DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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Director
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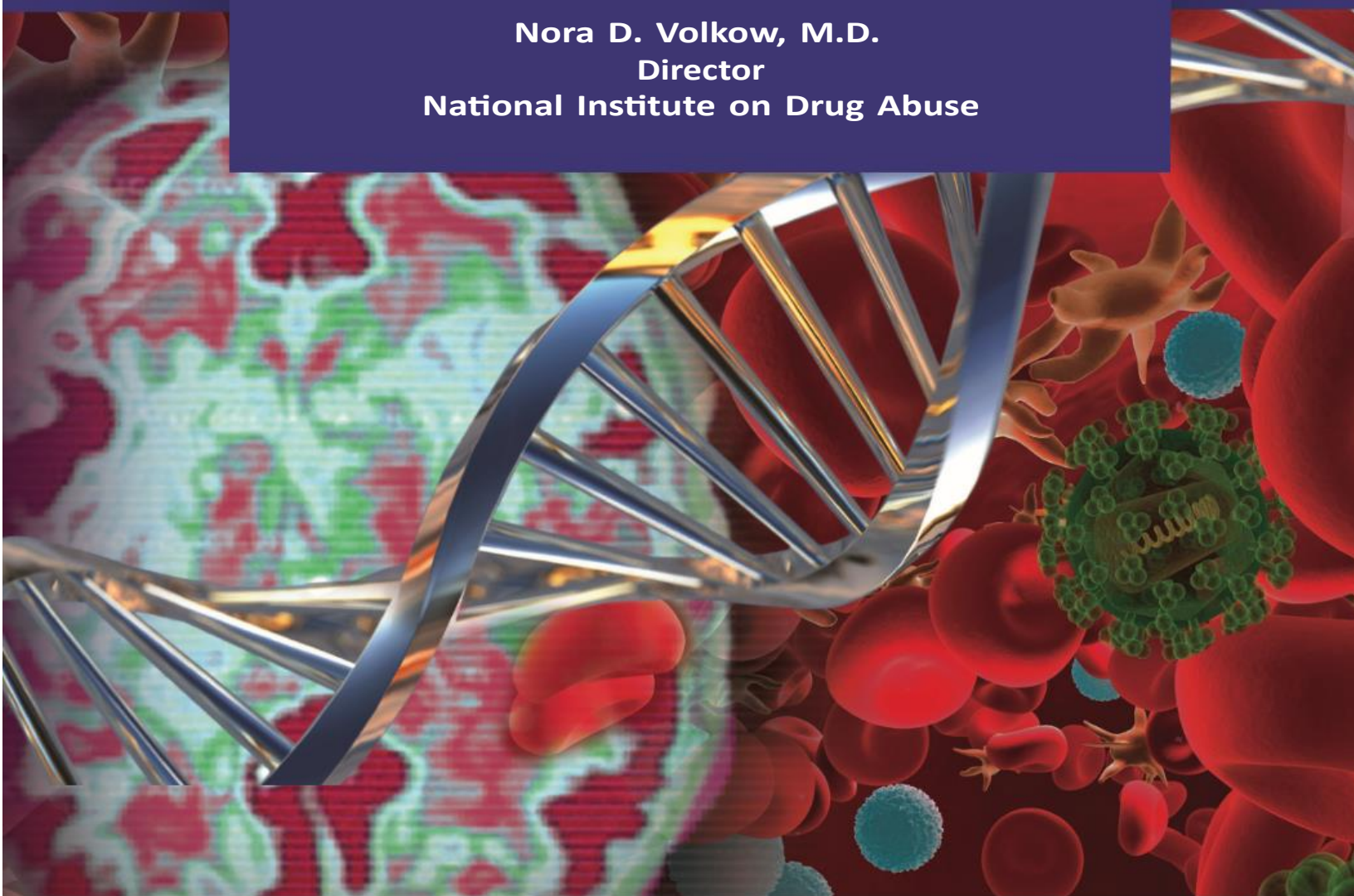

RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH (DNB)

Targeting GPR3 As A Novel Approach For Nicotine Cessation Therapeutic Development
Mogul AS, Laumann KN, Bautista M, Fowler JP, Blough BE, Gay EA, Fowler CD. Neuropsychopharmacology. 2025; 50(13): 2051-2062.
Tobacco use remains the leading cause of preventable death worldwide. Unfortunately, currently available cessation aids have limited long-term efficacy. GPR3 is a Gαs coupled receptor expressed in discrete brain regions, with notably high expression in cholinergic neurons of the medial habenula. Here, we investigated whether modulation of GPR3 could be a viable target for therapeutic development to promote nicotine cessation. We first examined whether our recently developed GPR3 receptor agonist, RTI-19318-32, could induce effects on intravenous nicotine self-administration at low, moderate or high nicotine doses in mice. We found that in both males and females, RTI-19318-32 significantly reduced nicotine intake at all self-administered nicotine doses, thereby supporting the validity of this therapeutic approach for individuals using varying levels of daily nicotine. RTI-19318-32 was further validated as being selective for GPR3, as it did not alter nicotine intake in GPR3 knockout mice, nor did it exert effects on anxiety-associated behavior or locomotion. While the higher RTI-19318-32 dose attenuated food-related reinforcement behavior, it was ineffective in altering baseline food consumption. Moreover, the lower RTI-19318-32 dose did not alter food reinforcement behavior, indicating selectivity in mediating nicotine intake. Finally, GPR3 expression co-localized with multiple nAChR subunits in the medial habenula, thereby supporting our proposed targeted approach for circuit engagement intentionally directed at modulating the drive to consume nicotine. Taken together, these data reveal the functional significance of agonist-inducted activation of the GPR3 receptor and establish the validity of focusing on therapeutic development of GPR3 ligands for nicotine cessation. R01DA058493, F30DA062492, U18DA062416, T32DA050558

5-HT2C Receptors In The Nucleus Accumbens Constrain The Rewarding Effects Of MDMA Pomrenze MB, Vaillancourt S, Salgado JS, Raymond KB, Llorach P, Sacai H, Rijsketic DR, Hietamies TM, Touponse GC, Cardozo Pinto DF, Rastegar Z, Casey AB, Eshel N, Malenka RC, Heifets BD. Mol Psychiatry. 2025; 30(11): 5405-5416.

MDMA is a promising adjunct to psychotherapy and has well-known abuse liability, although less than other amphetamine analogs. While the reinforcing dopamine (DA)-releasing properties of MDMA are on par with methamphetamine (METH), MDMA is a far more potent serotonin (5-HT) releaser, via the 5-HT transporter (SERT). MDMA-mediated 5-HT release in a major reward center, the nucleus accumbens (NAc), drives prosocial behaviors via 5-HT_{1B}R activation. We hypothesized that this prosocial mechanism contributes to the reduced reinforcing properties of MDMA compared to METH and used a platform of assays to predict the balance of prosocial and abuse-linked effects of (R)-MDMA, a novel entactogen in clinical development. NAc DA

release, measured by GRAB-DA photometry in vivo, increased in proportion to MDMA (7.5 and 15 mg/kg, i.p.) and METH (2 mg/kg i.p.)-conditioned place preference (CPP). Using conditional knockouts (cKOs) for DAT and SERT, microdialysis, and photometry, we found that MDMA-released 5-HT limited MDMA-released DA through actions in the NAc, rather than at ventral tegmental area DAergic cell bodies. SERT cKO reduced the MDMA dose required for CPP three-fold. This enhanced MDMA-CPP and increased DA release were replicated by intra-NAc infusion of either a 5-HT reuptake inhibitor (escitalopram) to prevent MDMA interaction with SERT, or a 5-HT_{2C}R antagonist (SB242084), but not by the 5-HT_{1B}R antagonist NAS-181. These data support separate mechanisms for the low abuse potential versus prosocial effect of MDMA. Using this platform of assays, (R)-MDMA is predicted to have prosocial effects and low abuse potential. P50DA042012

Ultra-processed Food Addiction In A Nationally Representative Sample Of Older Adults In The USA Loch, LK, Kirch M, Singer DC, Solway E, Roberts JS, Kullgren JT, Gearhardt AN. Addiction. Sept 29 2025: 1-12

Aims: Ultra-processed foods (UPFs; industrially produced foods typically containing unnaturally elevated levels of refined carbohydrates and/or added fats) became more widely introduced into the United States (US) food environment in the 1980s and have proliferated since. UPFs have been shown to trigger an addictive-like response. This study examines the prevalence of ultra-processed food addiction (UPFA) in older US adults and its association with various health domains.

