



DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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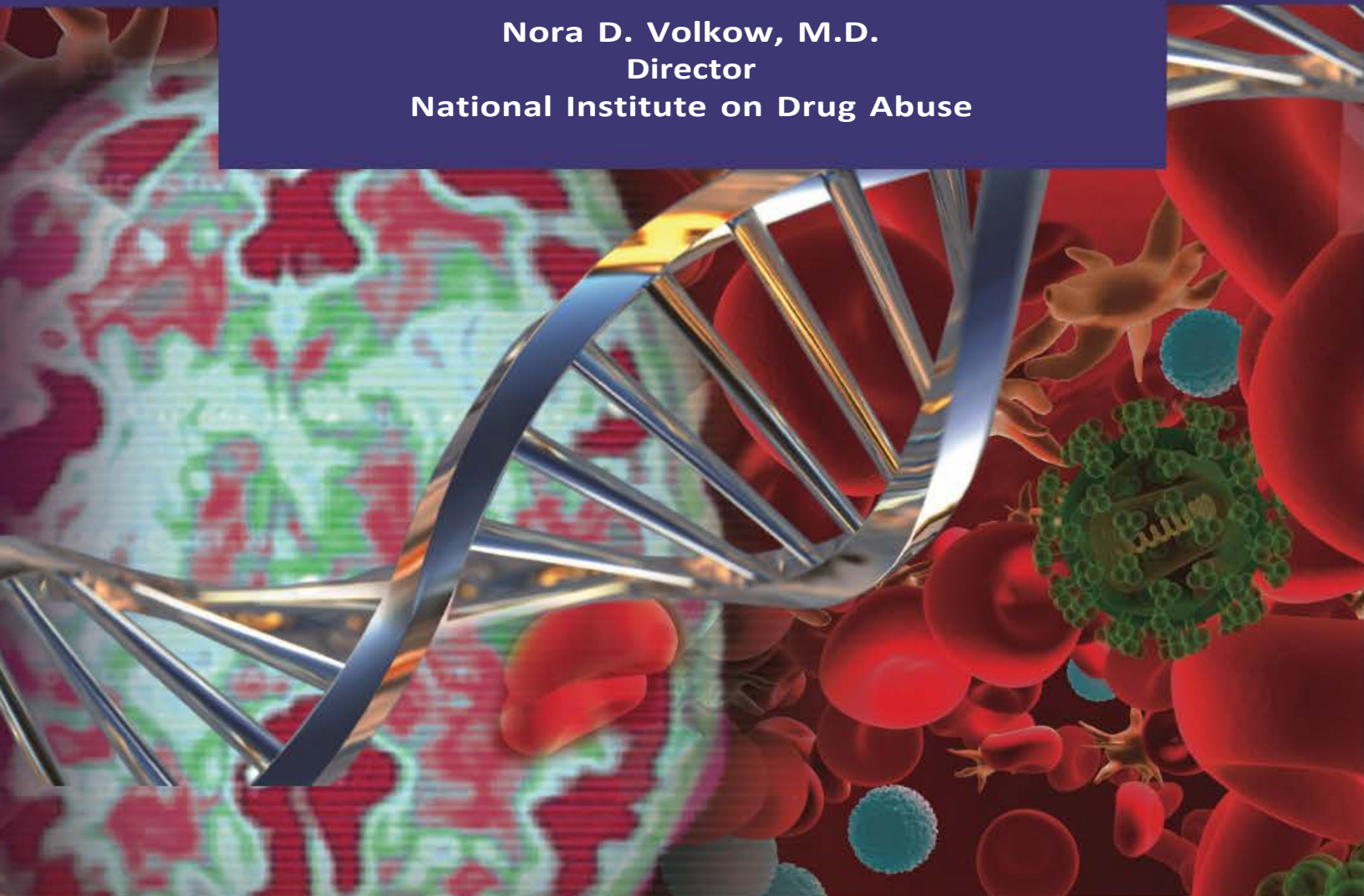


TABLE OF CONTENTS

RESEARCH HIGHLIGHTS	1
SENIOR LEADERSHIP CHANGES	22

RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Manipulating Δ FOSB In D1-Type Medium Spiny Neurons Of The Nucleus Accumbens Reshapes Whole-Brain Functional Connectivity

Sourty M, Nasseef MT, Champagnol-Di Liberti C, Mondino M, Noblet V, Parise EM, Markovic T, Browne CJ, Darcq E, Nestler EJ, Kieffer BL. *Biol Psychiatry*. 2024; 95(3): 266-274.

The transcription factor Δ FOSB, acting in the nucleus accumbens, has been shown to control transcriptional and behavioral responses to opioids and other drugs of abuse. However, circuit-level consequences of Δ FOSB induction on the rest of the brain, which are required for its regulation of complex behavior, remain unknown. We used an epigenetic approach in mice to suppress or activate the endogenous Fosb gene and thereby decrease or increase, respectively, levels of Δ FOSB selectively in D1-type medium spiny neurons of the nucleus accumbens and tested whether these modifications affect the organization of functional connectivity (FC) in the brain. We acquired functional magnetic resonance imaging data at rest and in response to a morphine challenge and analyzed both stationary and dynamic FC patterns. The 2 manipulations modified brainwide communication markedly and differently. Δ FOSB down- and upregulation had overlapping effects on prefrontal- and retrosplenial cortex-centered networks, but also generated specific FC signatures for epithalamus (habenula) and dopaminergic/serotonergic centers, respectively. Analysis of dynamic FC patterns showed that increasing Δ FOSB essentially altered responsivity to morphine and uncovered striking modifications of the roles of the epithalamus and amygdala in brain communication, particularly upon Δ FOSB downregulation. These novel findings illustrate how it is possible to link activity of a transcription factor within a single cell type of an identified brain region to consequent changes in circuit function brainwide by use of functional magnetic resonance imaging, and they pave the way for fundamental advances in bridging the gap between transcriptional and brain connectivity mechanisms underlying opioid addiction.

Multiscale Biochemical Mapping Of The Brain Through Deep-Learning-Enhanced High-Throughput Mass Spectrometry

Xie YR, Castro DC, Rubakhin SS, Trinklein TJ, Sweedler JV, Lam F. *Nat Methods*. 2024; 21(3): 521-530.

Spatial omics technologies can reveal the molecular intricacy of the brain. While mass spectrometry imaging (MSI) provides spatial localization of compounds, comprehensive biochemical profiling at a brain-wide scale in three dimensions by MSI with single-cell resolution has not been achieved. We demonstrate complementary brain-wide and single-cell biochemical mapping using MEISTER, an integrative experimental and computational mass spectrometry (MS) framework. Our framework integrates a deep-learning-based reconstruction that accelerates high-mass-resolving MS by 15-fold, multimodal registration creating three-dimensional (3D) molecular distributions and a data integration method fitting cell-specific mass spectra to 3D datasets. We imaged detailed lipid profiles in tissues with millions of pixels and in large single-cell populations acquired from the rat brain. We identified region-specific lipid contents and cell-specific localizations of lipids depending on both cell subpopulations and anatomical origins of the cells. Our workflow establishes a blueprint for future development of multiscale technologies for biochemical characterization of the brain.

[It Takes A Village: A Multi-brain Approach To Studying Multigenerational Family Communication](#) Dikker S, Brito NH, Dumas G. Dev Cogn Neurosci. 2024; 65: 101330.

Grandparents play a critical role in child rearing across the globe. Yet, there is a shortage of neurobiological research examining the relationship between grandparents and their grandchildren. We employ multi-brain neurocomputational models to simulate how changes in neurophysiological processes in both development and healthy aging affect multigenerational inter-brain coupling - a neural marker that has been linked to a range of socio-emotional and cognitive outcomes. The simulations suggest that grandparent-child interactions may be paired with higher inter-brain coupling than parent-child interactions, raising the possibility that the former may be more advantageous under certain conditions. Critically, this enhancement of inter-brain coupling for grandparent-child interactions is more pronounced in tri-generational interactions that also include a parent, which may speak to findings that grandparent involvement in childrearing is most beneficial if the parent is also an active household member. Together, these findings underscore that a better understanding of the neurobiological basis of cross-generational interactions is vital, and that such knowledge can be helpful in guiding interventions that consider the whole family. We advocate for a community neuroscience approach in developmental social neuroscience to capture the diversity of child-caregiver relationships in real-world settings.

[Social Odor Choice Buffers Drug Craving](#) Papastrat KM, Lis CA, Caprioli D, Pickard H, Puche AC, Ramsey LA, Venniuro M. Neuropsychopharmacology 2023; 49: 731-739.

Social interactions are rewarding and protective against substance use disorders, but it is unclear which specific aspect of the complex sensory social experience drives these effects. Here, we investigated the role of olfactory sensory experience on social interaction, social preference over cocaine, and cocaine craving in rats. First, we conducted bulbectomy on both male and female rats to evaluate the necessity of olfactory system experience on the acquisition and maintenance of volitional social interaction. Next, we assessed the effect of bulbectomy on rats given a choice between social interaction and cocaine. Finally, we evaluated the influence of olfactory sensory experience by training rats on volitional partner-associated odors, assessing their preference for partner odors over cocaine to achieve voluntary abstinence and assessing its effect on the incubation of cocaine craving. Bulbectomy impaired operant social interaction without affecting food and cocaine self-administration. Rats with intact olfactory systems preferred social interaction over cocaine, while rats with impaired olfactory sense showed a preference for cocaine. Providing access to a partner odor in a choice procedure led to cocaine abstinence, preventing incubation of cocaine craving, in contrast to forced abstinence or non-contingent exposure to cocaine and partner odors. Our data suggests the olfactory sensory experience is necessary and sufficient for volitional social reward. Furthermore, the active preference for partner odors over cocaine buffers drug craving. Based on these findings, translational research should explore the use of social sensory-based treatments utilizing odor-focused foundations for individuals with substance use disorders.

[A Zinc Finger Transcription Factor Enables Social Behaviors While Controlling Transposable Elements And Immune Response In Prefrontal Cortex](#) Truby NL, Kim RK, Silva GM, Qu X, Picone JA, Alemu R, Atiyeh CN, Neve RL, Liu J, Cui X, Hamilton PJ. Translational Psychiatry. 2024; 14(1): 59.

