized trials testing RRH with YEH, providing lessons learned and recommendations. **Conclusion:** Current research efforts to guide best practices are hampered by a lack of fidelity to HF principles, lack of randomized design, and lack of focus on youth. Lessons learned and recommendations from our work are offered to facilitate the future work of those who seek to end homelessness and address drug use and mental health problems among youth.

[From Trauma To Transmission: Exploring The Intersection Of Adversity, Substance Use, and HIV Risk In Women's Life Histories](#) West NS, Kussaga F, Rittenhouse A, Duroseau B, Knight D, Mbwambo J, Likindikoki S, Saleem HT. Int J Equity Health. 2023 Sep 1;22(1):174. PMID: 37658358
Background: At increased risk for poor health outcomes, physical and/or sexual violence, and onward transmission of HIV, women who use drugs and are living with HIV (WWUDHIV) are vulnerable and in need of services. Understanding the role of trauma across their life history may offer insights into HIV and drug use prevention and opportunities for intervention. **Methods:** The research team explored trauma and drug use among WWUDHIV in Dar es Salaam, Tanzania, by conducting in-depth interviews with 30 WWUDHIV from January-March 2019. Interviewers used semi-structured interview guides and asked questions about the life history as related to drug use. Interviews were audio recorded, transcribed, translated, coded, and life histories charted. **Results:** Participants described death of family members as traumatic catalysts for drug use. Sexual partners early in their life history were often the point of introduction to drugs and source of HIV acquisition. Death of partners was present across many life histories and was a traumatic event negatively influencing life trajectories, including start of sex work for survival or to support drug use. Sex work in turn often led to traumatic events including sexual and/or physical violence. HIV diagnosis for many participants followed the start of drug use, frequently occurred during pregnancy or severe illness and was described by most participants as a trauma. Despite this, particularly during pregnancy, HIV diagnosis was a turning point for some participant's desire to engage in drug use treatment. Traumatic events were often cumulative and regularly described as catalysts for poor mental health that could lead to new or increased drug use for coping. **Conclusions:** These findings suggest trauma is common in the life history of WWUDHIV and has negative impacts on drug use and HIV vulnerability. Using life history charting highlights the cumulative and cyclical nature of trauma and drug use in this population. This study allows for better understanding of trauma, drug use, and HIV prevention, which offers opportunities for intervention among a group with limited access to services: during adolescence for orphaned youth,

following the death of a child or partner, and when vulnerable women engage with the health system (HIV diagnosis, pregnancy, illness).

[HIV Information Avoidance, HIV Stigma, and Medical Mistrust Among Black Sexual Minority Men in the Southern United States: Associations with HIV Testing](#) Simon KA, Driver R, Rathus T, Cole A, Kalinowski J, Watson RJ, Eaton LA. AIDS Behav. 2023 Nov 13. Online ahead of print.

Uptake of HIV testing is a critical step in the HIV prevention and treatment care cascade. Barriers to HIV testing, however, remain and innovative research in this area is warranted to improve uptake of testing. As such, we investigated the role of HIV information avoidance - a novel construct potentially related to HIV testing. We analyzed this construct in relation to other factors known to impact HIV testing, namely HIV stigma and medical mistrust. Multiple linear regression analyses indicated that HIV information avoidance was negatively associated with HIV testing, while medical mistrust was positively associated with HIV testing. HIV testing stigma was not associated with HIV testing. This work contributes to the developing literature on HIV information avoidance and its relationships with HIV stigma and HIV testing uptake. Further, these findings can inform HIV testing interventions which often do not focus on HIV information avoidance. Future research on the mechanisms of information avoidance that are amenable to intervention, and the temporal ordering of the relationship between information avoidance and HIV testing is warranted.

[Treatment Initiation, Substance Use Trajectories, and the Social Determinants of Health in Persons Living With HIV Seeking Medication for Opioid Use Disorder](#) Cook RR, Jaworski EN, Hoffman KA, Waddell EN, Myers R, Korthuis PT, Vergara-Rodriguez P. Subst Abus. 2023 Oct; 44(4):301-312. Epub 2023 Oct 16. PMID: 37842910.