Design: In July 2022, a cross-sectional online and telephone survey was conducted using the University of Michigan National Poll on Healthy Aging (NPHA). Gender-stratified analyses examined the association between UPFA and perceptions of physical and mental health, and social isolation. Prevalence ratios were calculated, unadjusted and adjusted for age, race/ethnicity, education, and income.

Setting: Nationally representative sample of older adults (aged 50-80 years) in the United States.

Participants: The sample included 2038 older adults (49.4% aged 50-64 years and 50.6% aged 65-80 years, 51.2% women, M age = 63.6, standard deviation = 8.1).

MEASUREMENTS: The modified Yale Food Addiction Scale 2.0 (validated measure that applies the diagnostic criteria for substance use disorder to the overconsumption of UPFs) was used to assess diagnostic criteria for UPFA. Various self-reported items were used to assess health-related domains (i.e., physical and mental health, social isolation).

Findings: The overall prevalence of UPFA was 12.4%, higher among women (16.9%) than men (7.5%), with the highest rate in women aged 50-64 (21%). Men reporting being overweight were 19.14 (95% confidence interval [CI] [5.26-69.66]) times more likely to meet the criteria for UPFA. Women reporting being overweight were 11.44 (95% CI [4.56-28.71]) times more likely to meet UFPA criteria. Women and men reporting worse physical health were 1.93 (95% CI [1.26-2.98]) times and 2.99 (95% CI [1.70-5.26]) times more likely to meet the criteria for UPFA, respectively. Similarly, women reporting worse mental health were 2.78 (95% CI [1.79-4.32]) times more likely to meet the criteria for UPFA, with men 4.02 (95% CI [2.19-7.38]) times more likely. Lastly, women and men reporting feelings of social isolation were 3.40 (95% CI [2.16-5.34]) times and 3.35 (95% CI [1.83-6.14]) times more likely to meet UFPA criteria.

Conclusion: Ultra-processed food addiction appears to be prevalent among older adults in the United States, particularly among women who were in adolescence and early adulthood when the nutrient quality of the US food supply worsened. Addictive patterns of UPF intake appear to be associated with poorer physical health, mental health, and social well-being. R01DA055027

Epigenetic And Genetic Profiling Of Comorbidity Patterns Among Substance Dependence Diagnoses Pathak GA, Pietrzak RH, Lacobelle AM, Overstreet C, Wendt FR, Deak J, Friligkou E, Nunez YZ, Montalvo-Ortiz JL, Levey DF, Kranzler HR, Gelernter J, Polimanti R. Mol Psychiatry. 2025; 30(9): 4435-4443.
This study investigated the genetic and epigenetic mechanisms underlying the comorbidity of five substance dependence diagnoses (SDs; alcohol, AD; cannabis, CaD; cocaine, CoD; opioid, OD; tobacco, TD). A latent class analysis (LCA) was performed on 22,668 individuals from six cohorts to identify comorbid DSM-IV SD patterns. In subsets of this sample, we tested SD-latent classes with respect to polygenic overlap of psychiatric and psychosocial traits in 7659 individuals of European descent and epigenome-wide changes in 886 individuals of African, European, and Admixed-American descents. The LCA identified four latent classes related to SD comorbidities: AD + TD, CoD + TD, AD + CoD + OD + TD (i.e., polysubstance addiction, PSU), and TD. In the epigenome-wide association analysis, SPATA4 cg02833127 was associated with CoD + TD, AD + TD, and PSU latent classes. AD + TD latent class was also associated with CpG sites located on ARID1B, NOTCH1, SERTAD4, and SIN3B, while additional epigenome-wide significant associations with CoD + TD latent class were observed in ANO6 and MOV10 genes. PSU-latent class was also associated with a differentially methylated region in LDB1. We also observed shared polygenic score (PGS) associations for PSU, AD + TD, and CoD + TD latent classes (i.e., attention-deficit hyperactivity disorder, anxiety, educational attainment, and schizophrenia PGS). In contrast, TD-latent class was exclusively associated with posttraumatic stress disorder-PGS. Other specific associations were observed for PSU-latent class (subjective wellbeing-PGS and neuroticism-PGS) and AD + TD-latent class (bipolar disorder-PGS). In conclusion, we identified shared and unique genetic and epigenetic mechanisms underlying SD comorbidity patterns. These findings highlight the importance of modeling the co-occurrence of SD diagnoses when investigating the molecular basis of addiction-related traits. RF1MH132337, K01DA058807, R33DA047527

EPIDEMIOLOGY, SERVICES AND PREVENTION RESEARCH

Quantifying The Burden of Opioid Use Disorder And Non-fatal Opioid Overdose In American Indian And Alaskan Native Populations Using The Cerner Real-World Data™ Database Qeadan F, Madden EF, English K, Venner KL, Tingey B, Egbert J, Hipol FAS. J Racial Ethn Health Disparities. 2025; 12(4): 2717-2733.
Objective: This study evaluated the prevalence and incidence of opioid use disorder (OUD), rates of opioid overdose (OD), and rates of non-fatal (NF) OD in American Indian/Alaskan Native (AI/AN) populations.

Methods: We used de-identified patient data from Oracle Cerner Real-World Data™. Rates were estimated over time, and stratified by sex, age, marital status, insurance, and region. Mann-Kendall trend tests and Theil-Sen slopes assessed changes over time for each group while autoregressive modeling assessed differences between groups.
Results: The study identified trends in OUD and OD among 700,225 AI/AN patients aged 12 and above. Between 2012 and 2022, there was a significant upward trend in both OUD and OD rates ($p < 0.05$), with OUD diagnosed in 1.75% and OD in 0.38% of the population. The Western region of the US exhibited the highest rates of OUD and OD. The 35-49 age group showed the highest rates of OUD, while the 12-34 age group had the highest rates of OD. Marital status analysis revealed higher rates of OUD and OD among separated, widowed, or single patients. Additionally, individuals with Medicare or Medicaid insurance demonstrated the highest rates of OUD and OD.
Conclusion: Results show that rates of OUD, OD, and NF OD continue to rise among AI/AN individuals, with some regional and demographic variation. Our study provides foundational estimates of key AI/AN populations bearing greater burdens of opioid-related morbidity that federal, state, and tribal organizations can use to direct and develop targeted resources that can improve the health and well-being of AI/AN communities. 3R61DA049382-02S1

Qualitative Mediation Analysis: An Important Method For Exploring Mediating Mechanisms In Prevention Science Kim JJ, MacKinnon DP. Prev Sci. 2025; 26(7): 1076-1086. Mediating variables serve a primary role in devising intervention theories and applying them to practice. Prevention scientists have repeatedly called for understanding how and why an independent variable (X; e.g., intervention) is related to a dependent variable (Y; e.g., drug use). Quantitative mediation is used to describe mediating variables that intervene in the causal path from X to Y. Most methodological development for mediation analysis has focused on statistical methods and the assumptions necessary for valid application of these statistical methods. The current paper describes how qualitative methods extend into mediation research and the unique strength of qualitative mediation in identifying potential mediators and mechanisms of change not previously hypothesized. Taking examples from prevention research, the investigators outline how qualitative mediation generates unique and complementary information about mediating mechanisms that may only be available through interviews, focus groups, observation, archival analysis, and other qualitative methodology. In addition to describing cautions when using qualitative mediation including reliance of retrospective reports, potential to influence interviewees, and selective sampling the investigators underline how qualitative mediation analysis is particularly well suited for exploratory studies and extracting mechanisms of action for new or adapted interventions in prevention science. R37 DA009757, K01DA055118, R37 DA009757, K01DA055118