The neurobiological origins of social behaviors are incompletely understood. Here we utilized synthetic biology approaches to reprogram the function of ZFP189, a transcription factor whose expression and function in rodent prefrontal cortex was previously demonstrated to be protective against stress-induced social deficits. We created novel synthetic ZFP189 transcription factors

including ZFP189^{VPR}, which activates the transcription of target genes and therefore exerts opposite functional control from the endogenous, transcriptionally repressive ZFP189^{WT}. Following viral delivery of these synthetic ZFP189 transcription factors to mouse prefrontal cortex, we observe that ZFP189-mediated transcriptional control promotes mature dendritic spine morphology on transduced pyramidal neurons. Interestingly, inversion of ZFP189-mediated transcription in this brain area, achieved by viral delivery of synthetic ZFP189^{VPR}, precipitates social behavioral deficits in terms of social interaction, motivation, and the cognition necessary for the maintenance of social hierarchy, without other observable behavioral deficits. RNA sequencing of virally manipulated prefrontal cortex tissues reveals that ZFP189 transcription factors of opposing regulatory function (ZFP189^{WT} versus ZFP189^{VPR}) have opposite influence on the expression of genetic transposable elements as well as genes that participate in adaptive immune functions. Collectively, this work reveals that ZFP189 function in the prefrontal cortex coordinates structural and transcriptional neuroadaptations necessary for complex social behaviors while regulating transposable element-rich regions of DNA and the expression of immune-related genes. Given the evidence for a co-evolution of social behavior and the brain immune response, we posit that ZFP189 may have evolved to augment brain transposon-associated immune function as a way of enhancing an animal's capacity for functioning in social groups.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

[Is Age Of Onset And Duration Of Stimulant Therapy For ADHD Associated With Cocaine, Methamphetamine, And Prescription Stimulant Misuse?](#) McCabe SE, Figueroa O, McCabe VV, Schepis TS, Schulenberg JE, Veliz PT, Werner KS, Wilens TE. *Journal of Child Psychology and Psychiatry*. 2024; 65(1): 100-111.

Background: To assess whether age of onset and duration of stimulant therapy for attention-deficit/hyperactivity disorder (ADHD) are associated with cocaine, methamphetamine, and prescription stimulant misuse during adolescence. **Methods:** Nationally representative samples of US 10th and 12th grade students (N = 150,395) from the Monitoring the Future study were surveyed via self-administered questionnaires from 16 annual surveys (2005–2020). **Results:** An estimated 8.2% of youth received stimulant therapy for ADHD during their lifetime (n = 10,937). More than one in 10 of all youth reported past-year prescription stimulant misuse (10.4%)—past-year cocaine (4.4%) and methamphetamine (2.0%) use were less prevalent. Youth who initiated early stimulant therapy for ADHD (≤ 9 years old) and for long duration (≥ 6 years) did not have significantly increased adjusted odds of cocaine or methamphetamine use relative to population controls (i.e., non-ADHD and unmedicated ADHD youth). Youth who initiated late stimulant therapy for ADHD (≥ 10 years old) and for short duration (< 1 year) had significantly higher odds of past-year cocaine or prescription stimulant misuse in adolescence than those initiating early stimulant therapy for ADHD (≤ 9 years old) and for long duration (≥ 6 years). Youth who initiated late stimulant therapy for ADHD (≥ 10 years) for short duration (< 1 year) had significantly higher odds of past-year cocaine, methamphetamine, and prescription stimulant misuse versus population controls during adolescence. No differences in past-year cocaine, methamphetamine, and prescription stimulant misuse were found between individuals who only used nonstimulant therapy for ADHD relative to youth who initiated early stimulant therapy (≤ 9 years old) and for long duration (≥ 6 years). **Conclusions:** An inverse relationship was found between years of stimulant therapy and illicit and prescription stimulant misuse. Adolescents with later initiation and/or shorter duration of stimulant treatment for ADHD should be monitored for potential illicit and prescription stimulant misuse.

[Perceived Racism And Discrimination And Youth Substance Use In The United States - Intersections With Sex And Ethnicity](#) Dai HD, Thiel G, Hafer D. *Prev Med.* 2024; 178: 107811.

Objectives: This study sought to examine associations between U.S. adolescents' perceived racism and discrimination (PRD) at school and current substance use. **Methods:** Data were drawn from the Adolescent Behaviors and Experiences Survey (ABES), a probability sample of U.S. high school students in 2021 (n = 7705). Multivariable regression models were conducted to examine associations of PRD with current (past 30-day) use of tobacco products, marijuana, alcohol, and prescription opioid misuse. Interaction effects of PRD and demographic factors were tested.

Results: Among participants in the 2021 ABES, PRD was associated with higher odds of current use of tobacco (AOR = 1.3, p = 0.03), marijuana (AOR = 1.3, p = 0.03), alcohol (AOR = 1.2, p = 0.03), and misuse of prescription opioids (AOR = 1.6, p = 0.004). The effects of PRD on current tobacco and alcohol use differed by Hispanic and non-Hispanic adolescents (interaction effect = 0.007 and 0.01, respectively) with higher odds among Hispanic youth than among non-Hispanic counterparts. The associations of PRD and current tobacco use, marijuana use, alcohol use, and misuse of prescription opioids were moderated by sex with more pronounced effects on males than females. **Conclusions:** Efforts to promote awareness and create support environments that value diversity and inclusivity at school are needed to mitigate adolescent exposure to racism and discrimination.

[Lifetime Non-Fatal Overdose Experiences Among At-Risk Adolescents And Young Adults In The Emergency Department With Past-Year Opioid Use In The USA](#) Seewald L, Bonar E, Bohnert ASB, Carter PM, King CA, Losman ED, Bacon L, Wheeler T, Walton M. *Inj Prev.* 2024;ip-2023-045072.

Background: Adolescents and young adults with risk factors for opioid misuse and opioid use disorder are at elevated risk for overdose. We examined prior non-fatal overdose experiences among at-risk adolescents/young adults to inform prevention efforts. **Methods:** Adolescents/young adults (ages 16-30) in two US emergency departments self-reporting past year opioid misuse or opioid use plus a misuse risk factor completed a baseline survey as part of an ongoing randomised controlled trial. We describe baseline factors associated with (a) overall non-fatal overdose experiences and (b) groups based on substance(s) used during the worst overdose experience.

Results: Among 771 participants (27.9% male), 40.7% reported a non-fatal overdose experience. Compared with those without a prior overdose experience, those with prior overdose experience(s) were less likely to be heterosexual, and more likely to report a prior suicide attempt and greater peer substance misuse. Regarding the worst overdose experience, substance(s) included: 36.6% alcohol only, 28.0% alcohol and cannabis, 22.6% alcohol with other substance(s) and 12.7% other substance(s) only (e.g., opioids). Compared with the alcohol only group, the alcohol and cannabis group were younger and less likely to be heterosexual; the alcohol with other substance(s) group were older and had greater peer substance misuse; and the other substance(s) only group were more likely to be male, receive public assistance, screen positive for anxiety and less likely to be heterosexual. **Conclusions:** Among at-risk adolescents/young adults, findings support the need for tailored overdose prevention efforts based on substance(s) used, with consideration of sexuality, mental health and peer substance use.

[Preferences In Medications For Patients Seeking Treatment For Opioid Use Disorder: A Conjoint Analysis](#)

Muthulingam D, Hassett TC, Madden LM, Bromberg DJ, Fraenkel L, Altice FL. *J Subst Use Addict Treat.* 2023; 154: 209138.

Introduction: The opioid epidemic continues to be a public health crisis that has worsened during the COVID-19 pandemic. Medications for opioid use disorder (MOUD) are the most effective way to reduce complications from opioid use disorder (OUD), but uptake is limited by both structural and individual factors. To inform strategies addressing individual factors, we evaluated patients' preferences and trade-offs in treatment decisions using conjoint analysis. **Method:** We developed a conjoint analysis survey evaluating patients' preferences for FDA-approved MOUDs. We recruited patients with OUD presenting to initiate treatment. This survey included five attributes: induction, location and route of administration, impact on mortality, side effects, and withdrawal symptoms with cessation. Participants performed 12 choice sets, each with two hypothetical profiles and a "none" option. We used Hierarchical Bayes to identify relative importance of each attribute and part-worth utility scores of levels, which we compared using chi-squared analysis. We used the STROBE checklist to guide our reporting of this cross-sectional observational study. **Results:** Five-hundred and thirty participants completed the study. Location with route of administration was the most important attribute. Symptom relief during induction and withdrawal was a second priority. Mortality followed by side effects had lowest relative importance. Attribute levels with highest part-worth utilities showed patients preferred monthly pick-up from a pharmacy rather than daily supervised dosing; and oral medications more than injection/implants, despite the latter's infrequency. **Conclusion:** We measured treatment preferences among patients seeking to initiate OUD treatment to inform strategies to scale MOUD treatment uptake. Patients prioritize the route of administration in treatment preference-less frequent pick up, but also injections and implants were less preferred despite their convenience. Second, patients prioritize symptom relief during the induction and withdrawal procedures of medication. These transition periods influence the sustainability of treatment. Although health professionals prioritize mortality, it did not drive decision-making for patients. To our knowledge, this is the largest study on patients' preferences for MOUD among treatment-seeking people with OUD to date. Future analysis will evaluate patient preference heterogeneity to further target program planning, counseling, and decision aid development.

[Reduced Drug Use As An Alternative Valid Outcome In Individuals With Stimulant Use Disorders: Findings From 13 Multisite Randomized Clinical Trials](#)

Amin-Esmaeili M, Farokhnia M, Susukida R, Leggio L, Johnson RM, Crum RM, Mojtabei R. *Addiction.* 2024; 119(5): 833-843.

