DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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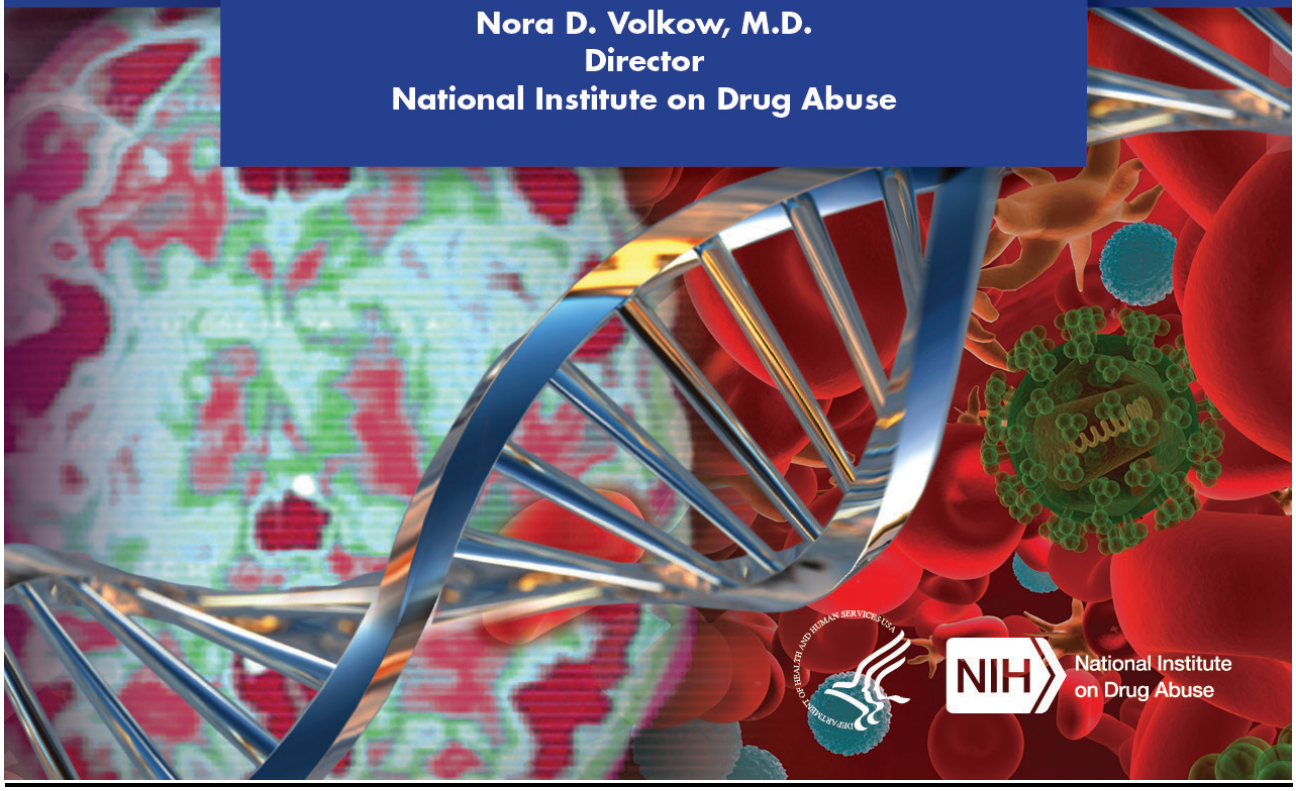

NIH National Institute on Drug Abuse

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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

A Paranigral VTA Nociceptin Circuit That Constrains Motivation For Reward Parker KE, Pedersen CE, Gomez AM, Spangler SM, Walicki MC, Feng SY, Stewart SL, Otis JM, Al-Hasani R, McCall JG, Sakers K, Bhatti DL, Copits BA, Gereau RW, Jhou T, Kash TJ, Dougherty JD, Stuber GD, Bruchas JR. Cell 2019 Jul 25; 178(3): 653-671.
Nociceptin and its receptor are widely distributed throughout the brain in regions associated with reward behavior, yet how and when they act is unknown. Here, we dissected the role of a nociceptin peptide circuit in reward seeking. We generated a *prepronociceptin* (*Pnoc*)-Cre mouse line that revealed a unique subpopulation of paranigral ventral tegmental area (pnVTA) neurons enriched in *prepronociceptin*. Fiber photometry recordings during progressive ratio operant behavior revealed pnVTA^{Pnoc} neurons become most active when mice stop seeking natural rewards. Selective pnVTA^{Pnoc} neuron ablation, inhibition, and conditional VTA nociceptin receptor (NOPR) deletion increased operant responding, revealing that the pnVTA^{Pnoc} nucleus and VTA NOPR signaling are necessary for regulating reward motivation. Additionally, optogenetic and chemogenetic activation of this pnVTA^{Pnoc} nucleus caused avoidance and decreased motivation for rewards. These findings provide insight into neuromodulatory circuits that regulate motivated behaviors through identification of a previously unknown neuropeptide-containing pnVTA nucleus that limits motivation for rewards.