Primary Prevention Of Drug Overdoses In Rural Low-resource And Tribal Communities: A Cluster Randomized Trial Komro KA, Livingston MD, Skinner JR, Livingston BJ, Kominsky TK, Jagtiani, Barry CM, Wagenaar AC, Cooper HLF, Harmon M, Ivanich E, LaBounty H, Gassaway, Talavera-Brown SL. Am J Public Health. 2025; 115(9): 1508–1517. **Objectives.** To determine the Connect intervention's effectiveness in reducing substance use among rural and tribal adolescents in northeastern Oklahoma. **Methods.** We conducted a 2-arm cluster randomized trial from 2021 to 2024, with 10 high schools per condition. **Results.** At baseline, 919 students were enrolled (mean age = 15 years), and the majority were American

Indian or White. Alcohol-use days during the past 30 days was reduced by 18% per survey wave in the intervention compared with the control condition (rate ratio [RR] = 0.82; 95% confidence interval [CI] = 0.72, 0.93; t = -3.02; P = .003), binge drinking was reduced by 26% (RR = 0.74; 95% CI = 0.64, 0.86; t = -3.90; P < .001), cannabis use was reduced by 11% (RR = 0.89; 95% CI = 0.80, 1.00; t = -2.03; P = .04), and prescription opioid misuse was reduced by 40% (RR = 0.60; 95% CI = 0.43, 0.85; t = -2.86; P = .004). Model-predicted means revealed the control condition followed the expected developmental trajectory of increased substance use and the intervention condition showed a flat or decreasing use pattern. **Conclusions.** The Connect intervention prevented the typical escalation of substance use during adolescence. **Trial Registration.** ClinicalTrials.gov NCT04839978. Registered on April 9, 2021. Version 10, April 30, 2025.

Predictors Of Medicaid Managed Care Plan Performance On Opioid Use Disorder Treatment Quality Metrics Stewart MT, Feltus SR, Andrews C, Hodgkin D, Thomas CP, Horgan CM. Drug Alcohol Depend. 2025; 274: 112742.

Introduction: Medicaid managed care plans (MCPs) and states play essential roles in supporting access to high-quality opioid use disorder (OUD) treatment services. This study aimed to identify MCP and state-level policies associated with better plan performance on indicators of quality OUD treatment.

Methods: Publicly available data on Medicaid MCPs' profit status, behavioral health contracting arrangements, market share, buprenorphine prior authorization and quantity limit policies and state Medicaid policies were linked with plan-level measures of OUD treatment quality from the National Committee on Quality Assurance (n = 107). Regression analyses were used to examine associations between Medicaid MCP characteristics, MCP buprenorphine policies, and features of the state policy environment with plan-level rates of OUD treatment initiation and engagement.

Results: The average OUD treatment initiation rate was 59.6 % and engagement was 30.9 %. MCPs with large market share had initiation and engagement rates 4.66 and 4.54 percentage points lower, respectively, than plans with small market share. Plans operating in states with 1115 SUD waivers had initiation and engagement rates 7.75 and 8.55 percentage points higher, respectively, than plans in states without waivers. Engagement rates among plans that required prior authorization for buprenorphine were 4.53 percentage points lower than plans without this restriction.

Conclusions: Findings suggest state and MCP policies are important pathways to improve initial and sustained OUD treatment. Further research into these relationships is needed. P30 DA035772, R01 DA049776

Trajectories Of Pain Impact And Pain Self-efficacy In People With HIV And Chronic Pain: Extending Findings From The Skills TO Manage Pain Randomized Clinical Trial McGill LS, Clay OJ, Edwards KA, Jones KF, Long DM, Johnson MO, Bair MJ, Browne LE, Liebschutz JM, Demonte W, Agil D, Burkholder G, Durr AL, Farel CE, Johnson B, Orris SM, Napravnik S, Thomas T, Merlin JS. J Acquir Immune Defic Syndr. 2025; 100(4): 347-354.

Background: People with HIV (PWH) frequently experience chronic pain, which negatively affects their health and functioning. To improve health outcomes, we need effective interventions for HIV-related chronic pain. Skills TO Manage Pain (STOMP), a novel pain self-management intervention tailored for PWH and chronic pain, has demonstrated efficacy in reducing pain

impact (measured by the Brief Pain Inventory) and improving pain self-efficacy immediately after a 12-week intervention and 3 months later.
Setting: We conducted this study at 2 Center for AIDS Research Network of Integrated Clinical Systems clinics.
Methods: We evaluated the efficacy of STOMP across 12 months by comparing trajectories of pain impact and pain self-efficacy among 244 adults (49% female, M age = 53.62) randomized equally to the STOMP intervention or an Enhanced Usual Care (EUC) control condition. We also examined whether pain self-efficacy is a mechanism of change that helps explain how STOMP affects pain impact.
Results: For 12 months, individuals who participated in STOMP reported lower pain impact and higher pain self-efficacy than those in EUC. Over time, the difference in pain impact attenuated slightly between the 2 groups but remained statistically significant. Pain self-efficacy remained significantly higher for the STOMP group. Individuals in STOMP showed greater improvements in their confidence to manage pain than those in EUC, resulting in less severe pain and reduced interference in daily life.
Conclusions: STOMP is an efficacious chronic pain intervention for PWH, improving pain outcomes 1 year later. Future research should evaluate mechanisms of change and best practices for implementing STOMP.

THERAPEUTICS AND MEDICAL CONSEQUENCES (TMC)

Xanomeline Treatment Attenuates Cocaine Self-administration In Rats And Nonhuman Primates Marsh SA, Heslep N, Paronis CA, Bergman J, Negus S, Banks ML. Neuropharmacology. 2025; 281: 110686.
The lack of an FDA-approved pharmacotherapy to combat cocaine use disorder (CUD) is an ongoing and urgent public health challenge. Emerging evidence suggests that the muscarinic acetylcholine system modulates mesolimbic dopamine release and thus may serve as a suitable target for novel CUD medications. The M1/M4-preferring muscarinic agonist xanomeline was recently approved by the Food and Drug Administration for schizophrenia management, and a previous study in male rats suggested that xanomeline treatment attenuated cocaine self-administration in a cocaine-vs-food choice procedure. The present study was conducted to further examine xanomeline treatment effectiveness on cocaine self-administration in male and female rats and nonhuman primates. Both male and female rats and monkeys were trained to self-administer cocaine during daily behavioral sessions. Repeated xanomeline treatment significantly decreased cocaine choice in rats similar to both pharmacological (amphetamine maintenance) and non-pharmacological (increasing alternative reinforcer value) positive controls. In separate groups of monkeys, acute xanomeline pretreatment decreased cocaine-vs-food choice in three out of four monkeys and selectively decreased cocaine-, but not food-maintained responding, under a multiple schedule of cocaine and food reinforcement in three out of four monkeys. Overall, the consistent effectiveness of xanomeline to reduce IV cocaine self-administration in both rodents and nonhuman primate supports its further evaluation as a CUD medication in humans. R01 DA055825, T32 DA007027

Association Of Endothelial Dysfunction With Chronic Marijuana Smoking And THC-Edible Use. Mohammadi L, Navabzadeh M, Jiménez-Téllez N, Han DD, Reagan E, Naughton J, Zhou LY, Almeida R, Castaneda LM, Abdelaal SA, Park KS, Uyemura K, Cheung CP, Onder MN, Goyal N, Rao P, Hellman J, Cheng J, Wu JC, Marcus GM, Springer ML. JAMA Cardiol. 2025; 10(8): 851-855.

Importance: Recreational and medicinal cannabis legalization has led to increased cannabis use. To understand the consequences for vascular health, we initiated the CANnabis: Does It Damage Endothelium (CANDIDE) study.

Objective: To investigate whether cannabis use is associated with vascular endothelial dysfunction.

Design, setting, and participants: In this cross-sectional study, age-matched healthy adults, aged 18 to 50 years, living in the San Francisco Bay Area, California, who neither smoke tobacco nor vape and were not frequently exposed to secondhand smoke were recruited into 3 cohorts: 2 chronic cannabis user groups (marijuana smokers and tetrahydrocannabinol [THC]-edible users) and 1 nonuser group. Participants were recruited from October 25, 2021, through August 1, 2024; analysis was completed September 2024. Participants' arterial flow-mediated dilation (FMD) and carotid-femoral pulse wave velocity (PWV) were measured. Human umbilical vein endothelial cells (HUVECs) were exposed to participant sera with and without vascular endothelial growth factor (VEGF) to assess the effects of user serum on endothelial nitric oxide production.