Background: People living with HIV and opioid use disorder (OUD) are disproportionally affected by adverse socio-structural exposures negatively affecting health, which have shown inconsistent associations with uptake of medications for OUD (MOUD). This study aimed to determine whether social determinants of health (SDOH) were associated with MOUD uptake and trajectories of substance use in a clinical trial of people seeking treatment. **Methods**: Data are from a 2018 to 2019 randomized trial comparing the effectiveness of different MOUD to achieve viral suppression among people living with HIV and OUD. SDOH were defined by variables mapping to Healthy People 2030 domains: education (Education Access and Quality), income (Economic Stability), homelessness (Neighborhood and Built Environment), criminal justice involvement (Social and Community Context), and recent SUD care (Health Care Access and Quality). Associations between SDOH and MOUD initiation were assessed with Cox proportional hazards models, and SDOH and substance use over time with generalized estimating equation models. **Results:** Participants (N = 114) averaged 47 years old, 63% were male, 56% were Black, and 12% Hispanic. Participants reported an average of 2.3 out of 5 positive SDOH indicators. Stable housing was the most commonly reported SDOH (61%), followed by no recent criminal justice involvement (59%), having a high school level education or greater (56%), income stability (45%), and recent SUD care (13%). Each additional favorable SDOH was associated with a 25% increase in the likelihood of MOUD initiation during the study. Positive SDOH were also associated with a decrease in the odds of baseline opioid use and a greater reduction in opioid use during subsequent weeks of the study. **Conclusions:** Positive social determinants of health, in aggregate, may increase the likelihood of MOUD treatment initiation among people living with HIV and OUD.

Office of Translational Initiatives and Program Innovations Research

Effects Of Inhaled Low-Concentration Xenon Gas On Naltrexone-Precipitated Withdrawal Symptoms In Morphine-Dependent Mice Kaufman MJ, Meloni EG, Qrareya AN, Paronis CA, Bogin, V, Drug and Alcohol Dependence. 2023 Sep 19:255:110967.

Opioid withdrawal symptoms (OWS) are highly aversive and prompt unprescribed opioid use, which increases morbidity, mortality, and, among individuals being treated for opioid use disorder (OUD), recurrence. OWS are driven by sympathetic nervous system (SNS) hyperactivity that occurs when blood opioid levels wane. We tested whether brief inhalation of xenon gas, which inhibits SNS activity and is used clinically for anesthesia and diagnostic imaging, attenuates naltrexone-precipitated withdrawal-like signs in morphine-dependent mice. Adult CD-1 mice were implanted with morphine sulfate-loaded (60 mg/ml) minipumps and maintained for 6 days to establish morphine dependence. On day 7, mice were given subcutaneous naltrexone (0.3 mg/kg) and placed in a sealed exposure chamber containing either 21% oxygen/balance nitrogen (controls) or 21% oxygen/added xenon peaking at 30%/balance nitrogen. After 10 minutes, mice were transferred to observation chambers and videorecorded for 45 minutes. Videos were scored in a blind manner for morphine withdrawal behaviors. Data were analyzed using 2-way ANOVAs testing for treatment and sex effects. Xenon-exposed mice exhibited fewer jumps ($P = 0.010$) and jumping suppression was detectible within the first 10-minute video segment, but no sex differences were detected. Brief inhalation of low concentration xenon rapidly and substantially attenuated naltrexone-precipitated jumping in morphine-dependent mice, suggesting that it can inhibit OWS. If xenon effects translate to humans with OUD, xenon inhalation may be effective for reducing OWS, unprescribed opioid use, and for easing OUD treatment initiation, which could help lower excess morbidity and mortality associated with OUD.

Virtual Reality Distraction for Reducing Acute Postoperative Pain After Hip Arthroplasty: A Randomized Trial Araujo-Duran J, Kopac O, Montalvo Campana M, Bakal O, Sessler DI, Hofstra RL, Shah K, Turan A, Ayad S. Anesth Analg. 2023 Sep 4.

Relaxation and distraction provided by virtual reality presentations might be analgesic and reduce the need for opioid analgesia. The authors tested the hypothesis that a virtual reality program decreases acute postoperative pain and opioid requirements in 106 adults recovering from elective primary total hip arthroplasty. They also evaluated whether virtual reality distraction improves patient mobility and reduces the need for antiemetics. Participating patients were randomized to 2- to 8-minute-long 3-dimensional immersive virtual reality relaxation and distraction video presentations or to 2-dimensional presentations of nature short films with neutral music that was chosen to be neither overly relaxing nor distracting, presented through identical headsets. The primary outcome was pain after virtual reality or sham video presentations, adjusted for pretreatment scores. There were no statistically significant or clinically meaningful reductions in pain scores or opioid consumption. As applied in this study, virtual reality interventions were not beneficial for acute postoperative pain.