Background: Total abstinence has historically been the goal of treatment for substance use disorders; however, there is a growing recognition of the health benefits associated with reduced use as a harm reduction measure in stimulant use disorders treatment. We aimed to assess the validity of reduced stimulant use as an outcome measure in randomized controlled trials (RCTs) of pharmacological interventions for stimulant use disorder. **Methods:** We conducted a secondary analysis of a pooled dataset of 13 RCTs. Participants were individuals seeking treatment for cocaine or methamphetamine use disorders ($N=2062$) in a wide range of treatment facilities in the United States. We validated reduced stimulant use against a set of clinical indicators drawn from harmonized measurements, including severity of problems caused by drug use, comorbid depression, global severity of substance use and improvement, severity of drug-seeking behavior, craving and high-risk behaviors, all assessed at the end of the trial, as well as follow-up urine toxicology. A series of mixed effect regression models was conducted to validate reduction in

frequency of use against no reduction in use and abstinence. **Results:** More participants reduced frequency of primary drug use than achieved abstinence (18.0% vs. 14.2%, respectively). Reduced use was significantly associated with decreases in craving for the primary drug [60.1%, 95% confidence interval (CI) = 54.3%–64.7%], drug seeking behaviors (41.0%, 95% CI = 36.6%–45.7%), depression severity (39.9%, 95% CI = 30.9%–48.3%), as well as multiple measures of global improvement in psychosocial functioning and severity of drug-related problems, albeit less strongly so than abstinence. Moreover, reduced use was associated with sustained clinical benefit at follow-up, as confirmed by negative urine tests (adjusted odds ratio compared with those with no reduction in use: 0.50, 95% CI = 0.35–0.71). **Conclusion:** Reduced frequency of stimulant use appears to be associated with meaningful improvement in various clinical indicators of recovery. Assessment of reduced use, in addition to abstinence, could broaden the scope of outcomes measured in randomized controlled trials of stimulant use disorders and facilitate the development of more diverse treatment approaches.

TREATMENT RESEARCH

Mixed Amphetamine Salts-extended Release (MAS-ER) As A Behavioral Treatment Augmentation Strategy For Cocaine Use Disorder: A Randomized Clinical Trial

Carpenter KM, Choi CJ, Basaraba C, Pavlicova M, Brooks DJ, Brezing CA, Bisaga A, Nunes EV, Mariani JJ, Levin FR. *Exp Clin Psychopharmacol.* 2024; 32(1): 112-127.

Psychosocial interventions remain the primary strategy for addressing cocaine use disorder (CUD), although many individuals do not benefit from these approaches. Amphetamine-based interventions have shown significant promise and may improve outcomes among individuals continuing to use cocaine in the context of behavioral interventions. One hundred forty-five adults (122 males) who used cocaine a minimum of 4 days in the prior month and met the criteria for a CUD enrolled in a two-stage intervention. All participants received a computer-delivered skills intervention and contingency management for reinforcing abstinence for a 1-month period. Participants demonstrating less than 3 weeks of abstinence in the first month were randomized to receive mixed amphetamine salts-extended release (MAS-ER) or placebo (80 mg/day) for 10 weeks under double-blind conditions. All participants continued with the behavioral intervention. The primary outcome was the proportion of individuals who achieved 3 consecutive weeks of abstinence as measured by urine toxicology confirmed self-report at the study end. The proportion of participants demonstrating 3 consecutive weeks of abstinence at study end did not differ between the medication groups: MAS-ER = 15.6% (7/45) and placebo = 12.2% (5/41). Participants who received MAS-ER reported greater reductions in the magnitude of wanting cocaine, although no group differences were noted in either the perceived improvement or the frequency of wanting cocaine. Retention rates were greater for both medication groups compared to behavioral responders. Overall, augmenting a behavioral intervention with MAS-ER did not significantly increase the abstinence rate among individuals continuing to use cocaine following a month of behavioral therapy alone.

R01DA034087

[A Preliminary Randomized Controlled Trial Of Repetitive Transcranial Magnetic Stimulation Applied To The Left Dorsolateral Prefrontal Cortex In Treatment Seeking](#)

[Participants With Cannabis Use Disorder](#) Sahlem GL, Kim B, Baker NL, Wong BL, Caruso MA, Campbell LA, Kaloani I, Sherman BJ, Ford TJ, Musleh AH, Kim JP, Williams NR, Manett AJ, Kratter IH, Short EB, Killeen TK, George MS, McRae-Clark AL. Drug Alcohol Depend. 2024; 254: 111035.

Background: Cannabis use disorder (CUD) is a common and consequential disorder. When applied to the dorsolateral prefrontal cortex (DLPFC), repetitive transcranial magnetic stimulation (rTMS) reduces craving across substance use disorders and may have therapeutic clinical effects when applied in serial-sessions. The present study sought to preliminarily determine whether serial-sessions of rTMS applied to the DLPFC had a therapeutic effect in CUD. **Methods:** This study was a two-site, phase-2, double-blind, randomized-controlled-trial. Seventy-two treatment-seeking participants (37.5% Women, mean age 30.2±9.9SD) with ≥moderate-CUD were randomized to active or sham rTMS (Beam-F3, 10Hz, 20-total-sessions, two-sessions-per-visit, two-visits-per-week, with cannabis cues) while undergoing a three-session motivational enhancement therapy intervention. The primary outcome was the change in craving between pre- and post- treatment (Marijuana Craving Questionnaire Short-Form-MCQ-SF). Secondary outcomes included the number of weeks of abstinence and the number of days-per-week of cannabis use during 4-weeks of follow-up. **Results:** There were no significant differences in craving between conditions. Participants who received active-rTMS reported numerically, but not significantly, more weeks of abstinence in the follow-up period than those who received sham-rTMS (15.5%-Active; 9.3%-Sham; rate ratio = 1.66 [95% CI: 0.84, 3.28]; p=0.14). Participants who received active-rTMS reported fewer days-per-week of cannabis use over the final two-weeks of the follow-up period than those receiving sham-rTMS (Active vs. Sham: -0.72; Z=-2.33, p=0.02). **Conclusions:** This trial suggests rTMS is safe and feasible in individuals with CUD and may have a therapeutic effect on frequency of cannabis use, though further study is needed with additional rTMS-sessions and a longer follow-up period. K24DA038240, K12DA031794, K23DA043628

[Randomized Controlled Trial Of Zolpidem As A Pharmacotherapy For Cannabis Use Disorder](#)

Lee DC, Schlienz NJ, Herrmann ES, Martin EL, Leoutsakos J, Budney AJ, Smith MT, Tompkins DA, Hampson AJ, Vandrey R. J Subst Use Addict Treat. 2024; 156: 209180.

Background: Sleep disturbance is commonly reported among individuals meeting criteria for cannabis use disorder (CUD), and people who use cannabis frequently report sleep disturbance as a contributor to failed quit attempts. The purpose of this study was to measure sleep in individuals enrolled in treatment for CUD, and to determine whether use of hypnotic medication during treatment increased abstinence rates. **Method:** The study enrolled 127 adults seeking treatment for CUD in a 12-week clinical trial and randomized to receive extended-release zolpidem (zolpidem-XR) or placebo. All participants received computerized behavioral therapy and abstinence-based contingency management. The study conducted in-home ambulatory polysomnography (PSG) assessments at baseline and during treatment to objectively measure sleep. Self-report measures of recent sleep, Insomnia Severity Index (ISI), and drug use (Timeline Follow-Back) were collected at each study visit, and the study confirmed self-reported abstinence via quantitative urine drug testing. **Result:** Participants randomized to placebo, but not zolpidem-XR exhibited significant sleep disturbance during week 1 of treatment. Sleep disturbance emerged in the zolpidem-XR group after study medication was stopped at the end of treatment. Though participants assigned to the zolpidem-XR condition had qualitatively greater rates of abstinence compared with placebo (27 % versus 15 % negative at end of treatment), the difference was not statistically significant. Treatment retention was

poor (about 50 % drop out in both groups) and medication adherence was a challenge without the use of contingent incentives. **Conclusion:** Results from this randomized controlled trial suggest that zolpidem-XR can attenuate abstinence-induced sleep disturbance early in treatment for CUD, but that sleep problems are likely to emerge after the medication is stopped. Further research should identify alternative pharmacotherapies and behavioral treatments for CUD and elucidate the role of sleep disturbance in the development and maintenance of CUD. U01DA031784, P30DA029926

[A Bacteriophage Virus-like Particle Vaccine Against Oxycodone Elicits High-titer And Long-lasting Antibodies That Sequester Drug In The Blood](#) Romano IG, Core SB, Lee NR, Mowry C, Van Rompay KKA, Huang Y, Chackerian B, Frieze KM. Vaccine. 2024; 42(3): 471-480.

Opioid use disorder (OUD) and opioid overdoses are public health emergencies. In 2021, 80,000 opioid overdose associated deaths were reported in the United States. Despite the availability of treatment strategies, including medications for opioid use disorder (MOUD) and naloxone, opioid overdoses continue to increase at an alarming rate. Opioid vaccines are a novel approach to combat the growing crisis with several candidates recently entering human clinical trials. In this study, we investigated Q β bacteriophage virus-like particles (VLPs) as a vaccine platform for immunogenic display of oxycodone. A derivative of oxycodone was conjugated to pre-formed Q β VLPs using a sulfhydryl-amine reactive heterobifunctional crosslinker with high loading of oxycodone. In mice, intramuscular immunization with Q β -oxycodone elicited high-titer, high-avidity and long-lasting antibody responses. Q β -oxycodone was also immunogenic after storage at ambient room temperature for over two weeks, demonstrating that the vaccine is highly thermostable. In mice, immunization with Q β -oxycodone elicited antibodies that sequester oxycodone in the serum, an important mechanism for preventing the adverse effects of opioid activity. Finally, Q β -oxycodone is immunogenic in nonhuman primates, eliciting serum oxycodone antibodies after intramuscular immunization of rhesus macaques. These data establish Q β -oxycodone as a promising opioid vaccine candidate. KL2TR001448,R01HL131696,F31DA059236,P51OD011107

[Pharmacokinetic Properties Of An FDA-approved Intranasal Nalmefene Formulation For The Treatment Of Opioid Overdose](#) Crystal R, Ellison M, Purdon C, Skolnick P. Clin Pharmacol Drug Dev. 2024; 13(1): 58-69.