Main outcomes and measures: FMD and PWV were direct physiological measurements, and VEGF-stimulated nitric oxide production was measured from HUVECs incubated in user serum samples.

Results: Among 55 participants (20 female [37%]; 35 male [63%], mean age, 31.3 [SD, 8.4] years) arterial FMD was significantly lower among the marijuana smokers (mean, 6.0% [SD, 2.6%]; P = .004) and lower among THC-edible users (mean, 4.6% [SD, 3.7%]; P = .003) than among nonusers (mean, 10.4% [SD, 5.2%]). VEGF-stimulated nitric oxide levels in endothelial cells treated with participants' sera were significantly lower for the marijuana smoker group (mean, 1.1 nmol/L [SD, 0.3 nmol/L]) than for the nonuser group (mean, 1.5 nmol/L [SD, 0.3 nmol/L]; P = .004) but were unaffected among the THC-edible users group compared with the nonusers (mean, 1.5 nmol/L [SD, 0.3 nmol/L]; P = .81). FMD was inversely correlated with smoking frequency (r = -0.7; P = .03). Other vascular properties showed no differences.

Conclusions: This cross-sectional study found that chronic cannabis smoking and THC ingestion were associated with endothelial dysfunction similar to that observed in tobacco smokers, although apparently occurring via distinct mechanisms. R01 DA058069

Focused Ultrasound Neuromodulation: Exploring A Novel Treatment For Severe Opioid Use Disorder Rezai A, Thompson-Lake DGY, D'Haese PF, Meyer N, Ranjan M, Farmer D, Finomore V, Marton JL, Hodder S, Carpenter J, Bhagwat A, Berry J, Tirumalai P, Adams G, Arsiwala TA, Blanke O, Mahoney JJ. Biol Psychiatry. 2025; 98(1): 56.

Background: Opioid use disorder remains a critical health care challenge because current therapeutic strategies have limitations that result in high recurrence and deaths. We evaluated the

safety and feasibility of focused ultrasound (FUS) neuromodulation to reduce substance cravings and use in severe opioid and co-occurring substance use disorders.
Methods: This prospective, open-label, single-arm study enrolled 8 participants with severe, primary opioid use disorder with co-occurring substance use. Participants received a 20-minute session of low-intensity FUS (220 kHz) neuromodulation targeting the bilateral nucleus accumbens (NAc) with follow-up for 90 days. Outcome measures included safety, tolerability, feasibility, and effects of FUS neuromodulation by assessment of adverse events, substance craving, substance use (self-report, urine toxicology), mood, neurological examinations, and anatomical and functional magnetic resonance imaging (fMRI) at 1, 7, 30, 60, and 90 days post-FUS.
Results: No serious device-related adverse events or imaging abnormalities were observed. Following FUS, participants demonstrated immediate ($p < .002$) and sustained ($p < .0001$; mean 91%) reductions in cue-induced opioid craving, with median ratings on a scale from 0 to 10 as follows: 6.9 (pre-FUS) versus 0.6 (90-day post-FUS). Craving reductions were similar for other illicit substances (e.g., methamphetamine [$p < .002$], cocaine [$p < .02$]). Decreases in opioid and co-occurring substance use were confirmed by urine toxicology. Seven participants remained abstinent at 30 days; 5 participants remained abstinent throughout 90 days post-FUS. Resting-state fMRI demonstrated decreased connectivity from the NAc to reward and cognitive regions post-FUS.
Conclusions: NAc FUS neuromodulation is safe and a potential adjunctive treatment for reducing drug cravings and use in individuals with severe opioid and co-occurring substance use disorders. Larger, sham-controlled, randomized studies are warranted. UH3 DA047714

Mirtazapine Reduces Hypothetical Methamphetamine Demand In Humans Rush CR, Santos GM, McMahan VM, Fraser A, Clark J, Luna Marti X, Walker JE, Shoptaw S, Coffin PO. Drug Alcohol Depend. 2025; 274: 112769.
Background: Previous trials showed mirtazapine reduces methamphetamine use. The present study determined the influence of mirtazapine treatment on the acute effects of methamphetamine.
Methods: We conducted a placebo-controlled, crossover, double-blind trial to determine the pharmacodynamic effects of intravenous methamphetamine (0, 30mg) after 5 days of mirtazapine (0, 30mg/day) treatment. Healthy adults with moderate to severe methamphetamine use disorder who had a positive baseline urine test for methamphetamine were enrolled. The order of mirtazapine and placebo was randomly assigned, and participants received a methamphetamine infusion during each treatment condition. Acute effects of methamphetamine were assessed using a drug purchasing task, a subjective effect questionnaire, and cardiovascular indices.
Results: Fifteen (15) participants (10 cisgender males, 4 cisgender females, 1 transgender female) enrolled in the trial. Intravenous methamphetamine produced prototypical stimulant-like effects (e.g., hypothetical drug demand; increased ratings of Like Effect, heart rate, blood pressure) when participants were treated with placebo. Mirtazapine significantly decreased methamphetamine demand. The subjective and cardiovascular effects of methamphetamine were

similar during mirtazapine and placebo treatment. Mirtazapine and infusions of methamphetamine, alone and combined, were well tolerated.
Conclusions: Mirtazapine reduced hypothetical drug demand and was well tolerated with saline or methamphetamine infusions. Considering these favorable findings, along with those from previous clinical trials, mirtazapine should continue to be tested as a putative pharmacotherapy for methamphetamine use disorder. U01DA051080

HIV RESEARCH

Pilot Study Of A Digital Health Intervention To Increase HIV And Sexually Transmitted Infection Testing Uptake And Reduce Condomless Sex And Substance Use Among Adolescents Cordova D, Bauermeister JA, Warner S, Jiang Z, Mendoza Lua F, Khreizat S, MacLeod J, Wells P, Neilands TB, Ovadje L, Delva J, Fessler KB, Smith VA, Boyer CB. J. Adolesc Health. 2025; S1054-139X(25)00223-X.
Purpose: Enhancing HIV/sexually transmitted infection testing and reducing unsafe sexual behaviors and substance use are crucial for public health, particularly among youth. This pilot study examines the Storytelling 4 Empowerment (S4E) intervention's preliminary efficacy in these areas.
Methods: Using a community-engaged research approach, we conducted a randomized controlled trial with 100 adolescents and young adults (mean age = 19.27, standard deviation = 1.62) at a youth-focused clinic in Southeast Michigan. Participants were randomized to S4E, a brief digital health intervention, or usual care. Assessments occurred at baseline, postintervention, 3 and 6 months, with statistical analyses estimating effect sizes.
Results: S4E participants demonstrated higher HIV (52% vs. 12%; h = 0.95) and sexually transmitted infection (52% vs. 20.4%; h = 0.74) testing at 6-month follow-up. Reductions in condomless sex (12.9% vs. 1%; h = 0.35) and binge drinking (11.2% vs. 1.6%; h = 0.02) were reported at 3 months. Both youth and providers in the S4E group reported better clinician-youth communication than controls, and youth showed increased improvement over time (Cohen's d = 1.19 at 6 months).
Discussion: The S4E intervention demonstrated significant improvements in testing, risk behaviors, and communication. These findings suggest the need for larger-scaled randomized controlled trials to confirm the intervention's efficacy for youth in clinical settings. R03DA041891