Genome-Wide Association Study Implicates CHRNA2 In Cannabis Use Disorder Demontis D, Rajagopal VM, Thorgeirsson TE, Als TD, Grove J, Leppälä K, Gudbjartsson DF, Pallesen J, Hjorthøj C, Reginsson GW, Tyrfingsson T, Runarsdottir V, Qvist P, Christensen JH, Bybjerg-Grauholm J, Bækvad-Hansen M, Huckins LM, Stahl EA, Timmermann A, Agerbo E, Hougaard DM, Werge T, Mors O, Mortensen PB, Nordentoft M, Daly MJ, Stefansson H, Stefansson K, Nyegaard M, Børglum AD. Nat Neurosci. 2019 Jul; 22(7):1066-1074.
Cannabis is the most frequently used illicit psychoactive substance worldwide; around one in ten users become dependent. The risk for cannabis use disorder (CUD) has a strong genetic component, with twin heritability estimates ranging from 51 to 70%. Here we performed a genome-wide association study of CUD in 2,387 cases and 48,985 controls, followed by replication in 5,501 cases and 301,041 controls. We report a genome-wide significant risk locus for CUD ($P = 9.31 \times 10^{-12}$) that replicates in an independent population ($P_{replication} = 3.27 \times 10^{-3}$, $P_{meta\text{-}analysis} = 9.09 \times 10^{-12}$). The index variant (rs56372821) is a strong expression quantitative trait locus for cholinergic receptor nicotinic α2 subunit (CHRNA2); analyses of the genetically regulated gene expression identified a significant association of CHRNA2 expression with CUD in brain tissue. At the polygenic level, analyses revealed a significant decrease in the risk of CUD with increased load of variants associated with cognitive performance. The results provide biological insights and inform on the genetic architecture of CUD.

Chronic Sleep Fragmentation Enhances Habenula Cholinergic Neural Activity Ge F, Mu P, Guo R, Cai L, Liu Z, Dong Y, Huang YH. Mol Psychiatry. 2019 Apr 12. [Epub ahead of print].
Sleep is essential to emotional health. Sleep disturbance, particularly REM sleep disturbance, profoundly impacts emotion regulation, but the underlying neural mechanisms remain elusive. Here we show that chronic REM sleep disturbance, achieved in mice by chronic sleep fragmentation (SF), enhanced neural activity in the medial habenula (mHb), a brain region increasingly implicated

in negative affect. Specifically, after a 5-day SF procedure that selectively fragmented REM sleep, cholinergic output neurons (ChNs) in the mHb exhibited increased spontaneous firing rate and enhanced firing regularity in brain slices. The SF-induced firing changes remained intact upon inhibition of glutamate, GABA, acetylcholine, and histamine receptors, suggesting cell-autonomous mechanisms independent of synaptic transmissions. Moreover, the SF-induced hyperactivity was not because of enhanced intrinsic membrane excitability, but was accompanied by depolarized resting membrane potential in mHb ChNs. Furthermore, inhibition of TASK-3 (KCNK9) channels, a subtype of two-pore domain K^+ channels, mimicked the SF effects by increasing the firing rate and regularity, as well as depolarizing the resting membrane potential in mHb ChNs in control-sleep mice. These effects of TASK-3 inhibition were absent in SF mice, suggesting reduced TASK-3 activity following SF. By contrast, inhibition of small-conductance Ca^{2+}-activated K^+ (SK) channels did not produce similar effects. Thus, SF compromised TASK-3 function in mHb ChNs, which likely led to depolarized resting membrane potential and increased spontaneous firing. These results not only demonstrate that selective REM sleep disturbance leads to hyperactivity of mHb ChNs, but also identify a key molecular substrate through which REM sleep disturbance may alter affect regulation.