Nalmefene is a high-affinity, long-duration opioid antagonist that was approved in 1995 as an injection for the treatment of opiate overdose, but subsequently withdrawn (2008) for reasons other than safety or effectiveness. The dramatic rise in opioid overdose deaths over the past 7-8 years catalyzed the development of an intranasal (IN) formulation of nalmefene for the emergency treatment of opioid overdose. The studies described here compare the pharmacokinetic properties and safety profiles of an IN formulation containing nalmefene (2.7 mg in 0.1 mL) to an approved 1 mg intramuscular (IM) dose. IN nalmefene produced maximum plasma concentrations that were significantly higher than observed following the IM dose (12.2 and 1.77 ng/mL, respectively). The time to reach maximum plasma concentrations was also faster following IN administration (0.25 and 0.33 hours, respectively) with significant differences in plasma concentrations manifested as early as 2.5 minutes after administration (NCT04759768). The plasma half-life of nalmefene was similar following IM and IN administration (10.6-11.4 hours). Furthermore, dose-normalized nalmefene exposure was similar for both 1 spray in each nostril and 2 sprays in the same nostril compared to a single spray in each nostril (NCT05219669). There were no sex differences in the pharmacokinetic properties of either IN or IM nalmefene. In an era when almost 90% of opioid overdose deaths have been linked to high-potency synthetic opioids, the ability to rapidly deliver high concentrations of nalmefene could represent an important tool for reducing both morbidity and mortality. U01DA046093

[Effects Of Naltrexone On Amphetamine Choice In Rhesus Monkeys And Rats](#) Robinson HL, Moerke MJ, Banks ML, Negus SS. *Exp Clin Psychopharmacol.* 2023; 31(6): 1080-1091.

Clinical amphetamine use is constrained by high abuse potential, and amphetamine use disorder is a persistent clinical problem with no approved medications for its treatment. The opioid antagonist naltrexone has been reported to reduce some abuse-related effects of amphetamine. This study used an amphetamine-versus-food choice procedure in rhesus monkeys and rats to test the hypothesis that naltrexone might serve as either (a) a maintenance medication for amphetamine use disorder treatment or (b) an "abuse-deterrent" adjunct to clinical amphetamine formulations. Male rhesus monkeys and male and female rats were trained to choose between increasing unit doses of intravenous amphetamine and an alternative food reinforcer during daily behavioral sessions. Experiment 1 evaluated effectiveness of continuous naltrexone maintenance to reduce amphetamine-versus-food choice in both monkeys and rats. Experiment 2 combined naltrexone with amphetamine in fixed-proportion amphetamine + naltrexone mixtures to evaluate the effectiveness of naltrexone in both species to reduce mixture choice relative to amphetamine-alone choice. Amphetamine maintained a dose-dependent increase in amphetamine choice in both monkeys and rats. Naltrexone maintenance did not significantly decrease amphetamine choice in either species. Addition of naltrexone to amphetamine reduced amphetamine choices per session in monkeys, but behavior was not reallocated to food choice, and in rats, the addition of naltrexone only decreased food choice without significantly affecting amphetamine choice. These results argue against the use of naltrexone as either (a) a maintenance medication for treatment of amphetamine use disorder or (b) an "abuse-deterrent" adjunct to amphetamine for clinical applications. R01DA026946, T32DA007027

[A Phase 1b Study To Investigate The Potential Interactions Between ASP8062 And Buprenorphine/naloxone In Patients With Opioid Use Disorder](#) Ito M, Walzer M, Blauwet MB, Spence A, Heo N, Kelsh D, Blahunka P, Erdman J, Nour Alsharif M, Marek GJ. *J Psychopharmacol.* 2023; 37(2): 144-154.

Background: There is an unmet need for therapeutics with greater efficacy and tolerability for the treatment of opioid use disorder (OUD). ASP8062 is a novel compound with positive allosteric modulator activity on the γ -aminobutyric acid type B receptor under development for use with standard-of-care treatment for patients with OUD. **Aims:** To investigate the safety, tolerability, interaction potential, and pharmacokinetics (PK) of ASP8062 in combination with buprenorphine/naloxone (B/N; Suboxone®). **Methods:** In this phase 1, randomized, double-masked, placebo-controlled study, patients with OUD began B/N (titrated to 16/4 mg/day) treatment upon enrollment (induction, Days 1-4; maintenance, Days 5-18; downward titration, Days 19-26; and discharge, Day 27). On Day 12, patients received a single dose of ASP8062 60 mg or placebo with B/N and underwent safety and PK assessments. Primary endpoints included frequency and severity of treatment-emergent adverse events (TEAEs), clinical laboratory tests, respiratory depression, and suicidal ideation. Secondary endpoints investigated the impact of ASP8062 on B/N PK. **Results:** Eighteen patients were randomized and completed the study (ASP8062, n = 12; placebo, n = 6). With this sample size typical for phase 1 drug-drug interaction studies, ASP8062 was well tolerated; most TEAEs were mild in severity, and none led to treatment withdrawal. ASP8062 did not enhance substance use-related TEAEs, respiratory depression, or suicidal ideation and did not have a clinically significant impact on the PK of B/N. **Conclusions:** In this phase 1 study, ASP8062 was safe, well tolerated, and did not enhance respiratory suppression induced by buprenorphine. TRIAL REGISTRATION: Clinicaltrials.gov identifier: NCT04447287. UG3DA051392

Effects Of Cannabinoid Agonists And Antagonists In Male Rats Discriminating The Synthetic Cannabinoid AM2201

AlKhelb D, Burke EL, Zvonok A, Iliopoulos-Tsoutsouvas C, Georgiadis MO, Jiang S, Ho TC, Nikas SP, Makriyannis A, Desai RI. Eur J Pharmacol. 2023; 960: 176168.

The synthetic forms of delta-9-tetrahydrocannabinol (Δ 9-THC), dronabinol or nabilone, have been approved to treat several indications. However, due to safety concerns their clinical utility remains limited. Consequently, there is a need for developing cannabinoid (CB) ligands that display better behavioral pharmacological profiles than Δ 9-THC. Here, we utilized drug discrimination methods to compare the interoceptive effects of CB ligands that vary in potency, efficacy, and selectivity at the CB receptors, including two ligands, AM411 and AM4089, that show CB1 partial agonist-like actions in vitro. Male rats were trained to discriminate 0.1 mg/kg AM2201 from saline under a fixed-ratio (FR) 10 response schedule of food reinforcement. After establishing AM2201's discriminative-stimulus effects, pretreatment tests with the CB1 antagonist/inverse agonist rimonabant blocked AM2201's effects, whereas the peripherally-restricted antagonist AM6545 had no effect. Next, the generalization profiles of AM411 and AM4089 with CB1 full agonists (JWH-018, CP-55,940, AM8936), partial agonist (Δ 9-THC), and non-cannabinoids (fentanyl, atropine) were compared. The CBs either fully (AM2201, CP-55,940, JWH-018, AM8936, Δ 9-THC) or partially (AM411, AM4089) substituted for AM2201, whereas fentanyl and atropine did not produce AM2201-like effects. All CB drugs were more potent than Δ 9-THC and correlation analysis confirmed that the relative behavioral potencies of CBs corresponded strongly with their relative affinities at the CB1 but not CB2 receptors. Together, our results further demonstrate that AM411 and AM4089 exhibit better pharmacological profiles compared to Δ 9-THC, in that they are more potent and display in vivo partial agonist-like actions that are centrally mediated via CB1 receptors. R37DA003801, P01DA009158, R21DA045882

HIV RESEARCH

Single-Cell Epigenetic, Transcriptional, And Protein Profiling Of Latent And Active HIV-1 Reservoir Revealed That IKZF3 Promotes HIV-1 Persistence

Wei Y, Davenport TC, Collora JA, Ma HK, Pinto-Santini D, Lama J, Alfaro R, Duerr A, Ho YC. Immunity. 2023; 56(11): 2584-2601.e7.

Understanding how HIV-1-infected cells proliferate and persist is key to HIV-1 eradication, but the heterogeneity and rarity of HIV-1-infected cells hamper mechanistic interrogations. Here, we used single-cell DOGMA-seq to simultaneously capture transcription factor accessibility, transcriptome, surface proteins, HIV-1 DNA, and HIV-1 RNA in memory CD4⁺ T cells from six people living with HIV-1 during viremia and after suppressive antiretroviral therapy. We identified increased transcription factor accessibility in latent HIV-1-infected cells (RORC) and transcriptionally active HIV-1-infected cells (interferon regulatory transcription factor [IRF] and activator protein 1 [AP-1]). A proliferation program (IKZF3, IL21, BIRC5, and MKI67 co-expression) promoted the survival of transcriptionally active HIV-1-infected cells. Both latent and transcriptionally active HIV-1-infected cells had increased IKZF3 (Aiolos) expression. Distinct epigenetic programs drove the heterogeneous cellular states of HIV-1-infected cells: IRF:activation, Eomes:cytotoxic effector differentiation, AP-1:migration, and cell death. Our study revealed the single-cell epigenetic, transcriptional, and protein states of latent and transcriptionally active HIV-1-infected cells and cellular programs promoting HIV-1 persistence.

[Fentanyl Dysregulates Neuroinflammation And Disrupts Blood-brain Barrier Integrity In HIV-1 Tat Transgenic Mice](#)

Rademeyer KM, R Nass S, Jones AM, Ohene-Nyako M, Hauser KF, McRae M. J Neurovirol. 2024; 30(1): 1-21.

Opioid overdose deaths have dramatically increased by 781% from 1999 to 2021. In the setting of HIV, opioid drug abuse exacerbates neurotoxic effects of HIV in the brain, as opioids enhance viral replication, promote neuronal dysfunction and injury, and dysregulate an already compromised inflammatory response. Despite the rise in fentanyl abuse and the close association between opioid abuse and HIV infection, the interactive comorbidity between fentanyl abuse and HIV has yet to be examined in vivo. The HIV-1 Tat-transgenic mouse model was used to understand the interactive effects between fentanyl and HIV. Tat is an essential protein produced during HIV that drives the transcription of new virions and exerts neurotoxic effects within the brain. The Tat-transgenic mouse model uses a glial fibrillary acidic protein (GFAP)-driven tetracycline promoter which limits Tat production to the brain and this model is well used for examining mechanisms related to neuroHIV. After 7 days of fentanyl exposure, brains were harvested. Tight junction proteins, the vascular cell adhesion molecule, and platelet-derived growth factor receptor- β were measured to examine the integrity of the blood brain barrier. The immune response was assessed using a mouse-specific multiplex chemokine assay. For the first time in vivo, we demonstrate that fentanyl by itself can severely disrupt the blood-brain barrier and dysregulate the immune response. In addition, we reveal associations between inflammatory markers and tight junction proteins at the blood-brain barrier.