Willingness To Use Oral And Long-acting Injectable PrEP In Substance-using Men Who Have Sex With Men (SU-MSM) In High HIV Incidence Southern U.S. Cities: A NIDA Clinical Trials Network Study Tross S, Laschober TC, Paschen-Wolff M, Ertl M, Nelson CM, Wright L, Lancaster C, Feaster DJ, Monger M, Toal P, Fegley JP, Meche D, Hankey C, Woodhouse C, Spector A, Dresser L, Moran L, Jelstrom E, Haynes L, Shoptaw S, Hatch MA. AIDS Behav. 2025; 29(4): 1192-1204.
In Southern U.S. states with high HIV incidence and low HIV Pre-Exposure Prophylaxis (PrEP) uptake, enhanced efforts to increase interest in and willingness to use PrEP are needed. This

implementation survey examined the associations of sociodemographic background, substance use, and sexual risk behaviors with willingness to use daily oral and long-acting injectable (LAI) PrEP among substance using men who have sex with men (SU-MSM). Participants were 225 SU-MSM recruited from sexually transmitted infection (STI) clinics, syringe services programs (SSPs), and substance use treatment programs (SUTPs) in eight Southern U.S. cities. Rates of willingness were high for both daily oral PrEP (78%) and LAI PrEP (66%). In multivariable analyses, distinct factors were associated with willingness towards each. For daily oral PrEP, greater willingness was associated with condomless anal sex, less frequent non-injection opioid use, prior PrEP awareness, and past use of PrEP. For LAI PrEP, greater willingness was associated with Black race, identifying as gay, being single, and higher injection drug use frequency. Lower willingness to use LAI PrEP was associated with higher non-injection opioid use frequency. Findings about willingness to use LAI PrEP, as a relatively newer modality, and greater willingness among Black SU-MSM as a disproportionately HIV-impacted population, are especially important. These findings argue for the necessity to enhance PrEP promotion efforts that distinguish between oral and LAI PrEP and that are specifically tailored to major SU-MSM subgroups in the Southern U.S. UG1DA013035, UG1DA013714

CENTER FOR CLINICAL TRIALS NETWORK (CCTN)

A Longitudinal Observational Study With Ecological Momentary Assessment And Deep Learning To Predict Non-prescribed Opioid Use, Treatment Retention, And Medication Nonadherence Among Persons Receiving Medication Treatment For Opioid Use Disorder

Heinz MV, Price GD, Singh A, Bhattacharya S, Chen CH, Asyyed A, Does MB, Hassanpour S, Hichborn E, Kotz D, Lambert-Harris CA, Li Z, McLeman B, Mishra V, Stanger C, Subramaniam G, Wu W, Campbell CI, Marsch LA, Jacobson NC. J Subst Use Addict Treat. 2025; 173: 209685.

Background: Despite effective treatments for opioid use disorder (OUD), relapse and treatment drop-out diminish their efficacy, increasing the risks of adverse outcomes, including death. Predicting important outcomes, including non-prescribed opioid use (NPOU) and treatment discontinuation among persons receiving medications for OUD (MOUD) can provide a proactive approach to these challenges. Our study uses ecological momentary assessment (EMA) and deep learning to predict momentary NPOU, medication nonadherence, and treatment retention in MOUD patients.

Methods: Study participants included adults receiving MOUD at a large outpatient treatment program. We predicted NPOU (EMA-based), medication nonadherence (Electronic Health Record [EHR]- and EMA-based), and treatment retention (EHR-based) using context-sensitive EMAs (e.g., stress, pain, social setting). We used recurrent deep learning models with 7-day sliding windows to predict the next-day outcomes, using Area Under the ROC Curve (AUC) for assessment. We employed SHapley additive ExPlanations (SHAP) to understand feature latency and importance.

Results: Participants comprised 62 adults with 14,322 observations. Model performance varied across EMA subtypes and outcomes with AUCs spanning 0.58-0.97. Recent substance use was the best performing predictor for EMA-based NPOU (AUC = 0.97). Life-contextual factors were

best performers for EMA-based medication nonadherence (AUC = 0.68) and retention (AUC = 0.89), and substance use risk factors (e.g., nicotine and alcohol use) and self-reported MOUD adherence performed best for predicting EHR-based medication nonadherence (AUC = 0.79). SHAP revealed varying latencies between predictors and outcomes.
Conclusions: Findings support the effectiveness of EMA and deep learning for forecasting actionable outcomes in persons receiving MOUD. These insights will enable the development of personalized dynamic risk profiles and just-in-time adaptive interventions (JITAIs) to mitigate high-risk OUD outcomes. P30 DA029926, UG1 DA040309, UG1 DA040314

Buprenorphine Treatment For Opioid Use Disorder In Non-Addiction Specialty Settings Huebler S, Jones AL, Zhao H, Nelson RE, Hagedorn HJ, Hawkins EJ, Gordon AJ. JAMA Network Open. 2025; 8(11): e2543543.
No abstract available in PubMed (abstract created by staff from article)
Background: Increasing patient access to buprenorphine medication for opioid use disorder (B-MOUD) is a national priority for sustaining progress in preventing deaths from opioid use disorder (OUD). The historical relegation of OUD care to substance use disorder (SUD) addiction specialty care clinics has created access barriers. Experts advocate treating OUD in commonly used health care touchpoints, particularly office-based primary care, mental health, and pain (PC-MH-P) clinics. In 2018, the Department of Veterans Affairs (VA) established the Stepped Care for Opioid Use Disorder Train the Trainer (SCOUTT) Initiative with a goal to increase B-MOUD prescribing in PC-MH-P settings.
Methods: This retrospective cohort study of B-MOUD prescribing in VA facilities used electronic health records from the Corporate Data Warehouse. Included patients had at least 1 OUD *ICD-10* code and received an outpatient B-MOUD prescription between 2016 and 2024. Linear regressions, weighted by annual cohort size, were used to model differences in percentage of B-MOUD from PC-MH-P vs specialty SUD settings within SCOUTT and non-SCOUTT facilities using group-time interaction.
Results: Between 2016 and 2024, SUD settings provided the most B-MOUD prescriptions annually; however, their share decreased from 78.5% to 63.5% ($P < .001$). In SCOUTT facilities, the percentage of B-MOUD prescriptions from PC-MH-P settings was 16.6% in 2016 and 44.1% in 2024. In non-SCOUTT facilities, these percentages were 23.2% in 2016 and 33.9% in 2024.
Conclusions: In this study, provision of B-MOUD rapidly shifted toward PC-MH-P settings from SUD settings and greater shifts were observed in VA facilities participating in SCOUTT. A train-the-trainer intervention, in which trained prescribers are equipped to spread B-MOUD knowledge and prescribing practices, may have played a role in accelerating the integration of B-MOUD prescribing into more accessible health care settings. This VA initiative may be a model to encourage B-MOUD prescribing in PC-MH-P settings in other large health care systems.

Early Change In Depressive Symptom Severity With Naltrexone-Bupropion Combination And Its Association With Reduction In Methamphetamine Use In ADAPT-2 Trial Jha MK, Ghitza UE, Shoptaw S, Minhajuddin A, Kuruvila S, Wakhlu S, Nunes EV, Schmitz J, Coffin PO, Bart G, Carmody T, Trivedi MH. J Clin Psychiatry. 2025; 86(3): 25m15825.

Objective: This study evaluated whether depressive symptom severity improved early with extended-release naltrexone and bupropion combination (naltrexone bupropion) compared to a placebo in individuals with moderate/severe methamphetamine use disorder and predicted subsequent use of methamphetamine.
Methods: This secondary analysis from the Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder (ADAPT-2) trial, which was conducted from May 23, 2017-July 25, 2019, included 326 individuals with a 9-item Patient Health Questionnaire (PHQ-9) score ≥5 at baseline. Repeated-measures mixed model analyses evaluated early (baseline-to-week-4) changes in depressive symptom severity with naltrexone-bupropion versus placebo and provided slope estimates for PHQ-9 change. Additional depression outcomes included response (≥50% reduction in PHQ-9 from baseline) and remission (PHQ-9 ≤4). Methamphetamine treatment response was ascribed if 3 out of 4 urine drug screens were negative during weeks 5 and 6. Logistic regression analyses evaluated whether changes in depression predicted methamphetamine treatment response. Covariates included age, sex, race, ethnicity, and baseline PHQ-9.
Results: There was a greater reduction in PHQ-9 scores at week 4 with naltrexone-bupropion versus placebo (estimate = -2.52; standard error = 0.81). At week 4, depression response (odds ratio [OR] = 2.54; 95% confidence limit [CL], 1.42-4.55) and remission (OR = 3.04; 95% CL, 1.57-5.87) were more likely with naltrexone-bupropion versus placebo. Greater baseline-to-week 4 reduction in PHQ-9 was associated with a higher likelihood of methamphetamine treatment response (OR = 3.74, 95% CL, 1.28-10.93) and explained 24.8% (95% CI, 6.7%-60.3%) of the effect of naltrexone-bupropion on methamphetamine treatment response.
Conclusion: Use of naltrexone bupropion was associated with early reduction in depressive symptom severity compared to a placebo, which was associated with a higher likelihood of reduction in subsequent methamphetamine use.
Trial Registration: ClinicalTrials.gov identifier: NCT03078075.