Sequential Replay Of Nonspatial Task States In The Human Hippocampus Schuck NW, Niv Y. Science 2019 Jun; 364(6447): pii: eaaw5181.
Sequential neural activity patterns related to spatial experiences are "replayed" in the hippocampus of rodents during rest. We investigated whether replay of nonspatial sequences can be detected noninvasively in the human hippocampus. Participants underwent functional magnetic resonance imaging (fMRI) while resting after performing a decision-making task with sequential structure. Hippocampal fMRI patterns recorded at rest reflected sequentiality of previously experienced task states, with consecutive patterns corresponding to nearby states. Hippocampal sequentiality correlated with the fidelity of task representations recorded in the orbitofrontal cortex during decision-making, which were themselves related to better task performance. Our findings suggest that hippocampal replay may be important for building representations of complex, abstract tasks elsewhere in the brain and establish feasibility of investigating fast replay signals with fMRI.

7-Hydroxymitragynine Is An Active Metabolite of Mitragynine And A Key Mediator of Its Analgesic Effects Kruegel AC, Uprety R, Grinnell SG, Langreck C, Pekarskaya EA, Le Rouzic V, Ansonoff M, Gassaway MM, Pintar JE, Pasternak GW, Javitch JA, Majumdar S, Sames D. J. ACS Cent Sci. 2019 Jun 26; 5(6):992-1001.
Mitragyna speciosa, more commonly known as kratom, is a plant native to Southeast Asia, the leaves of which have been used traditionally as a stimulant, analgesic, and treatment for opioid addiction. Recently, growing use of the plant in the United States and concerns that kratom represents an uncontrolled drug with potential abuse liability, have highlighted the need for more careful study of its pharmacological activity. The major active alkaloid found in kratom, mitragynine, has been reported to have opioid agonist and analgesic activity in vitro and in animal models, consistent with the purported effects of kratom leaf in humans. However, preliminary research has provided some evidence that mitragynine and related compounds may act as atypical opioid agonists, inducing therapeutic effects such as analgesia, while limiting the negative side effects typical of classical opioids. Here we report evidence that an active metabolite plays an important role in mediating the analgesic effects of mitragynine. We find that mitragynine is converted in vitro in both mouse and human liver preparations to the much more potent mu-opioid receptor agonist 7-hydroxymitragynine and that this conversion is mediated by cytochrome P450 3A isoforms. Further, we show that 7-hydroxymitragynine is formed from mitragynine in mice and

that brain concentrations of this metabolite are sufficient to explain most or all of the opioid-receptor-mediated analgesic activity of mitragynine. At the same time, mitragynine is found in the brains of mice at very high concentrations relative to its opioid receptor binding affinity, suggesting that it does not directly activate opioid receptors. The results presented here provide a metabolism-dependent mechanism for the analgesic effects of mitragynine and clarify the importance of route of administration for determining the activity of this compound. Further, they raise important questions about the interpretation of existing data on mitragynine and highlight critical areas for further research in animals and humans.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Prediction Of Onset Of Substance-Induced Psychotic Disorder And Its Progression To Schizophrenia In A Swedish National Sample Kendler KS, Ohlsson H, Sundquist J, Sundquist K. Am J Psychiatry. 2019. [Epub ahead of print].

The objective of this study was to clarify the etiology of substance-induced psychotic disorder and its progression to schizophrenia in a Swedish national sample. Individuals with a registration of substance-induced psychotic disorder between 1997 and 2015 in national medical registries (N=7,606) were followed up for a mean of 84 months. Data from medical, criminal, and pharmacy registries on first-degree through third-degree relatives were used to calculate familial risk scores for nonaffective psychosis, drug abuse, and alcohol use disorder. Individuals with substance-induced psychotic disorder had large elevations in standardized familial risk scores for drug abuse (+1.09, 95% CI=1.02, 1.15) and alcohol use disorder (+0.98, 95% CI=0.93, 1.03) and modest elevations for nonaffective psychosis (+0.35, 95% CI=0.30, 0.41). The cumulative risk for progression to schizophrenia was 11.3%; it was lowest for alcohol-induced and highest for cannabis-induced psychotic disorder, and it was predicted by early age at diagnosis of substance-induced psychotic disorder, male sex, and further registrations for episodes of drug abuse, alcohol use disorder, and substance-induced psychotic disorder. A risk prediction model found that 47% of individuals who converted to schizophrenia were in the upper 20% of risk. Familial risk scores for drug abuse and alcohol use disorder did not significantly discriminate those who converted to schizophrenia from those who did not, while familial risk score for nonaffective psychosis did (0.67, 95% CI=0.40, 0.95, versus 0.33, 95% CI=0.28, 0.39). Familial risk scores for nonaffective psychosis were indistinguishable between individuals with schizophrenia with and without prior substance-induced psychosis. Assignment of early retirement by the Swedish Social Insurance Agency strongly discriminated between individuals with substance-induced psychotic disorder with and without later schizophrenia. Substance-induced psychotic disorder appears to result from substantial drug exposure in individuals at high familial risk for substance abuse and moderately elevated familial risk for psychosis. Familial risk for psychosis, but not substance abuse, predicts progression from substance-induced psychosis to schizophrenia. Schizophrenia following substance-induced psychosis is likely a drug-precipitated disorder in highly vulnerable individuals, not a syndrome predominantly caused by drug exposure.