CLINICAL TRIALS NETWORK RESEARCH

Nurse Care Management for Opioid Use Disorder Treatment: The PROUD Cluster Randomized Clinical Trial Wartko PD, Bobb JF, Boudreau DM, Matthews AG, McCormack J, Lee AK, Qiu H, Yu O, Hyun N, Idu AE, Campbell CI, Saxon AJ, Liu DS, Altschuler A, Samet JH,

Labelle CT, Zare-Mehrjerdi M, Stotts AL, Braciszewski JM, Murphy MT, Dryden D, Arnsten JH, Cunningham CO, Horigian VE, Szapocznik J, Glass JE, Caldeiro RM, Phillips RC, Shea M, Bart G, Schwartz RP, McNeely J, Liebschutz JM, Tsui JI, Merrill JO, Lapham GT, Addis M, Bradley KA; PROUD Trial Collaborators; Ghiroli MM, Hamilton LK, Hu Y, LaHue JS, Loree AM, Murphy SM, Northrup TF, Shmueli-Blumberg D, Silva AJ, Weinstein ZM, Wong MT, Burganowski RP. JAMA Intern Med. 2023 Dec 1;183(12):1343-1354. PMID: 37902748; PMCID: PMC10616772.
Objective: To assess whether implementation of the Massachusetts model of nurse care management for OUD in PC increases OUD treatment with buprenorphine or extended-release injectable naltrexone and secondarily decreases acute care utilization. **Design, setting, and participants:** The Primary Care Opioid Use Disorders Treatment (PROUD) trial was a mixed-methods, implementation-effectiveness cluster randomized clinical trial conducted in 6 diverse health systems across 5 US states. Two PC clinics in each system were randomized to intervention or usual care (UC) stratified by system. Data were obtained from electronic health records and insurance claims. Primary care patients were included if they were 16 to 90 years old and visited a participating clinic from up to 3 years before a system's randomization date through 2 years after. **Main outcomes and measures:** The primary outcome was a clinic-level measure of patient-years of OUD treatment (buprenorphine or extended-release injectable naltrexone) per 10,000 PC patients during the 2 years post-randomization (follow-up). The secondary outcome, among patients with OUD pre-randomization, was a patient-level measure of the number of days of acute care utilization during follow-up. **Results:** During the baseline period, a total of 130,623 patients were seen in intervention clinics, and 159,459 patients were seen in UC clinics. Intervention clinics provided 8.2 more patient-years of OUD treatment per 10,000 PC patients compared with UC clinics. Most of the benefit accrued in 2 health systems and in patients new to clinics or newly treated for OUD post-randomization. Qualitative data indicated that keys to successful implementation included broad commitment to treat OUD in PC from system leaders and PC teams, full financial coverage for OUD treatment, and straightforward pathways for patients to access nurse care managers. Acute care utilization did not differ between intervention and UC clinics. **Conclusions and relevance:** The PROUD cluster randomized clinical trial intervention meaningfully increased PC OUD treatment, albeit unevenly across health systems; however, it did not decrease acute care utilization among patients with OUD.

[Assessment of Screening Tools to Identify Substance Use Disorders Among Adolescents](#)
Levy S, Brogna M, Minegishi M, Subramaniam G, McCormack J, Kline M, Menzin E, Allende-Richter S, Fuller A, Lewis M, Collins J, Hubbard Z, Mitchell SG, Weiss R, Weitzman E. JAMA Netw Open. 2023 May 1;6(5):e2314422. PMID: 37213103; PMCID: PMC10203888.
Objective: To evaluate the psychometric properties of 3 brief substance use screening tools (Screening to Brief Intervention [S2BI]; Brief Screener for Tobacco, Alcohol, and Drugs [BSTAD]; and Tobacco, Alcohol, Prescription Medication, and Other Substances [TAPS]) with adolescents aged 12 to 17 years. **Design, setting, and participants:** This cross-sectional validation study was conducted on participants aged 12 to 17 years who were recruited virtually and in person from 3 health care settings in Massachusetts: (1) an outpatient adolescent SUD treatment program at a pediatric hospital, (2) an adolescent medicine program at a community pediatric practice affiliated with an academic institution, and (3) 1 of 28 participating pediatric primary care practices. Participants were randomly assigned to complete 1 of the 3 electronic screening tools via self-administration, followed by a brief electronic assessment battery and a research assistant-administered diagnostic interview as the criterion standard measure for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnoses of SUDs. **Main outcomes and**

measures: The main outcome was a DSM-5 diagnosis of tobacco/nicotine, alcohol, or cannabis use disorder as determined by the criterion standard World Mental Health Composite International Diagnostic Interview Substance Abuse Module. Classification accuracy of the 3 substance use screening tools was assessed by examining the agreement between the criterion, using sensitivity and specificity, based on cut points for each tool for use disorder, chosen a priori from previous studies. **Results:** This study included 798 adolescents, with a mean (SD) age of 14.6 years. The majority of participants identified as female (415) and were White (524). High agreement between screening results and the criterion standard measure was observed, with area under the curve values ranging from 0.89 to 1 for nicotine, alcohol, and cannabis use disorders for each of the 3 screening tools. **Conclusions and relevance:** These findings suggest that screening tools that use questions on past-year frequency of use are effective for identifying adolescents with SUDs. Future work could examine whether these tools have differing properties when used with different groups of adolescents in different settings.