[Cannabis Use And Biomarkers Of Inflammation, Immune Activation, And Microbial Translocation In Persons With HIV](#)

Okafor CN, Somasunderam A, Lake JE, Gelfond J, Javanbakht M, Gorbach P, Shoptaw S, Schmitz J. Cannabis Cannabinoid Res. 2024 Feb 9 [Online ahead of print].

Background: The relationship between cannabis and inflammation among persons with HIV (PWH) remains unclear. We examined whether the cannabis metabolite 11-nor-9-carboxy THC (THC-COOH) is associated with lower levels of plasma biomarkers of inflammation, immune activation, and microbial translocation in PWH. We hypothesized that cannabis use would be associated with lower levels of plasma inflammatory biomarkers than noncannabis use. **Methods:** We quantified THC-COOH in plasma, with THC-COOH levels between 5.1-69.9 $\mu\text{g/L}$ and ≥ 70 $\mu\text{g/L}$ being classified as moderate and heavy cannabis use, respectively, with noncannabis use defined as undetected THC-COOH. We measured a panel of plasma biomarkers of inflammation (interleukin [IL]-1- β , tumor necrosis factor- α , IL-18, IL-6, and C-reactive protein), immune activation (CD14 and CD163), and microbial translocation (iFABP2 and lipopolysaccharide binding protein [LBP]), with all biomarkers collected on the same day. We used a cross-sectional design and linear regression models to test whether cannabis use is associated with lower biomarker levels. **Results:** Participants were (N=107) sexual minority men with HIV (median age=32 years, IQR=28, 38), of whom 65% were virally suppressed; 36%, 44%, and 20% were classified as nonuse, moderate, and heavy cannabis, respectively. In linear regression models adjusted for viral suppression, stimulant use, and CD4 counts, heavy cannabis use was significantly associated with lower levels of log₁₀ LBP (β =-0.14, 95% confidence interval: -0.24 to -0.04; false discovery rate=0.0029; partial eta squared=0.07) than noncannabis users. No precise associations were observed for other biomarkers (all $p > 0.05$). **Conclusions:** Our findings suggest that cannabis use may be associated with lower plasma LBP. Further work is needed to clarify the relationship between cannabis use and biomarkers of microbial translocation in PWH. U01DA036267

Implementing A Peer-Supported, Integrated Strategy For Substance Use Disorder Care In An Outpatient Infectious Disease Clinic Is Associated With Improved Patient Outcomes

Falade-Nwulia O, Agee T, Kelly SM, Park JN, Schwartz S, Hsu J, Schweizer N, Jones J, Keruly J, Shah N, Lesko CR, Lucas GM, Sulkowski M. *Int J Drug Policy*. 2023; 121: 104191.

Background: Substance use disorder (SUD) and infectious disease (ID) care integration may lead to improvements in SUD and ID outcomes. We assessed implementation of integrating peer-supported SUD care in an outpatient ID setting. **Methods:** In this implementation study, we describe REcovery in Specialty care Through medication and OutREach (RESTORE), a low-threshold SUD program implemented in a Baltimore outpatient ID clinic. Key program components were clinician training and support in SUD care, prescription of SUD treatment medications, and peer-based psychosocial support provided by peer recovery specialists. We assessed clinician adoption of RESTORE and compared patient outcomes from baseline to 6 months. **Results:** Between January 2019 and January 2022, the number of ID clinicians (N=61) who prescribed buprenorphine increased eightfold from 3 (5%) to 24 (39%). Of 258 ID patients referred to RESTORE, 182 (71%) engaged, 137 consented to study participation. Mean age in the study sample was 52.1 (SD=10.4), 63% were male, 84% were Black/African-American. Among 127 (93%) who completed 6-month follow-up, fewer participants reported illicit/non-prescribed opioid use in the past 30 days at follow-up (32%) compared to baseline (52%; $p<0.001$). Similar reductions were noted for cocaine use (47% to 34%; $p=0.006$), emergency department visits (23% to 9%; $p=0.002$), and inpatient hospitalizations (15% to 7%; $p=0.025$). **Conclusion:** SUD care integration into an outpatient ID care setting using a peer-supported implementation strategy was adopted by clinicians and improved clinical outcomes for patients. This strategy is a promising approach to treating people with infectious diseases and SUD.

Come Back When You're Infected: Pharmacy Access To Sterile Syringes In An Arizona Secret Shopper Study, 2023

Russell DM, Meyerson BE, Mahoney AN, Garnett I, Ferrell C, Newgass K, Agley JD, Crosby RA, Bentele KG, Vadieli N, Frank D, Linde-Krieger LB. *Harm Reduct J*. 2024; 21(1): 49.

Background: Pharmacies are critical healthcare partners in community efforts to eliminate bloodborne illnesses. Pharmacy sale of sterile syringes is central to this effort. **Methods** A mixed methods “secret shopper” syringe purchase study was conducted in the fall of 2022 with 38 community pharmacies in Maricopa and Pima Counties, Arizona. Pharmacies were geomapped to within 2 miles of areas identified as having a potentially high volume of illicit drug commerce. Daytime venue sampling was used whereby separate investigators with lived/living drug use experience attempted to purchase syringes without a prescription. Investigator response when prompted for purchase rationale was “to protect myself from HIV and hepatitis C.” A 24-item instrument measured sales outcome, pharmacy staff interaction (hostile/neutral/friendly), and the buyer’s subjective experience. **Results:** Only 24.6% ($n = 28$) of 114 purchase attempts across the 38 pharmacies resulted in syringe sale. Less than one quarter (21.1%) of pharmacies always sold, while 44.7% never sold. Independent and food store pharmacies tended not to sell syringes. There emerged distinct pharmacy staff interactions characterized by body language, customer query, normalization or othering response, response to purchase request and closure. Pharmacy discretion and pharmacy policy not to sell syringes without a prescription limited sterile syringe access. Investigators reported frequent and adverse emotional impact due to pharmacy staff negative and stigmatizing interactions. **Conclusions** Pharmacies miss opportunities to advance efforts to eliminate bloodborne infections by stringent no-sale policy and discretion about syringe sale. State regulatory policy facilitating pharmacy syringe sales, limiting pharmacist discretion for syringe sales, and targeting pharmacy-staff level education may help advance the achievement of public health goals to eliminate bloodborne infections in Arizona.

OFFICE OF TRANSLATIONAL INITIATIVES AND PROGRAM INNOVATIONS (OTIPI)

Placental Cytochrome P450 Methylomes In Infants Exposed To Prenatal Opioids: Exploring The Effects Of Neonatal Opioid Withdrawal Syndrome On Health Horizons

Radhakrishna U, Sadhasivam S, Radhakrishnan R, Forray A, Muvvala SB, Metpally RP, Patel S, Rawal RM, Vishweswaraiah S, Bahado-Singh RO, Nath SK. *Front Genet.* 2024; 14: 1292148.

Background: Neonatal opioid withdrawal syndrome (NOWS), arises due to increased opioid use during pregnancy. Cytochrome P450 (CYP) enzymes play a pivotal role in metabolizing a wide range of substances in the human body, including opioids, other drugs, toxins, and endogenous compounds. The association between CYP gene methylation and opioid effects is unexplored and it could offer promising insights. **Objective:** To investigate the impact of prenatal opioid exposure on disrupted CYPs in infants and their anticipated long-term clinical implications. **Study Design:** DNA methylation levels of CYP genes were analyzed in a cohort of 96 placental tissues using Illumina Infinium MethylationEPIC (850 k) BeadChips. This involved three groups of placental tissues: 32 from mothers with infants exposed to opioids prenatally requiring pharmacologic treatment for NOWS, 32 from mothers with prenatally opioid-exposed infants not needing NOWS treatment, and 32 from unexposed control mothers. **Results:** The study identified 20 significantly differentially methylated CpG sites associated with 17 distinct CYP genes, with 14 CpGs showing reduced methylation across 14 genes (CYP19A1, CYP1A2, CYP4V2, CYP1B1, CYP24A1, CYP26B1, CYP26C1, CYP2C18, CYP2C9, CYP2U1, CYP39A1, CYP2R1, CYP4Z1, CYP2D7P1 and), while 8 exhibited hypermethylation (CYP51A1, CYP26B1, CYP2R1, CYP2U1, CYP4X1, CYP1A2, CYP2W1, and CYP4V2). Genes such as CYP1A2, CYP26B1, CYP2R1, CYP2U1, and CYP4V2 exhibited both increased and decreased methylation. These genes are crucial for metabolizing eicosanoids, fatty acids, drugs, and diverse substances. **Conclusion:** The study identified profound methylation changes in multiple CYP genes in the placental tissues relevant to NOWS. This suggests that disruption of DNA methylation patterns in CYP transcripts might play a role in NOWS and may serve as valuable biomarkers, suggesting a future pathway for personalized treatment. Further research is needed to confirm these findings and explore their potential for diagnosis and treatment.

Telehealth Treatment For Opioid Use Disorder During Pregnancy Coffey MJ, Weng M, Jimes C, Brigham S, Lira MC. *JAMA Network Open.* 2024; 7(3): 1- 4.

Although successful treatment exists for pregnant women with Opioid Use Disorder (OUD), OUD is still credited with high rates of morbidity and mortality. The use of buprenorphine for treatment during pregnancy is safe, effective, and reduces mortality, but pregnant women face obstacles to treatment. Digital technology, such as telehealth, has emerged as a promising method for providing and increasing access to OUD care. Here, the authors show that of 94 women offered OUD care via telehealth, seventy-five women (79.8%) received continuous OUD care throughout their pregnancies, and nineteen (20.2%) did not. Of the women who had continued care, six (8.0%) transferred their care to prenatal clinicians. Among the remaining sixty-nine (92.0%) who continued with telehealth, sixty-five (94.2%) had continuous care, thirteen (13.8%) were lost to follow-up, and six (6.4%) were discharged due to administrative or financial reasons. A total of fifty-two (82.6%) carried to term; there were nine (13.0%) spontaneous terminations and three (4.3%) medical terminations. Overall, the outcomes add to the supporting evidence of the effectiveness of telehealth-based treatment in pregnant women with OUD.

CLINICAL TRIALS NETWORK RESEARCH

[Medication Treatment For Opioid Use Disorder Among Rural Primary Care Patients](#) Hser YI, Zhu Y, Baldwin LM, Mooney LJ, Saxon AJ. *J Rural Health*. 2024; 40(1): 195-199.