Understanding The Characteristics And Comorbidities Of Primary Care Patients With Risky Opioid Use: Baseline Data From The Multi-site "Subthreshold Opioid Use Disorder Prevention" (STOP) Trial Rostam-Abadi Y, Liebschutz JM, Subramaniam G, Stone R, Appleton N, Mazel S, Alexander K, Brill SB, Case A, Gelberg L, Gordon AJ, Hong H, Incze MA, Kawasaki SS, Kim T, Kline M, Lovejoy TI, McCormack J, Zhang S, McNeely J. J Gen Intern Med. 2025; 40(12): 2906-2915.
Background: A majority of the 8.9 million Americans with opioid misuse have mild or no symptoms of opioid use disorder (OUD), but they may be at elevated risk of developing more severe OUD, overdose, or other health consequences of opioid use. The "Subthreshold Opioid Use Disorder Prevention"(STOP) Trial is evaluating a collaborative care intervention for risky opioid use in primary care. Here, we describe baseline characteristics of participants to understand their needs and assess the generalizability of the sample.
Methods: Recruitment at five primary care sites spanned March 2021-May 2023. Adult patients who screened positive for subthreshold OUD (current illicit or non-medical opioid use without meeting DSM-5 criteria for moderate-severe OUD) were eligible. Baseline assessments

measured self-reported demographic characteristics, other substance use, pain, and physical and mental health symptoms. Descriptive statistics summarize characteristics of the enrolled sample across sites.
Results: Among the 202 participants, the majority identified as female (63.4%), white (70.8%), and non-Hispanic (96.5%), with mean age 55.7 (SD: 12.7) years. Nearly half (49.0%) had problem or high-risk use of prescription opioids, and most received a prescription for opioid medication in the past six months (74.8%). Many participants reported current problem use or high-risk use of alcohol (47.0%) or cannabis (31.2%). Approximately one-third endorsed mental health symptoms, including moderate-severe anxiety (35.6%), depression (31.2%), or sleep disturbance (29.7%), and 20.3% reported a past suicide attempt. In the prior six months, 14.7% had experienced a nonfatal overdose. Moderate-severe pain was reported by 63.4%, and 60.4% rated their general health as fair or poor.
Conclusions: Patients with subthreshold OUD had high rates of polysubstance use and comorbidities that may present challenges to reducing risky opioid use. The STOP trial presents an opportunity to detect and address subthreshold OUD in a cohort with considerable medical and social needs, within primary care settings.
Clinical trials registration: ClinicalTrials.gov NCT04218201.

Personally-tailored Opioid-overdose And Medication For Opioid Use Disorder (MOUD) Education (TOME) Significantly Increases MOUD And Overdose Knowledge In Peripartum Individuals: Results From A Randomized Controlled Pilot Trial Winhusen TJ, Kropp F, Smid MC, Young JL, Davies TH, Lewis D, Rosa C, Dilawar M, Krans EE, Hodgkins C, Cochran G, Lofwall MR. Drug Alcohol Depend. 2025; 275: 112795.
Background: Overdose is a leading cause of pregnancy-associated mortality in the US. Our personally-tailored opioid-overdose (OOD) and medication for opioid use disorder (MOUD) education intervention has been shown to significantly improve MOUD/OOD knowledge in out-of-treatment persons using illicit opioids. We evaluated the ability of the intervention modified for peripartum (pregnant or within one year postpartum) individuals, the personally-tailored OOD and MOUD education (TOME) intervention, to increase MOUD (primary) and OOD (key secondary) knowledge.
Methods: A six-site, two-arm, open-label, trial with 131 peripartum individuals receiving MOUD (methadone or buprenorphine) randomized to TOME, a 15-minute, computer-facilitated, individually-tailored intervention, or Control. TOME participants received education on MOUD and OOD questions they missed in a pre-test. Control participants received SAMHSA handouts on OOD and MOUD. All participants were scheduled for a 3-week post-test.
Results: Participants were enrolled in MOUD for an average of 15.6 months (SD=20.4) at baseline, with 30.5 % enrolled in methadone and 69.5 % enrolled in buprenorphine treatment. On the pre-test, participants answered 66.7 % of the MOUD and 82.1 % of the OOD questions correctly on average. Linear regressions indicated that participants' MOUD (X^2=33.96, $p < 0.001$) and OOD (X^2=45.78, $p < 0.001$) knowledge increased significantly more in the TOME, relative to Control, group.

Conclusions: In a sample of peripartum patients enrolled in MOUD for a substantial length of time, TOME significantly increased MOUD and OOD knowledge. Taken together with past research, these findings suggest that there are gaps in MOUD and OOD knowledge in individuals with opioid use disorder that can be addressed with brief personally-tailored education. UG1 DA013720, UG1 DA049444, UG1 DA013727, UG1 DA049436, U10 DA013732

INTRAMURAL RESESARCH PROGRAM (IRP)

Cocaine Chemogenetics Blunts Drug-seeking By Synthetic Physiology Gomez JL, Magnus CJ, Bonaventura J, Solis O, Curry FP, Levinstein MR, Budinich RC, Carlton ML, Ventriglia EN, Lam S, Wang L, Schoenborn I, Dunne W, Michaelides M, Sternson SM. Nature. 2025; 646 (8085): 746-753.

Chemical feedback is ubiquitous in physiology but is challenging to study without perturbing basal functions. One example is addictive drugs, which elicit a positive-feedback cycle of drug-seeking and ingestion by acting on the brain to increase dopamine signalling[1-3]. However, interfering with this process by altering basal dopamine also adversely affects learning, movement, attention and wakefulness[4]. Here, inspired by physiological control systems, we developed a highly selective synthetic physiology approach to interfere with the positive-feedback cycle of addiction by installing a cocaine-dependent opposing signalling process into this body-brain signalling loop. We used protein engineering to create cocaine-gated ion channels that are selective for cocaine over other drugs and endogenous molecules. Expression of an excitatory cocaine-gated channel in the rat lateral habenula, a brain region that is normally inhibited by cocaine, suppressed cocaine self-administration without affecting food motivation. This artificial cocaine-activated chemogenetic process reduced the cocaine-induced extracellular dopamine rise in the nucleus accumbens. Our results show that cocaine chemogenetics is a selective approach for countering drug reinforcement by clamping dopamine release in the presence of cocaine. In the future, chemogenetic receptors could be developed for additional addictive drugs or hormones and metabolites, which would facilitate efforts to probe their neural circuit mechanisms using a synthetic physiology approach. As these chemogenetic ion channels are specific for cocaine over natural rewards, they may also offer a route towards gene therapies for cocaine addiction. ZIA DA000069

VTA Monosynaptic Connections By Local Glutamate And GABA Neurons And Their Distinct Roles In Behavior Barbano MF, Wang H, Zhang S, Shevelkin AV, Yu KJ, Richie CT, Liu B, Hahn S, Ye R, Morales M. Nat Commun. 2025; 16 (1): 8500.

The ventral tegmental area (VTA) dopamine neurons have been implicated in diverse behaviors. These $VTA^{dopamine}$ neurons are intermixed with neurons that co-transmit glutamate and GABA ($VTA^{glutamate\text{-}GABA}$), transmit glutamate ($VTA^{glutamate\text{-}only}$) or GABA ($VTA^{GABA\text{-}only}$). In dual recombinase vglut2-Cre/vgat-Flp transgenic mice, we combined quantitative ultrastructural analysis with 3D correlative light and electron microscopy and found that $VTA^{glutamate\text{-}only}$ neurons frequently established synapses on $VTA^{dopamine}$ and

$VTA^{glutamate\text{-}only}$ neurons, and that $VTA^{GABA\text{-}only}$ neurons mostly synapsed on $VTA^{dopamine}$ neurons. By selective targeting of VTA subpopulations of neurons, we demonstrated that activation of $VTA^{glutamate\text{-}only}$ neurons is rewarding and decreases feeding behavior, while activation of $VTA^{GABA\text{-}only}$ neurons is aversive. We found that activation of $VTA^{glutamate\text{-}only}$ or $VTA^{GABA\text{-}only}$ neurons negatively affected learning to obtain food reward, and impaired cue-induced reinstatement of food-seeking behavior. Collectively, we demonstrated the monosynaptic properties of an unexpected VTA microcircuitry in which distinct neuronal components integrate information related to reward, aversion, and feeding.