Individual-Level Risk Prediction of Return to Use During Opioid Use Disorder Treatment

Objective: To develop an individual-level prediction tool for risk of return to use in opioid use disorder. **Design, setting, and participants:** This decision analytical model used predictive modeling with individual-level data from 3 multicenter, pragmatic, randomized clinical trials of at least 12 weeks' duration. The clinical trials covered a variety of treatment settings, including federally licensed treatment sites, physician practices, and inpatient treatment facilities. All 3 trials enrolled adult participants older than 18 years, with broad pragmatic inclusion and few exclusion criteria except for major medical and unstable psychiatric comorbidities. **Main outcomes and measures:** Predictive models were developed for return to use, which was defined as 4 consecutive weeks of urine drug screen (UDS) results either missing or positive for nonprescribed opioids by week 12 of treatment. **Results:** The overall sample included 2,199 trial participants. The final model based on 4 predictors at treatment entry (heroin use days, morphine- and cocaine-positive UDS results, and heroin injection in the past 30 days) yielded an area under the receiver operating characteristic curve (AUROC) of 0.67. Adding UDS in the first 3 treatment weeks improved model performance. A simplified score (CTN-0094 OUD Return-to-Use Risk Score) provided good clinical risk stratification wherein patients with weekly opioid-negative UDS results in the 3 weeks after treatment initiation had a 13% risk of return to use compared with 85% for those with 3 weeks of opioid-positive or missing UDS results. **Conclusions and relevance:** The prediction model described in this study may be a universal risk measure for return to opioid use by treatment week 3. Interventions to prevent return to regular use should focus on this critical early treatment period.

Implementation Of Substance Use Screening In Rural Federally-Qualified Health Center Clinics Identified High Rates Of Unhealthy Alcohol and Cannabis Use Among Adult Primary Care Patients

Background: Screening for substance use in rural primary care clinics faces unique challenges due to limited resources, high patient volumes, and multiple demands on providers. To explore the potential for electronic health record (EHR)-integrated screening in this context, we conducted an

implementation feasibility study with a rural federally-qualified health center (FQHC) in Maine. This was an ancillary study to a NIDA Clinical Trials Network study of screening in urban primary care clinics (CTN-0062). **Methods:** Researchers worked with stakeholders from three FQHC clinics to define and implement their optimal screening approach. Clinics used the Tobacco, Alcohol, Prescription Medication, and Other Substance (TAPS) Tool, completed on tablet computers in the waiting room, and results were immediately recorded in the EHR. Adult patients presenting for annual preventive care visits, but not those with other visit types, were eligible for screening. Data were analyzed for the first 12 months following implementation at each clinic to assess screening rates and prevalence of reported unhealthy substance use, and documentation of counseling using an EHR-integrated clinical decision support tool, for patients screening positive for moderate-high risk alcohol or drug use. **Results:** Screening was completed by 3,749 patients, representing 93.4% of those with screening-eligible annual preventive care visits, and 18.5% of adult patients presenting for any type of primary care visit. Screening was self-administered in 92.9% of cases. The prevalence of moderate-high risk substance use detected on screening was 14.6% for tobacco, 30.4% for alcohol, 10.8% for cannabis, 0.3% for illicit drugs, and 0.6% for non-medical use of prescription drugs. Brief substance use counseling was documented for 17.4% of patients with any moderate-high risk alcohol or drug use. **Conclusions:** Self-administered EHR-integrated screening was feasible to implement, and detected substantial alcohol, cannabis, and tobacco use in rural FQHC clinics. Counseling was documented for a minority of patients with moderate-high risk use, possibly indicating a need for better support of primary care providers in addressing substance use. There is potential to broaden the reach of screening by offering it at routine medical visits rather than restricting to annual preventive care visits, within these and other rural primary care clinics.