Purpose: To investigate the prevalence of opioid use disorder (OUD) and medication treatment for OUD (MOUD) receipt in rural primary care settings and identify characteristics associated with MOUD among patients with OUD. **Methods:** Secondary analyses based on electronic health records of all adult patients who visited 1 of the 6 rural primary care clinic sites from October 2019 to January 2021. Mixed effects logistic regression was conducted to assess MOUD receipt (Y/N) in relation to patient characteristics (eg, demographics, other substance use disorders [SUDs], mental health disorders, and chronic pain) and the number of MOUD prescribers per clinic. **Findings:** The prevalence of OUD varied from 0.7% to 8.2% (Mean [SD] = 3.3% [95% CI: 0.4, 6.1]) among 36,762 primary care patients across 6 clinic sites. Among 1,164 patients with OUD, on average 50.1% received MOUD (95% CI: 28.0, 72.3). Patients in clinics with more than 3 MOUD prescribers had more than 3 times the odds of receiving MOUD (OR = 3.42; 95% CI, 1.22-9.62) as those in clinics with fewer than 3 prescribers. MOUD was positively associated with younger age (18-30 [OR = 6.97; 95% CI, 3.37-14.42], 31-64 [OR = 5.03; 95% CI, 2.64-9.57], relative to those 65 and older), having other co-occurring SUDs (OR = 3.77; 95% CI, 2.57-5.52), being male (OR = 1.50; 95% CI, 1.12-2.01), and negatively associated with having chronic pain disorders (OR = 0.69; 95% CI, 0.50-0.94). **Conclusions:** The prevalence of OUD and MOUD are high but vary considerably across rural primary care clinics; primary care MOUD prescribers play a key role on MOUD access in rural settings.

[Urine Toxicology Profiles Of Emergency Department Patients With Untreated Opioid Use Disorder: A Multi-Site View](#) Cowan E, Perrone J, Dziura J, Edelman EJ, Hawk K, Herring A, McCormack R, Murphy A, Phadke M, Fiellin DA, D'Onofrio G. *J Emerg Med*. 2023; 65(4): e357-e365.

Background: Opioid overdose deaths in 2021 were the highest ever, driven by fentanyl and polysubstance use. **Objective:** The aim of the study was to characterize drug use, assessed by urine drug screens (UDSs), in patients with untreated opioid use disorder (OUD) presenting to 28 emergency departments (EDs) nationally and by region. **Methods:** We analyzed UDSs from patients enrolled in the CTN-0099 ED-INNOVATION (Emergency Department-Initiated Buprenorphine Validation) trial between July 12, 2020 and March 9, 2022. Participants were adult ED patients with OUD not engaged in addiction treatment with a UDS positive for an opioid, but negative for methadone. Sites were divided into "East" and "West" regions. **Results:** A UDS was available for all 925 enrolled participants, 543 from East and 382 from West. Fentanyl was in 702 specimens (76%) (n = 485 [89%] East vs. n = 217 [57%] West; p < 0.01) and was the only opioid in 269 (29%). After fentanyl, the most common opioids were morphine (presumably heroin; n = 411 [44%]; n = 192 [35%] East vs. n = 219 [57%] West; p < 0.01) and buprenorphine (n = 329 [36%]; n = 186 [35%] East vs. n = 143 [37%] West; p = 0.32). The most common drugs found with opioids were stimulants (n = 545 [59%]), tetrahydrocannabinol (n = 417 [45%]), and benzodiazepines (n = 151 [16%]). Amphetamine-type stimulants were more common in West (n = 209 [55%] vs. East (n = 125 [23%]). Cocaine was more common in East (n = 223 [41%]) vs. West (n = 82 [21%]). The presence of multiple drugs was common (n = 759 [82%]). **Conclusions:** Most participants had UDS specimens containing multiple substances; a high proportion had fentanyl, stimulants, and buprenorphine. Regional differences were noted. Given the increased risk of death with fentanyl and polysubstance use, ED providers should be providing risk reduction counseling, treatment, and referral.

Computational Phenotypes For Patients With Opioid-Related Disorders Presenting To The Emergency Department

Taylor RA, Gilson A, Schulz W, Lopez K, Young P, Pandya S, Coppi A, Chartash D, Fiellin D, D'Onofrio G. PLoS One. 2023; 18(9): e0291572.

Objective: We aimed to discover computationally-derived phenotypes of opioid-related patient presentations to the ED via clinical notes and structured electronic health record (EHR) data.

Methods: This was a retrospective study of ED visits from 2013-2020 across ten sites within a regional healthcare network. We derived phenotypes from visits for patients ≥ 18 years of age with at least one prior or current documentation of an opioid-related diagnosis. Natural language processing was used to extract clinical entities from notes, which were combined with structured data within the EHR to create a set of features. We performed latent dirichlet allocation to identify topics within these features. Groups of patient presentations with similar attributes were identified by cluster analysis.

Results: In total 82,577 ED visits met inclusion criteria. The 30 topics were discovered ranging from those related to substance use disorder, chronic conditions, mental health, and medical management. Clustering on these topics identified nine unique cohorts with one-year survivals ranging from 84.2-96.8%, rates of one-year ED returns from 9-34%, rates of one-year opioid event 10-17%, rates of medications for opioid use disorder from 17-43%, and a median Carlson comorbidity index of 2-8. Two cohorts of phenotypes were identified related to chronic substance use disorder, or acute overdose. **Conclusions:** Our results indicate distinct phenotypic clusters with varying patient-oriented outcomes which provide future targets better allocation of resources and therapeutics. This highlights the heterogeneity of the overall population, and the need to develop targeted interventions for each population.

Retention And Critical Outcomes Among New Methadone Maintenance Patients Following Extended Take-Home Reforms: A Retrospective Observational Cohort Study

Williams AR, Krawczyk N, Hu MC, Harpel L, Aydinoglo N, Cerda M, Rotrosen J, Nunes EV. Lancet Reg Health Am. 2023; 28: 100636.

Background: Use of electronic health records to compare retention in treatment, opioid use, and adverse events among patients newly entering methadone maintenance in the post-reform period in comparison with year-ago, unexposed, controls. **Methods:** Retrospective observational cohort study across 9 OTPs, geographically dispersed, in the National Institute of Drug Abuse (NIDA) Clinical Trials Network. Newly enrolled patients between April 15 and October 14, 2020 (post-COVID, reform period) v. March 15-September 14, 2019 (pre-COVID, control period) were assessed. The primary outcome was 6-month retention. Secondary outcomes were opioid use and adverse events including emergency department visits, hospitalizations, and overdose. **Findings:** 821 individuals were newly admitted in the post-COVID and year-ago control periods, average age of 38.3 (SD 11.1), 58.9% male. The only difference across pre- and post-reform groups was the prevalence of psychostimulant use disorder (25.7% vs 32.9%, $p = 0.02$). Retention was non-inferior (60.0% vs 60.1%) as were hazards of adverse events in the aggregate ($X^2(1) = 0.55$, $p = 0.46$) in the post-COVID period. However, rates of month-level opioid use were higher among post-COVID intakes compared to pre-COVID controls (64.8% vs 51.1%, $p < 0.001$). Moderator analyses accounting for stimulant use and site-level variation in take-home schedules did not change findings.

Interpretation: Policies allowing for extended take-home schedules were not associated with worse retention or adverse events despite slightly elevated rates of measured opioid use while in care. Relaxed guidelines were not associated with measurable increased harms and findings could inform future studies with prospective trials.

Potential Effect Of Antidepressants On Remission From Cocaine Use Disorder - A Nationwide Matched Retrospective Cohort Study Gao Z, Winhusen TJ, Gorenflo M, Ghitza UE, Nunes E, Saxon AJ, Korthis T, Brady K, Luo SX, Davis PB, Kaelber DC, Xu R. *Drug Alcohol Depend.* 2023; 251: 110958.

Background: Cocaine use disorder (CUD) is a significant public health issue for which there is no Food and Drug Administration-approved pharmacotherapy. Depressive disorders are common psychiatric comorbidity amongst individuals with CUD. **Methods:** A retrospective cohort study was conducted among 161,544 patients diagnosed with CUD and depression to evaluate the effectiveness of 13 antidepressants on CUD remission. For any antidepressant found to be associated with CUD remission that had an additional indication, we conducted an additional analysis to evaluate the effectiveness of the candidate drug in patients with CUD with that indication. We then analyzed publicly genomic and functional databases to identify potential explanatory mechanisms of action of the candidate drug in the treatment of CUD. **Results:** Among these antidepressants, bupropion was associated with higher rates of CUD remission compared to propensity-score matched patients prescribed other antidepressants: hazard ratio (HR) and 95% confidence interval (CI) 1.57 (95% CI: 1.27-1.94). Bupropion is also approved for smoking cessation. We identified CUD patients with co-occurring nicotine dependence and observed that patients prescribed bupropion displayed a higher rate of CUD remission compared to matched individuals prescribed other drugs for nicotine dependence: 1.38 (95% CI: 1.11-1.71). Genetic and functional analyses revealed that bupropion interacts with four protein-encoding genes (COMT, DRD2, SLC6A3, and SLC6A4) which are also associated with CUD and targets CUD-associated pathways including serotonergic synapses, cocaine addiction, and dopaminergic synapses. **Conclusions:** Our findings suggest that bupropion might be considered a treatment for improving CUD remission in patients with CUD and co-occurring depression or nicotine dependence.

Prep For People Who Use Opioids: A NIDA Clinical Trials Network Survey Study In Southern U.S. Cities Where HIV Incidence Is High Hatch MA, Laschober TC, Paschen-Wolff M, Ertl MM, Nelson CM, Wright L, Lancaster C, Feaster DJ, Forrest D, Hankey C, Monger M, Fegley JP, Irving R, Young C, Rose J, Spector A, Dresser L, Moran L, Jelstrom E, Tross S. *Drug Alcohol Depend.* 2024; 257: 111133.