Distinct Amygdala Neuronal Populations Control Opioid Use And Withdrawal In Mice

Tortorelli LS, Oo HZ, Hahn S, Alvarez-Bagnarol Y, Carrasquillo Y, Vendruscolo LF. Biol Psychiatry. 2025; S0006-3223(25)01438-6.

Background: Opioid use disorder (OUD) is a chronic and recurring psychiatric disorder that is associated with high morbidity and mortality. The central nucleus of the amygdala (CeA) undergoes neuroadaptations in both humans with OUD and opioid-dependent rodents. As part of a heterogeneous microcircuit, the CeA integrates internal and external sensory inputs that drive innate and adaptive behaviors. Key CeA neuronal populations, including protein kinase C-δ (PKC-δ), corticotropin-releasing factor (CRF), and somatostatin (SST) neurons, regulate behaviors that are disrupted in addiction, such as pain, stress, reward function, and anxiety/arousal. We hypothesized that these CeA neuronal populations differentially regulate opioid-related behaviors.

Methods: We used in situ hybridization to characterize the expression of μ opioid receptor (MOR) (Oprm1), and we used behavioral and molecular approaches to assess the functional role of these CeA neuronal populations in opioid-dependent mice.

Results: We identified a decrease in Oprm1 messenger RNA (mRNA) expression in the CeA in opioid-dependent mice that were undergoing withdrawal compared with nondependent mice. In contrast, the expression of PKC-δ (Prkcd), CRF (Crh), and SST (Sst) mRNA levels remained unchanged. The chemogenetic inhibition of $CeA^{PKC\text{-}\delta}$ neurons decreased fentanyl vapor self-administration and alleviated fentanyl withdrawal-induced hyperalgesia. The inhibition of CeA^{CRF} neurons reduced irritability and somatic withdrawal signs. The activation of CeA^{SST} neurons reduced somatic withdrawal signs.

Conclusions: These findings suggest that distinct CeA neuronal populations uniquely regulate different aspects of opioid use and withdrawal, highlighting cell type-specific targets for potential therapeutic interventions.

Modification Of Brain Connectome On Association Between Adverse Childhood Experiences And Development Of Mental Disorders In Preadolescence. Xiao X, Hammond CJ, Salmeron BJ, Wang D, Gu H, Zhai T, Murray L, Quam A, Hill J, Nguyen H, Lu H, Hoffman EA, Janes AC, Ross TJ, Yang Y. JAMA Netw Open. 2025; 8(9): :e2533136.

Importance: Adverse childhood experiences (ACEs) are common and account for more than 25% of psychiatric disorders in youths, but the underlying neurobiological mechanisms associated with risk and resilience among children exposed to ACEs are poorly understood.

Objectives: To examine associations between ACEs and transdiagnostic psychopathology during the transition to adolescence and to test whether these associations are modified by whole-brain functional connectivity.

Design, setting, and participants: This cohort study used data from the longitudinal Adolescent Brain Cognitive Development (ABCD) Study's baseline through 2-year follow-up assessments. A total of 6813 children aged 9 to 11 years at baseline were recruited from 21 US sites between June 1, 2016, and October 31, 2018. Data were analyzed from September 2023 to April 2025.

Exposure: Lifetime ACEs, assessed from child and parent reports, through 2-year follow-up.

Main outcomes and measures: Cumulative number of current DSM-5 psychiatric disorders obtained from the computerized self-administered Kiddie Schedule for Affective Disorders and Schizophrenia for DSM-5 (KSADS-5) through 2-year follow-up and a machine learning-based latent connectome variate (CV) score derived from baseline resting-state functional magnetic resonance imaging data.

Results: Among 6813 children (mean [SD] age at baseline, 10.0 [0.6] years; 3413 girls [50.1%]) with available baseline neuroimaging, behavioral, and covariate data, the mean (SD) ACE score was 2.3 (1.7) at baseline. ACE scores were significantly associated with the cumulative number of KSADS-5 diagnoses at baseline ($\beta = 0.11$; 95% CI, 0.10-0.12; $P < .001$) and 2-year follow-up ($\beta = 0.14$; 95% CI, 0.12-0.15; $P < .001$). Baseline CV score modified associations between ACEs and psychiatric disorders across the 2 years ($\beta = -0.02$; 95% CI, -0.03 to -0.01; $t = -3.34$; $P < .001$). Post hoc investigation showed that the modification of the CV score on associations between ACEs and psychopathology was specific to the threat-related ACEs ($\beta = -0.04$; 95% CI, -0.06 to -0.02; $t = -3.67$; $P < .001$) and was pronounced for girls ($\beta = -0.06$; 95% CI, -0.09 to -0.02; $t = -3.33$; $P < .001$).

Conclusions and relevance: In this cohort study of children, a whole-brain functional connectivity score derived from neuroimaging data modified the association between ACEs and psychiatric disorders. This modification was particularly seen against threat-related ACEs and was pronounced for female youths. These findings suggest that functional connectivity strength in a broad system relevant to cognitive control may protect preadolescents who have experienced lifetime ACEs-especially girls and those experiencing threat-related ACEs-from developing transdiagnostic psychopathology.

Distinct Prelimbic Cortex Ensembles Encode Response Execution And Inhibition Madangopal R, Zhao Y, Heins C, Zhou J, Liang B, Barbera G, Lam KC, Komer LE, Weber SJ, Thompson DJ, Gera Y, Pham DQ, Savell KE, Warren BL, Caprioli D, Venniro M, Bossert JM,

Ramsey LA, Jedema HP, Schoenbaum G, Lin DT, Shaham Y, Pereira F, Hope BT. Proc Natl Acad Sci U S A. 2025; 122 (37): e2505378122.
Learning when to initiate or withhold actions is essential for survival, requiring the integration of past experiences with new information to adapt to changing environments. The prelimbic cortex (PL) plays a central role in this process, with a stable PL neuronal population (ensemble) recruited during operant reward learning to encode response execution. However, it is unknown how this established reward-learning ensemble adapts to changing reward contingencies, such as reward omission during extinction. Specifically, does the same ensemble adjust its activity to support behavior suppression, or is a distinct ensemble recruited for this new learning? Our data reveal that operant extinction learning recruits a distinct PL Extinction ensemble to support response inhibition, and concerted engagement of both ensembles encodes both ongoing and subsequent context-specific behavior. Using single-cell calcium imaging, we longitudinally tracked PL neurons in rats as they pressed a lever for food rewards (Training), learned to suppress responding upon reward omission (Extinction), and reinstated responding following a noncontingent "priming" pellet (Reinstatement). We trained decoders on individual rats' PL activity patterns to predict trial-wise responses and used an in silico deletion approach to identify separate PL Training and Extinction ensembles associated with response execution and inhibition, respectively. Critically, both ensembles were reengaged and maintained their distinct roles during Reinstatement. These findings highlight ensemble-based encoding of multiple, even opposing, learned associations within the same region, demonstrating how selective ensemble recruitment enables behavioral flexibility under changing contingencies. ZIA-DA000467, ZIA-DA000434

ADOLESCENT BRAIN COGNITIVE STUDY (ABCD Study®)

Stimulant Medications Affect Arousal And Reward, Not Attention Networks Kay BP, Wheelock MD, Siegel JS, Raut RV, Chauvin RJ, Metoki A, Rajesh A, Eck A, Pollaro J, Wang A, Suljic V, Adeyemo B, Baden NJ, Scheidter KM, Monk JS, Whiting FI, Ramirez-Perez N, Krimmel SR, Shinohara RT, Tervo-Clemmens B, Hermosillo RJM, Nelson SM, Hendrickson TJ, Madison T, Moore LA, Miranda-Domínguez Ó, Randolph A, Feczko E, Roland JL, Nicol GE, Laumann TO, Marek S, Gordon EM, Raichle ME, Barch DM, Fair DA, Dosenbach NUF. Cell. 2025; 188(26): 7529-7546.e20.
Prescription stimulants (e.g., methylphenidate) are thought to improve attention, but evidence from prior fMRI studies is conflicted. We utilized resting-state fMRI data from the Adolescent Brain Cognitive Development Study (n = 11,875; 8-11 years old) and validated the functional connectivity findings in a precision imaging drug trial with highly sampled (n = 5, 165-210 min each) healthy adults (methylphenidate 40 mg). Stimulant-related connectivity differences in sensorimotor regions matched fMRI patterns of daytime arousal, sleeping longer at night, and norepinephrine transporter expression. Taking stimulants reversed the effects of sleep deprivation on connectivity and school grades. Connectivity was also changed in salience and parietal memory networks, which are important for dopamine-mediated, reward-motivated learning, but not the brain's attention systems (e.g., dorsal attention network). The combined noradrenergic

and dopaminergic effects of stimulants may drive brain organization towards a more wakeful and rewarded configuration, improving task effort and persistence without effects on attention networks.