[Associations Between Stimulant Use and Return To Illicit Opioid Use Following Initiation Onto Medication For Opioid Use Disorder](#) Foot C, Korthuis PT, Tsui JI, Luo SX, Chan B, Cook RR. Addiction. 2024 Jan; 119(1):149-157. Epub 2023 Sep 15. PMID: 37712113.
Objective: The aim of this study was to estimate how ongoing stimulant use affects return to illicit opioid use after initiation onto medication for opioid use disorder (MOUD). **Design, setting and participants:** This was a secondary analysis of pooled data from two clinical trials comparing buprenorphine (BUP-NX) and extended-release naltrexone (XR-NTX). Thirteen opioid treatment programs and HIV clinics across 10 states in the United States from 2014 to 2019 took part in this study. A total of 528 participants who initiated MOUD as part of trial participation were included. Nearly half (49%) were between 30 and 49 years of age, 69% were male and 66% were non-Hispanic White. **Measurements:** The primary outcome was first self-reported day of non-prescribed opioid use following MOUD initiation, and the exposure of interest was daily stimulant use (methamphetamine, amphetamines or cocaine). Both were defined using time-line follow-back. Among participants reporting at least 1 day of illicit opioid use, we also examined relapse to ongoing use, defined as (1) 7 days of continuous opioid use or (2) 4 consecutive weeks with self-reported opioid use, one or more positive urine drug screens (UDS) for opioids or one or more missing UDS. **Findings:** Forty-seven per cent of participants reported stimulant use following MOUD initiation, 58% returned to illicit opioid use and 66% of those relapsed to ongoing use. Stimulant use was strongly associated with increased risk of misusing opioids after MOUD initiation when measured daily and over a 7-day. Using stimulants weekly or more often was associated with increased likelihood of relapse to ongoing opioid use compared with less than weekly or no stimulant use. **Conclusions:** People initiated on medication for opioid use disorder who subsequently use stimulants appear to be more likely to return to and continue using non-prescribed opioids compared with those without stimulant use. The association appears to be

stronger among patients who initiate buprenorphine compared with those who initiate extended-release naltrexone.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

[A Genetically Informed Registered Report On Adverse Childhood Experiences and Mental Health](#) Baldwin JR, Sallis HM, Schoeler T, Taylor MJ, Kwong ASF, Tielbeek JJ, Barkhuizen W, Warrier V, Howe LD, Danese A, McCrory E, Rijsdijk F, Larsson H, Lundström S, Karlsson R, Lichtenstein P, Munafò M, Pingault JB. Nat Hum Behav. 2023 Feb; 7(2):269-290.
Children who experience adversities have an elevated risk of mental health problems. However, the extent to which adverse childhood experiences (ACEs) cause mental health problems remains unclear, as previous associations may partly reflect genetic confounding. In this Registered Report, we used DNA from 11,407 children from the United Kingdom and the United States to investigate gene-environment correlations and genetic confounding of the associations between ACEs and mental health. Regarding gene-environment correlations, children with higher polygenic scores for mental health problems had a small increase in odds of ACEs. Regarding genetic confounding, elevated risk of mental health problems in children exposed to ACEs was at least partially due to pre-existing genetic risk. However, some ACEs (such as childhood maltreatment and parental mental illness) remained associated with mental health problems independent of genetic confounding. These findings suggest that interventions addressing heritable psychiatric vulnerabilities in children exposed to ACEs may help reduce their risk of mental health problems.

[Brain Functional Connectome Defines a Transdiagnostic Dimension Shared by Cognitive Function and Psychopathology in Preadolescents](#) Xiao X, Hammond C, Salmeron BJ, Wang D, Gu H, Zhai T, Nguyen H, Lu H, Ross TJ, Yang Y. Biol Psychiatry. 2023 Sep 26:S0006-3223(23)01593-7.
Background: Cognitive function and general psychopathology are two important classes of human behavior dimensions that are individually related to mental disorders across diagnostic categories. However, whether these two transdiagnostic dimensions are linked to common or distinct brain networks that convey resilience or risk for the development of psychiatric disorders remains unclear. **Methods:** The current study is a longitudinal investigation with 11,875 youths from the Adolescent Brain Cognitive Development (ABCD) Study at ages 9 to 10 years at the onset of the study. A machine learning approach based on canonical correlation analysis was used to identify latent dimensional associations of the resting-state functional connectome with multidomain behavioral assessments including cognitive functions and psychopathological measures. For the latent resting-state functional connectivity factor showing a robust behavioral association, its ability to predict psychiatric disorders was assessed using 2-year follow-up data, and its genetic association was evaluated using twin data from the same cohort. **Results:** A latent functional connectome pattern was identified that showed a strong and generalizable association with the multidomain behavioral assessments (5-fold cross-validation: $\rho = 0.68$-0.73 for the training set [n = 5096]; $\rho = 0.56$-0.58 for the test set [n = 1476]). This functional connectome pattern was highly heritable (h2 = 74.42%, 95% CI: 56.76%-85.42%), exhibited a dose-response relationship with the cumulative number of psychiatric disorders assessed concurrently and at 2 years post-magnetic resonance imaging scan, and predicted the transition of diagnosis across disorders over the 2-year follow-up period. **Conclusions:** These findings provide preliminary evidence for a transdiagnostic

connectome-based measure that underlies individual differences in the development of psychiatric disorders during early adolescence.