Background: People who use opioids (PWUO) are at increased risk for HIV. Pre-exposure prophylaxis (PrEP) is effective but underutilized as HIV prevention among PWUO. This study examined predictors of willingness to take daily oral PrEP and long-acting injectable (LAI) PrEP among PWUO across eight Southern urban cities with high HIV incidence. **Methods:** HIV-negative PWUO (N = 308) seeking services in community-based programs participated in this cross-sectional survey study. Measures included demographics, sexual risk behavior, substance use frequency, and awareness of and willingness to take oral and injectable PrEP. Data were analyzed using mixed-effects models. **Results:** Willingness to take daily oral and LAI PrEP was moderately high (69.16% and 62.02%, respectively). Half had heard of PrEP, but only 4% had ever taken it. Only education and condomless vaginal sex predicted willingness to take oral PrEP. Only education predicted willingness to take LAI PrEP. Polysubstance use was prevalent, with substantial proportions of PWUO reporting frequent use of injection drugs (opioids or stimulants, 79.5%), non-injection opioids (73.3%), non-injection stimulants (71.1%), cannabis (62.6%), and hazardous drinking (29.6%). About 20% reported past-year condomless anal sex, and one-third reported past-year condomless vaginal sex. **Conclusions:** PWUO in this study were amenable to PrEP, particularly in light of education and condomless vaginal sex. Careful consideration for matching PrEP messaging to the PWUO audience is needed. PrEP promotion should expand beyond men who

have sex with men to include groups such as these predominantly heterosexual, polysubstance-using PWUO with HIV risk who were open to both formulations of PrEP.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

A Precision Functional Atlas Of Personalized Network Topography And

Probabilities

Hermosillo RJM, Moore LA, Feczko E, Miranda-Domínguez Ó, Pines A, Dworetzky A, Conan G, Mooney MA, Randolph A, Graham A, Adeyemo B, Earl E, Perrone A, Carrasco CM, Uriarte-Lopez J, Snider K, Doyle O, Cordova M, Koirala S, Grimsrud GJ, Byington N, Nelson SM, Gratton C, Petersen S, Feldstein Ewing SW, Nagel BJ, Dosenbach NUF, Satterthwaite TD, Fair DA. Nat Neurosci. 2024 Mar 26 [Online ahead of print].

Although the general location of functional neural networks is similar across individuals, there is vast person-to-person topographic variability. To capture this, we implemented precision brain mapping functional magnetic resonance imaging methods to establish an open-source, method-flexible set of precision functional network atlases-the Masonic Institute for the Developing Brain (MIDB) Precision Brain Atlas. This atlas is an evolving resource comprising 53,273 individual-specific network maps, from more than 9,900 individuals, across ages and cohorts, including the Adolescent Brain Cognitive Development study, the Developmental Human Connectome Project and others. We also generated probabilistic network maps across multiple ages and integration zones (using a new overlapping mapping technique, Overlapping MultiNetwork Imaging). Using regions of high network invariance improved the reproducibility of executive function statistical maps in brain-wide associations compared to group average-based parcellations. Finally, we provide a potential use case for probabilistic maps for targeted neuromodulation. The atlas is expandable to alternative datasets with an online interface encouraging the scientific community to explore and contribute to understanding the human brain function more precisely.

Patterns of Social Determinants of Health and Child Mental Health, Cognition, and Physical

Health

Xiao Y, Mann JJ, Chow JC, Brown TT, Snowden LR, Yip PS, Tsai AC, Hou Y, Pathak J, Wang F, Su C. JAMA Pediatr. 2023; 177(12): 1294-1305.

Importance: Social determinants of health (SDOH) influence child health. However, most previous studies have used individual, small-set, or cherry-picked SDOH variables without examining unbiased computed SDOH patterns from high-dimensional SDOH factors to investigate associations with child mental health, cognition, and physical health. **Objective:** To identify SDOH patterns and estimate their associations with children's mental, cognitive, and physical developmental outcomes. **Design, setting, and participants:** This population-based cohort study included children aged 9 to 10 years at baseline and their caregivers enrolled in the Adolescent Brain Cognitive Development (ABCD) Study between 2016 and 2021. The ABCD Study includes 21 sites across 17 states. **Exposures:** Eighty-four neighborhood-level, geocoded variables spanning 7 domains of SDOH, including bias, education, physical and health infrastructure, natural environment, socioeconomic status, social context, and crime and drugs, were studied. Hierarchical agglomerative clustering was used to identify SDOH patterns. **Main outcomes and measures:** Associations of SDOH and child mental health (internalizing and externalizing behaviors) and suicidal behaviors, cognitive function (performance, reading skills), and physical health (body mass index, exercise, sleep disorder) were estimated using mixed-effects linear and logistic regression models. **Results:** Among 10 504 children (baseline median [SD] age, 9.9 [0.6] years; 5510 boys [52.5%] and 4994 girls [47.5%]; 229 Asian [2.2%], 1468 Black [14.0%], 2128 Hispanic [20.3%],

5565 White [53.0%], and 1108 multiracial [10.5%]), 4 SDOH patterns were identified: pattern 1, affluence (4078 children [38.8%]); pattern 2, high-stigma environment (2661 children [25.3%]); pattern 3, high socioeconomic deprivation (2653 children [25.3%]); and pattern 4, high crime and drug sales, low education, and high population density (1112 children [10.6%]). The SDOH patterns were distinctly associated with child health outcomes. Children exposed to socioeconomic deprivation (SDOH pattern 3) showed the worst health profiles, manifesting more internalizing ($\beta = 0.75$; 95% CI, 0.14-1.37) and externalizing ($\beta = 1.43$; 95% CI, 0.83-2.02) mental health problems, lower cognitive performance, and adverse physical health. **Conclusions:** This study shows that an unbiased quantitative analysis of multidimensional SDOH can permit the determination of how SDOH patterns are associated with child developmental outcomes. Children exposed to socioeconomic deprivation showed the worst outcomes relative to other SDOH categories. These findings suggest the need to determine whether improvement in socioeconomic conditions can enhance child developmental outcomes.

Personalized Functional Brain Network Topography Is Associated With Individual

Differences In Youth Cognition Keller AS, Pines AR, Shanmugan S, Sydnor VJ, Cui Z, Bertolero MA, Barzilay R, Alexander-Bloch AF, Byington N, Chen A, Conan GM, Davatzikos C, Feczko E, Hendrickson TJ, Houghton A, Larsen B, Li H, Miranda-Dominguez O, Roalf DR, Perrone A, Shetty A, Shinohara RT, Fan Y, Fair DA, Satterthwaite TD. Nat Commun. 2023; 14(1): 8411.

Individual differences in cognition during childhood are associated with important social, physical, and mental health outcomes in adolescence and adulthood. Given that cortical surface arealization during development reflects the brain's functional prioritization, quantifying variation in the topography of functional brain networks across the developing cortex may provide insight regarding individual differences in cognition. We test this idea by defining personalized functional networks (PFNs) that account for interindividual heterogeneity in functional brain network topography in 9-10 year olds from the Adolescent Brain Cognitive DevelopmentSM Study. Across matched discovery ($n = 3525$) and replication ($n = 3447$) samples, the total cortical representation of fronto-parietal PFNs positively correlates with general cognition. Cross-validated ridge regressions trained on PFN topography predict cognition in unseen data across domains, with prediction accuracy increasing along the cortex's sensorimotor-association organizational axis. These results establish that functional network topography heterogeneity is associated with individual differences in cognition before the critical transition into adolescence.

Cannabis Use And Neurocognitive Performance At 13-14 Years-Old: Optimizing Assessment With Hair Toxicology In The Adolescent Brain Cognitive Development (ABCD) Study

Wade NE, Wallace AL, Huestis MA, Lisdahl KM, Sullivan RM, Tapert SF. Addict Behav. 2024; 150: 107930.

Objective: Cannabis is widely used, including in early adolescence, with prevalence rates varying by measurement method (e.g., toxicology vs. self-report). Critical neurocognitive development occurs throughout adolescence. Given conflicting prior brain-behavior results in cannabis research, improved measurement of cannabis use in younger adolescents is needed.

Methods: Data from the Adolescent Brain Cognitive Development (ABCD) Study Year 4 follow-up (participant age: 13-14 years-old) included hair samples assessed by LC-MS/MS and GC-MS/MS, quantifying THCCOOH (THC metabolite), THC, and cannabidiol concentrations, and the NIH Toolbox Cognitive Battery. Youth whose hair was positive for cannabinoids or reported past-year cannabis use were included in a Cannabis Use (CU) group ($n = 123$) and matched with non-using Controls on sociodemographics ($n = 123$). Standard and nested ANCOVAs assessed group status predicting cognitive performance, controlling for family relationships. Follow-up correlations

assessed cannabinoid hair concentration, self-reported cannabis use, and neurocognition. **Results:** CU scored lower on Picture Memory ($p = .03$) than Controls. Within the CU group, THCCOOH negatively correlated with Picture Vocabulary ($r = -0.20$, $p = .03$) and Flanker Inhibitory Control and Attention ($r = -0.19$, $p = .04$), and past-year cannabis use was negatively associated with List Sorting Working Memory ($r = -0.33$, $p = .0002$) and Picture Sequence Memory ($r = -0.19$, $p = .04$) performances. **Conclusions:** Youth who had used cannabis showed lower scores on an episodic memory task, and more cannabis use was linked to poorer performances on verbal, inhibitory, working memory, and episodic memory tasks. Combining hair toxicology with self-report revealed more brain-behavior relationships than self-report data alone. These youth will be followed to determine long-term substance use and neurocognition trajectories.

Transportation, Childcare, Lodging, And Meals: Key For Participant Engagement And Inclusion Of Historically Underrepresented Populations In The Healthy Brain And Child Development Birth Cohort

Zgierska AE, Gramly T, Prestayko N, Symons Downs D, Murray TM, Yerby LG, Howell B, Stahlman B, Cruz J, Agolli A, Horan H, Hilliard F, Croff JM; HEALthy Brain and Child Development (HBCD) Consortium. J Clin Transl Sci. 2024; 8(1): e38.

Introduction: Participant recruitment and retention (R&R) are well-documented challenges in longitudinal studies, especially those involving populations historically underrepresented in research and vulnerable groups (e.g., pregnant people or young children and their families), as is the focus of the HEALthy Brain and Child Development (HBCD) birth cohort study. Subpar access to transportation, overnight lodging, childcare, or meals can compromise R&R; yet, guidance on how to overcome these "logistical barriers" is sparse. This study's goal was to learn about the HBCD sites' plans and develop best practice recommendations for the HBCD consortium for addressing these logistical barriers. **Methods:** The HBCD's workgroups developed a survey asking the HBCD sites about their plans for supporting research-related transportation, lodging, childcare, and meals, and about the presence of institutional policies to guide their approach. Descriptive statistics described the quantitative survey data. Qualitative survey responses were brief, not warranting formal qualitative analysis; their content was summarized. **Results:** Twenty-eight respondents, representing unique recruitment locations across the U.S., completed the survey. The results indicated substantial heterogeneity across the respondents in their approach toward supporting research-related transportation, lodging, childcare, and meals. Three respondents were aware of institutional policies guiding research-related transportation (10.7%) or childcare (10.7%).