Modeling Psychopathology In High-dimensional Vector Space Using The High-dimensional Symptom Space (HDSS) Model Can Operationalize Precision Psychiatry In US Adolescents. Wild MG, Cutler RA. Sci Rep. 2025; 15(1): 35084.
Symptoms of psychopathology vary across people, limiting inferences about origins and treatments of disorders for any one person. The high-dimensional symptom space (HDSS) model offers a novel framework for understanding psychopathology by representing symptoms as vectors within a multidimensional space. Unlike traditional categorical and dimensional models, HDSS uses geometric distances to empirically characterize a person's unique experience of symptoms, with the option to integrate social and cultural factors for more precise, personalized treatments. Using data from the adolescent brain and cognitive development (ABCD) study, we demonstrate that HDSS preserves individual specificity, effectively captures dynamic trajectories of psychological distress, and accommodates clinical heterogeneity. Results indicate that HDSS distances correspond to symptom severity and capture nuanced patterns of psychological distress over time, offering a comprehensive and individualized understanding of psychopathology. This model allows for a person-centered understanding of psychopathology, highlighting unique symptom patterns and their evolution over time. HDSS represents a significant advancement in personalized psychological care, providing a data-driven framework for understanding psychopathology symptoms, and implementing effective interventions.

Integrating Multilevel, Multidomain And Multimodal Neuroimaging Factors To Predict Early Alcohol Exposure Trajectories Using Explainable AI. Ferariu A, Chang H, Kumar A, Sahl A, Gorka S, Wang L, Thompson WK, Zhang FDev Cogn Neurosci. 2025; 75: 101597.
Various multilevel, multidomain factors at the individual-, family-, and environmental-level, and changes in neurobiology have been associated with the likelihood of developing alcohol use disorder (AUD) or binge drinking later in life. Prior studies have examined only limited subsets of these factors, typically focusing on cross-sectional associations with alcohol initiation, binge drinking, or AUD rather than exploring longitudinal alcohol use trajectories. Our study addresses these gaps by applying machine learning methods to a comprehensive set of multilevel, multidomain factors and multimodal brain imaging features (including brain structure and functional connectivity) to prospectively predict early alcohol sipping trajectories. Using data from the Adolescent Brain Cognitive Development Study, we identified functional connectivity features and multilevel factors that distinguish youth with an increasing alcohol sipping trajectory from those who initially experimented with alcohol but reduced their consumption over time. Moreover, structural and functional features predicted differences between youth who increasingly sipped over time and those who did not engage in alcohol experimentation. Interactions between age, socioeconomical status and positive attitudes towards drinking could predict a pattern of increasing alcohol sipping over time. These trends could inform how individual, family, environmental and neurobiological factors impact the development of different alcohol sipping trajectories over time.

Cognitive Resilience And Vulnerability To Socioeconomic Disadvantage: Predictors Across Individual, Family, School, And Neighborhood Contexts. Shariq D, Romeo RR, Gard AM. Dev Sci. 2026; 29(1): e70105.

Though much research links socioeconomic disadvantage to cognitive difficulties during adolescence, many youth demonstrate resilience. Person-centered approaches can be used to quantify this developmental heterogeneity and challenge deficit-centered frameworks. This study leverages person-centered and data-driven methods to quantify and characterize cognitive heterogeneity in a socioeconomically diverse sample of early adolescents from the Adolescent Brain Cognitive Development Study (N = 9839; 47.7% female sex; Mage = 9.90 years; 46.7% White). Four profiles were identified based on their access to socioeconomic resources (SER) and multi-domain cognitive functioning, including two profiles characterized by moderate-to-high SER (74.5%) and two profiles characterized by low SER (25.5%). Among youth in low-SER environments, 88.6% demonstrated cognitive performance scores similar to youth with moderate-to-high access to SER ("cognitive resilience"), whereas 11.4% demonstrated markedly lower performance relative to the other profiles (i.e., 1.3-2.3 SD below the sample mean; "cognitive vulnerability"). Ridge regression identified ecological factors associated with profile membership at the individual level and within family, neighborhood, and school contexts. Suburban residence (odds ratio [OR] = 1.30), advanced pubertal maturity (OR = 1.20), bilingualism (OR = 1.14), and greater caregiver monitoring (OR = 1.10) were most strongly associated with lower-SER youths' membership in the resilient versus the vulnerable profile. Results emphasize the need to challenge deficit-centered frameworks by investigating heterogeneity within profiles of adversity-exposed youth and identifying context-specific risk and protective factors. U24 DA041147, U01 DA051039, U01 DA041120, U01 DA051018, U01 DA041093

Psychopathology And Gaming Disorder In Adolescents Falcione K, Weber R. JAMA Netw Open. 2025; 8(7): e2528532.

Importance: Although gaming disorder is recognized as a diagnosable behavioral addiction, uncertainty remains regarding its directional association with adolescent psychopathology. Clarifying this association is crucial for refining diagnostic frameworks and developing targeted interventions.

Objective: To examine directional longitudinal associations between psychopathology and gaming disorder among adolescents using the Interaction of Person-Affect-Cognition-Execution model as a theoretical framework.

Design, setting, and participants: This cohort study used data from the Adolescent Brain Cognitive Development Study (release 5.1), analyzing 4289 adolescents in the US who played video games and completed 3 waves of data collection (at ages 11-12, 12-13, and 13-14 years) between January 1, 2018, and December 31, 2022. Statistical analysis was performed from December 2024 to March 2025.

Main outcomes and measures: Psychopathology was assessed using caregiver reports from the Child Behavior Checklist, which provided measures of depression, attention-deficit/hyperactivity disorder (ADHD), social problems, anxiety, and conduct disorder or aggression. Additional

person-centered core characteristics (eg, negative life events, family conflict, bullying, and impulsivity) were incorporated. Gaming disorder was measured using the Video Game Addiction Questionnaire, which aligns with the DSM-5 criteria for internet gaming disorder.
Results: This cohort comprised 4289 adolescents (mean [SD] age, 168.8 [8.2] months; 2391 of 4288 [56%] males). Household income varied widely, with 1374 of 3877 households (35%) reporting an income from $100 000 to $199 000. Cross-lagged panel models (CLPMs) demonstrated that higher baseline levels of psychopathology were associated with an increased risk for subsequent gaming disorder from the 2-year to the 3-year follow-up (β = 0.03 [95% CI, 0.002-0.06]; P = .003) and from 3-year to the 4-year follow-up (β = 0.07 [95% CI, 0.04-0.10]; P < .001). Even when controlling for other personal core characteristics associated with increased risk, there was still a small to medium effect size of psychopathology associated with gaming disorder from the 3-year to the 4-year follow-up (β = 0.04 [95% CI, 0.002-0.07]; P = .04). In contrast, gaming disorder was not associated with later increases in psychopathology. Hierarchical mixed-effects models that accounted for both the panel structure and grouping of the data corroborated the results from the CLPMs.
Conclusions and relevance: The results of this cohort study suggest that psychopathology is significantly associated with the development of gaming disorder among adolescents. Clinical efforts to address underlying mental health issues, particularly for internalizing symptoms such as depression, anxiety, social problems, and ADHD, may reduce the incidence and severity of gaming disorder.