[Generalizable Prediction Of Childhood ADHD Symptoms From Neurocognitive Testing and Youth Characteristics](#) Weigard A, McCurry KL, Shapiro Z, Martz ME, Angstadt M, Heitzeg MM, Dinov ID, Sripada C. Transl Psychiatry. 2023 Jun 24; 13(1):225.
Childhood attention-deficit/hyperactivity disorder (ADHD) symptoms are believed to result from disrupted neurocognitive development. However, evidence for the clinical and predictive value of neurocognitive assessments in this context has been mixed, and there have been no large-scale efforts to quantify their potential for use in generalizable models that predict individuals' ADHD symptoms in new data. Using data drawn from the Adolescent Brain Cognitive Development Study (ABCD), a consortium that recruited a diverse sample of over 10,000 youth (ages 9-10 at baseline) across 21 U.S. sites, we develop and test cross-validated machine learning models for predicting youths' ADHD symptoms using neurocognitive abilities, demographics, and child and family characteristics. Models used baseline demographic and biometric measures, geocoded neighborhood data, youth reports of child and family characteristics, and neurocognitive tests to predict parent- and teacher-reported ADHD symptoms at the 1-year and 2-year follow-up time points. Predictive models explained 15-20% of the variance in 1-year ADHD symptoms for ABCD Study sites that were left out of the model-fitting process and 12-13% of the variance in 2-year ADHD symptoms. Models displayed high generalizability across study sites and trivial loss of predictive power when transferred from training data to left-out data. Features from multiple domains contributed meaningfully to prediction, including neurocognition, sex, self-reported impulsivity, parental monitoring, and screen time. This work quantifies the information value of neurocognitive abilities and other child characteristics for predicting ADHD symptoms and provides a foundational method for predicting individual youths' symptoms in new data across contexts.

[Skin-Deep Resilience and Early Adolescence: Neighborhood Disadvantage, Executive Functioning, and Pubertal Development In Minority Youth](#) Barton AW, Yu T, Gong Q, Chen E, Miller GE, Brody GH. J Youth Adolesc. 2024 Feb; 53(2):284-293.
Skin-deep resilience, in which youth overcome adversity and achieve success in psychological and academic domains but at a cost to their physiological well-being, has been documented in late adolescence and adulthood. However, its potential to emerge at earlier developmental stages is unknown. To address this gap, secondary data analyses were executed using waves 1 and 2 of the Adolescent Brain Cognitive Development study (n = 7712; ages 9-10 years at baseline [mean: 9.92; SD = 0.63]; 47.1% female; 66.1% White, 13.4% Black, and 20.6% Hispanic). The results indicated high levels of executive functioning were associated with improved psychological and behavioral outcomes at one-year follow-up. However, for racial and ethnic minority (i.e., Black or Hispanic) youth from disadvantaged neighborhoods, high levels of executive functioning were also associated with accelerated pubertal development. No significant interaction was observed among White youth. The findings suggest the skin-deep resilience pattern may be evident in early adolescence.

[The Role of Individual Discrimination and Structural Stigma in the Mental Health of Sexual Minority Youth](#) Gordon JH, Tran KT, Visoki E, Argabright ST, DiDomenico GE, Saiegh E, Hoffman KW, Erez G, Barzilay R. J Am Acad Child Adolesc Psychiatry. 2023 Jul 6:S0890-8567(23)00375-1.
Objective: Sexual minority (SM) youth experience a greater mental health burden compared with their heterosexual peers. This study aimed to characterize mental health disparities among SM

compared with non-SM youth, test main and interactive associations of SM identity and stressors targeting SM youth at the individual level (interpersonal SM discrimination) and structural level (state-level structural SM stigma) with youth mental health, and explore the contribution of interpersonal SM discrimination to the mental health burden of SM youth. **Method:** Participants included 11,622 youth (ages 9-13; 47.6% assigned female at birth) from the Adolescent Brain Cognitive Development (ABCD) Study. Linear mixed-effects models tested main and interactive associations of SM identity, interpersonal SM discrimination, and structural SM stigma with mental health measures (self-reported overall psychopathology, suicidal ideation, and suicide attempts), adjusting for demographics and other interpersonal stressors not specific to SM (other discrimination types, peer victimization, and cyberbullying). Longitudinal mediation models tested whether interpersonal SM discrimination mediated the associations between SM identity and mental health measures. **Results:** SM youth (n = 1,051) experienced more interpersonal SM discrimination and overall psychopathology compared with their non-SM peers (n = 10,571). Adjusting for demographics, there were significant associations (main effects) of interpersonal SM discrimination and structural SM stigma with overall psychopathology. When further adjusting for other non-SM-related stressors, the main effect of structural SM stigma was no longer significant. Interpersonal SM discrimination was also significantly associated with suicidal ideation and attempt, accounting for demographics, while structural SM stigma was not. Accounting for both demographics and other non-SM stressors, there was a significant interaction between SM identity and structural SM stigma in association with psychopathology (p = .02), such that, compared with their peers, SM youth showed a greater association between structural SM stigma and psychopathology. Longitudinal mediation revealed that interpersonal SM discrimination was a significant mediator explaining approximately 10% to 15% of the variance of the pathways between SM identity and all mental health outcomes. **Conclusion:** Results delineate contributions of interpersonal discrimination and structural stigma targeting SM youth to their heightened mental health burden in early adolescence. These findings underscore the need to address microlevel and macrolevel SM discrimination and structural stigma when caring for this population.