Conclusions: This study highlighted heterogeneity in approaches and scarcity of institutional policies regarding research-related transportation, lodging, childcare, and meals, underscoring the need for guidance in this area to ensure equitable support of participant R&R across different settings and populations, so that participants are representative of the larger community, and increase research result validity and generalizability.

INTRAMURAL RESEARCH

Midbrain Signaling Of Identity Prediction Errors Depends On Orbitofrontal Cortex Networks

Liu Q, Zhao Y, Attanti S, Voss JL, Schoenbaum G, Kahnt T. Nat Commun. 2024; 15(1): 1704
Outcome-guided behavior requires knowledge about the identity of future rewards. Previous work across species has shown that the dopaminergic midbrain responds to violations in expected reward identity and that the lateral orbitofrontal cortex (OFC) represents reward identity expectations. Here we used network-targeted transcranial magnetic stimulation (TMS) and

functional magnetic resonance imaging (fMRI) during a trans-reinforcer reversal learning task to test the hypothesis that outcome expectations in the lateral OFC contribute to the computation of identity prediction errors (iPE) in the midbrain. Network-targeted TMS aiming at lateral OFC reduced the global connectedness of the lateral OFC and impaired reward identity learning in the first block of trials. Critically, TMS disrupted neural representations of expected reward identity in the OFC and modulated iPE responses in the midbrain. These results support the idea that iPE signals in the dopaminergic midbrain are computed based on outcome expectations represented in the lateral OFC.

Combined Treatment With Naloxone And The Alpha2 Adrenoceptor Antagonist Atipamezole Reversed Brain Hypoxia Induced By A Fentanyl-Xylazine Mixture In A Rat Model

Choi S, Irwin MR, Noya MR, Shaham Y, Kiyatkin EA., *Neuropsychopharmacology*. 2023 Dec 20 [Online ahead of print].

Xylazine, a veterinary tranquilizer known by drug users as "Tranq", is being increasingly detected in people who overdose on opioid drugs, indicating enhanced health risk of fentanyl-lazine mixtures. We recently found that xylazine potentiates fentanyl- and heroin-induced brain hypoxia and eliminates the rebound-like post-hypoxic oxygen increases. Here, we used oxygen sensors coupled with high-speed amperometry in rats of both sexes to explore the treatment potential of naloxone plus atipamezole, a selective α_2 -adrenoceptor antagonist, in reversing brain (nucleus accumbens) and periphery (subcutaneous space) hypoxia induced by a fentanyl-xylazine mixture. Pretreatment with naloxone (0.2 mg/kg, IV) fully blocked brain and peripheral hypoxia induced by fentanyl (20 μ g/kg, IV), but only partially decreased hypoxia induced by a fentanyl-xylazine mixture. Pretreatment with atipamezole + naloxone was more potent than naloxone alone in blocking the hypoxic effects of the fentanyl-xylazine mixture. Both naloxone and naloxone + atipamezole, delivered at the peak of brain hypoxia (3 min post fentanyl-xylazine exposure), reversed the rapid initial brain hypoxia, but only naloxone + atipamezole decreased the prolonged weaker hypoxia. There were no sex differences in the effects of the different drugs and their combinations on brain and peripheral oxygen responses. Results indicate that combined treatment with naloxone and atipamezole is more effective than naloxone alone in reversing the hypoxic effects of fentanyl-xylazine mixtures. Naloxone + atipamezole treatment should be considered in preventing overdoses induced by fentanyl-xylazine mixtures in humans.

μ -Opioid Receptor Antagonism Facilitates The Anxiolytic-Like Effect Of Oxytocin In Mice

Nisbett KE, Vendruscolo LF, Koob GF., *Transl Psychiatry*. 2024; 14(1): 125.

Mood and anxiety disorders are leading causes of disability worldwide and are major contributors to the global burden of diseases. Neuropeptides, such as oxytocin and opioid peptides, are important for emotion regulation. Previous studies have demonstrated that oxytocin reduced depression- and anxiety-like behavior in male and female mice, and opioid receptor activation reduced depression-like behavior. However, it remains unclear whether the endogenous opioid system interacts with the oxytocin system to facilitate emotion regulation in male and female mice. We hypothesized that opioid receptor blockade would inhibit the anxiolytic- and antidepressant-like effects of oxytocin. In this study, we systemically administered naloxone, a preferential μ -opioid receptor antagonist, and then intracerebroventricularly administered oxytocin. We then tested mice on the elevated zero maze and the tail suspension tests, respective tests of anxiety- and depression-like behavior. Contrary to our initial hypothesis, naloxone potentiated the anxiolytic-like, but not the antidepressant-like, effect of oxytocin. Using a selective μ -opioid receptor antagonist, D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH₂, and a selective κ -opioid receptor antagonist, norbinaltorphimine, we demonstrate that μ -opioid

receptor blockade potentiated the anxiolytic-like effect of oxytocin, whereas κ -opioid receptor blockade inhibited the oxytocin-induced anxiolytic-like effects. The present results suggest that endogenous opioids can regulate the oxytocin system to modulate anxiety-like behavior. Potential clinical implications of these findings are discussed.

Unique Pharmacodynamic Properties And Low Abuse Liability Of The μ -Opioid Receptor

Ligand (S)-Methadone Levinstein MR, De Oliveira PA, Casajuana-Martin N, Quiroz C, Budinich RC, Rais R, Rea W, Ventriglia EN, Llopart N, Casadó-Anguera V, Moreno E, Walther D, Glatfelter GC, Weinshenker D, Zarate CA Jr, Casadó V, Baumann MH, Pardo L, Ferré S, Michaelides M., Mol Psychiatry. 2023 Dec 25 [Online ahead of print].

(R,S)-methadone ((R,S)-MTD) is a μ -opioid receptor (MOR) agonist comprised of (R)-MTD and (S)-MTD enantiomers. (S)-MTD is being developed as an antidepressant and is considered an N-methyl-D-aspartate receptor (NMDAR) antagonist. We compared the pharmacology of (R)-MTD and (S)-MTD and found they bind to MORs, but not NMDARs, and induce full analgesia. Unlike (R)-MTD, (S)-MTD was a weak reinforcer that failed to affect extracellular dopamine or induce locomotor stimulation. Furthermore, (S)-MTD antagonized motor and dopamine releasing effects of (R)-MTD. (S)-MTD acted as a partial agonist at MOR, with complete loss of efficacy at the MOR-galanin Gal₁ receptor (Gal₁R) heteromer, a key mediator of the dopaminergic effects of opioids. In sum, we report novel and unique pharmacodynamic properties of (S)-MTD that are relevant to its potential mechanism of action and therapeutic use. One-sentence summary: (S)-MTD, like (R)-MTD, binds to and activates MORs in vitro, but (S)-MTD antagonizes the MOR-Gal₁R heteromer, decreasing its abuse liability.

Lateral Hypothalamic Glutamatergic Inputs To VTA Glutamatergic Neurons Mediate Prioritization Of Innate Defensive Behavior Over Feeding

Barbano MF, Zhang S, Chen E, Espinoza O, Mohammad U, Alvarez-Bagnarol Y, Liu B, Hahn S, Morales M. Nat Commun. 2024; 15(1): 403.

The lateral hypothalamus (LH) is involved in feeding behavior and defense responses by interacting with different brain structures, including the Ventral Tegmental Area (VTA). Emerging evidence indicates that LH-glutamatergic neurons infrequently synapse on VTA-dopamine neurons but preferentially establish multiple synapses on VTA-glutamatergic neurons. Here, we demonstrated that LH-glutamatergic inputs to VTA promoted active avoidance, long-term aversion, and escape attempts. By testing feeding in the presence of a predator, we observed that ongoing feeding was decreased, and that this predator-induced decrease in feeding was abolished by photoinhibition of the LH-glutamatergic inputs to VTA. By VTA specific neuronal ablation, we established that predator-induced decreases in feeding were mediated by VTA-glutamatergic neurons but not by dopamine or GABA neurons. Thus, we provided evidence for an unanticipated neuronal circuitry between LH-glutamatergic inputs to VTA-glutamatergic neurons that plays a role in prioritizing escape, and in the switch from feeding to escape in mice.

SENIOR LEADERSHIP CHANGES

Iván Montoya, M.D., M.P.H. has been selected as Director of NIDA's Division of Therapeutics and Medical Consequences (DTMC). Iván is a psychiatrist and epidemiologist who specializes in the development of therapeutics for substance use disorders (SUDs). Iván served as Acting DTMC Director since July 2021 and under his skillful leadership, DTMC has achieved significant progress toward the advancement of NIDA's mission. For example, the Division greatly enhanced the pipelines of medications for opioid and stimulant use disorders with 15 new compounds added in 2023 alone. Currently, DTMC has 98 active medication development projects, and 61 of them are clinical trials. Through Iván's leadership, the Division supported the research to successfully obtain the New Drug Application for the intranasal formulation of nalmefene, and this compound is now on the market. Additionally, the Division supported the successful Investigational New Drug filing of the first anti-fentanyl monoclonal antibody, which is now being evaluated in humans. Iván has also fostered strong partnerships with pharmaceutical companies to promote evaluation of SUD compounds. For example, the Addiction Treatment Discovery Program is evaluating compounds from 23 different companies, and the grant program is funding 40 projects with 34 different companies. For DTMC, this is an unprecedented number of industry collaborations. Iván received his M.D. from the University of Antioquia, Medellin, Colombia, an M.P.H. from the Johns Hopkins School of Public Health. He completed a residency training in Psychiatry at the St. Vincent Hospital, University of Maryland Medical Center, and Johns Hopkins Hospital. He also completed a Fulbright-Hubert H. Humphrey Fellowship in Substance Abuse at Johns Hopkins University, a Merrell Dow Fellowship in drug abuse research, and a post-doctoral fellowship at NIDA Intramural Research Program. He is board certified in psychiatry in Colombia.



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