INTRAMURAL RESEARCH

Alkoxy Chain Length Governs the Potency Of 2-Benzylbenzimidazole 'Nitazene' Opioids Associated With Human Overdose Glatfelter GC, Vandeputte MM, Chen L, Walther D, Tsai M-HM, Shi L, Stove CP, Baumann MH. 2023. Psychopharmacology 240, 2573–2584.
Rationale: Novel synthetic opioids (NSOs) are emerging in recreational drug markets worldwide. In particular, 2-benzylbenzimidazole 'nitazene' compounds are problematic NSOs associated with serious clinical consequences, including fatal respiratory depression. Evidence from in vitro studies shows that alkoxy chain length can influence the potency of nitazenes at the mu-opioid receptor (MOR). However, structure-activity relationships (SARs) of nitazenes for inducing opioid-like effects in animal models are not well understood compared to relevant opioids contributing to the ongoing opioid crisis (e.g., fentanyl). **Objectives:** Here, we examined the in vitro and in vivo effects of nitazene analogues with varying alkoxy chain lengths (i.e., metonitazene, etonitazene, isotonitazene, protonitazene, and butonitazene) as compared to reference opioids (i.e., morphine and fentanyl). **Methods and results:** Nitazene analogues displayed nanomolar affinities for MOR in rat brain membranes and picomolar potencies to activate MOR in transfected cells. All compounds induced opioid-like effects on locomotor activity, hot plate latency, and body temperature in male mice, and alkoxy chain length markedly influenced potency. Etonitazene, with an ethoxy chain, was

the most potent analogue in MOR functional assays (EC_{50} = 30 pM, E_{max} = 103%) and across all in vivo endpoints (ED_{50} = 3-12 μg/kg). In vivo SARs revealed that ethoxy, isopropoxy, and propoxy chains engendered higher potencies than fentanyl, whereas methoxy and butoxy analogues were less potent. MOR functional potencies, but not MOR affinities, were positively correlated with in vivo potencies to induce opioid effects. **Conclusions:** Overall, our data show that certain nitazene NSOs are more potent than fentanyl as MOR agonists in mice, highlighting concerns regarding the high potential for overdose in humans who are exposed to these compounds.

High-Precision Mapping Reveals the Structure Of Odor Coding In the Human Brain Sagar V, Shanahan LK, Zelano CM, Gottfried JA, Kahnt T, 2023. Nat Neurosci 26, 1595–1602.
Odor perception is inherently subjective. Previous work has shown that odorous molecules evoke distributed activity patterns in olfactory cortices, but how these patterns map on to subjective odor percepts remains unclear. In the present study, we collected neuroimaging responses to 160 odors from 3 individual subjects (18 h per subject) to probe the neural coding scheme underlying idiosyncratic odor perception. We found that activity in the orbitofrontal cortex (OFC) represents the fine-grained perceptual identity of odors over and above coarsely defined percepts, whereas this difference is less pronounced in the piriform cortex (PirC) and amygdala. Furthermore, the implementation of perceptual encoding models enabled us to predict olfactory functional magnetic resonance imaging responses to new odors, revealing that the dimensionality of the encoded perceptual spaces increases from the PirC to the OFC. Whereas encoding of lower-order dimensions generalizes across subjects, encoding of higher-order dimensions is idiosyncratic. These results provide new insights into cortical mechanisms of odor coding and suggest that subjective olfactory percepts reside in the OFC.

Brain Functional Connectome Defines a Transdiagnostic Dimension Shared by Cognitive Function and Psychopathology in Preadolescents Xiao X, Hammond C, Salmeron BJ, Wang D, Gu H, Zhai T, Nguyen H, Lu H, Ross TJ, Yang Y. 2023. Biological Psychiatry S0006322323015937.
Background: Cognitive function and general psychopathology are two important classes of human behavior dimensions that are individually related to mental disorders across diagnostic categories. However, whether these two transdiagnostic dimensions are linked to common or distinct brain networks that convey resilience or risk for the development of psychiatric disorders remains unclear. **Methods:** The current study is a longitudinal investigation with 11,875 youths from the Adolescent Brain Cognitive Development (ABCD) Study at ages 9 to 10 years at the onset of the study. A machine learning approach based on canonical correlation analysis was used to identify latent dimensional associations of the resting-state functional connectome with multidomain behavioral assessments including cognitive functions and psychopathological measures. For the latent resting-state functional connectivity factor showing a robust behavioral association, its ability to predict psychiatric disorders was assessed using 2-year follow-up data, and its genetic association was evaluated using twin data from the same cohort. **Results:** A latent functional connectome pattern was identified that showed a strong and generalizable association with the multidomain behavioral assessments (5-fold cross-validation: ρ = 0.68-0.73 for the training set [n = 5096]; ρ = 0.56-0.58 for the test set [n = 1476]). This functional connectome pattern was highly heritable (h2 = 74.42%, 95% CI: 56.76%-85.42%), exhibited a dose-response relationship with the cumulative number of psychiatric disorders assessed concurrently and at 2 years post-magnetic resonance imaging scan, and predicted the transition of diagnosis across disorders over the 2-year follow-up period. **Conclusions:** These findings provide preliminary evidence for a transdiagnostic

connectome-based measure that underlies individual differences in the development of psychiatric disorders during early adolescence.

[A Linguistic Analysis Of Dehumanization Toward Substance Use Across Three Decades Of News Articles](#) Giorgi S, Habib DRS, Bellew D, Sherman G, Curtis B. 2023. Front Public Health 11, 1275975.
Introduction: Substances and the people who use them have been dehumanized for decades. As a result, lawmakers and healthcare providers have implemented policies that subjected millions to criminalization, incarceration, and inadequate resources to support health and wellbeing. While there have been recent shifts in public opinion on issues such as legalization, in the case of marijuana in the U.S., or addiction as a disease, dehumanization and stigma are still leading barriers for individuals seeking treatment. Integral to the narrative of "substance users" as thoughtless zombies or violent criminals is their portrayal in popular media, such as films and news.
Methods: This study attempts to quantify the dehumanization of people who use substances (PWUS) across time using a large corpus of over 3 million news articles. We apply a computational linguistic framework for measuring dehumanization across three decades of *New York Times* articles. **Results:** We show that (1) levels of dehumanization remain high, and (2) while marijuana has become less dehumanized over time, attitudes toward other substances such as heroin and cocaine remain stable. **Discussion:** This work highlights the importance of a holistic view of substance use that places all substances within the context of addiction as a disease, prioritizes the humanization of PWUS, and centers around harm reduction.

[Anterior Hypothalamic Parvalbumin Neurons Are Glutamatergic and Promote Escape Behavior](#) Laing BT, Anderson MS, Bonaventura J, Jayan A, Sarsfield S, Gajendiran A, Michaelides M, Aponte Y. 2023. Current Biology 33, 3215-3228.e7.
The anterior hypothalamic area (AHA) is a critical structure for defensive responding. Here, we identified a cluster of parvalbumin-expressing neurons in the AHA (AHA^{PV}) that are glutamatergic with fast-spiking properties and send axonal projections to the dorsal premammillary nucleus (PMD). Using in vivo functional imaging, optogenetics, and behavioral assays, we determined the role of these AHA^{PV} neurons in regulating behaviors essential for survival. We observed that AHA^{PV} neuronal activity significantly increases when mice are exposed to a predator, and in a real-time place preference assay, we found that AHA^{PV} neuron photoactivation is aversive. Moreover, activation of both AHA^{PV} neurons and the AHA^{PV} → PMD pathway triggers escape responding during a predator-looming test. Furthermore, escape responding is impaired after AHA^{PV} neuron ablation, and anxiety-like behavior as measured by the open field and elevated plus maze assays does not seem to be affected by AHA^{PV} neuron ablation. Finally, whole-brain metabolic mapping using positron emission tomography combined with AHA^{PV} neuron photoactivation revealed discrete activation of downstream areas involved in arousal, affective, and defensive behaviors including the amygdala and the substantia nigra. Our results indicate that AHA^{PV} neurons are a functional glutamatergic circuit element mediating defensive behaviors, thus expanding the identity of genetically defined neurons orchestrating fight-or-flight responses. Together, our work will serve as a foundation for understanding neuropsychiatric disorders triggered by escape such as post-traumatic stress disorder (PTSD).