Pain-Related Nucleus Accumbens Function: Modulation By Reward And Sleep Disruption Seminowicz DA, Remeniuk B, Krimmel SR, Smith MT, Barrett FS, Wulff AB, Furman AJ, Geuter S, Lindquist MA, Irwin MR, Finan PH. Pain. 2019; 160(5): 1196-1207.

The nucleus accumbens (NAc) has been implicated in sleep, reward, and pain modulation, but the relationship between these functional roles is unclear. This study aimed to determine whether NAc function at the onset and offset of a noxious thermal stimulus is enhanced by rewarding music, and

whether that effect is reversed by experimental sleep disruption. Twenty-one healthy subjects underwent functional magnetic resonance imaging scans on 2 separate days after both uninterrupted sleep and experimental sleep disruption. During functional magnetic resonance imaging scans, participants experienced noxious stimulation while listening to individualized rewarding or neutral music. Behavioral results revealed that rewarding music significantly reduced pain intensity compared with neutral music, and disrupted sleep was associated with decreased pain intensity in the context of listening to music. In whole-brain family-wise error cluster-corrected analysis, the NAc was activated at pain onset, but not during tonic pain or at pain offset. Sleep disruption attenuated NAc activation at pain onset and during tonic pain. Rewarding music altered NAc connectivity with key nodes of the corticostriatal circuits during pain onset. Sleep disruption increased reward-related connectivity between the NAc and the anterior midcingulate cortex at pain onset. This study thus indicates that experimental sleep disruption modulates NAc function during the onset of pain in a manner that may be conditional on the presence of competing reward-related stimuli. These findings point to potential mechanisms for the interaction between sleep, reward, and pain, and suggest that sleep disruption affects both the detection and processing of aversive stimuli that may have important implications for chronic pain.

Exploring The Components Of An Efficacious Computer Brief Intervention For Reducing Marijuana Use Among Adults In The Emergency Department Waller R, Bonar EE, Fernandez AC, Walton MA, Chermack ST, Cunningham RM, Blow FC. J Subst Abuse Treat. 2019; 99:67-72.
To examine the efficacious components of a computer-delivered brief intervention (CBI) for reducing marijuana use among adults presenting to a low-income urban emergency department (ED), which a prior report found to decrease marijuana use at a 6-month follow-up. Participants were 237 ED patients reporting recent drug use (46% male; 54% African-American; mean age, 30.7) who were randomized to receive a CBI consisting of an interactive program guided by a virtual health counselor. The primary outcome was past 30-day marijuana use at 6-month follow-up assessed using the Timeline Follow-Back (TLFB). Intervention components related to change in marijuana use at 6-month follow-up examined in the current study included participant responses to items within five CBI domains that were rooted in motivational interviewing: goals for change, strengths, evoking-change (concerns about use and benefits of change), challenges, and tools for change. The evoking-change domain was related to significant reductions in marijuana use at 6 months ($B = -2.91$, $SE = 1.10$, $p < .01$). Within this domain, items focused on concerns about family and friends were related to reductions in marijuana use of up to 5.5 fewer days of marijuana use in the past month ($B = -5.49$, $SE = 1.63$, $p < .01$). An ED-based brief intervention, delivered by computer, was effective in reducing marijuana use. Intervention components focused on perceived concerns about use and benefits of change in relation to family and friends were critical domains within a CBI associated with reductions in marijuana use at 6-month follow-up.

Access To Office-Based Buprenorphine Treatment In Areas With High Rates Of Opioid-Related Mortality: An Audit Study Beetham T, Saloner B, Wakeman SE, Gaye M, Barnett ML. Ann Intern Med. 2019; 171: 1-9.
Improving access to treatment for opioid use disorder is a national priority, but little is known about the barriers encountered by patients seeking buprenorphine-naloxone ("buprenorphine") treatment. Objective: To assess real-world access to buprenorphine treatment for uninsured or Medicaid-covered patients reporting current heroin use. Design: Audit survey ("secret shopper" study). Setting: 6 U.S. jurisdictions with a high burden of opioid-related mortality (Massachusetts, Maryland, New Hampshire, West Virginia, Ohio, and the District of Columbia).

Participants: From July to November 2018, callers contacted 546 publicly listed buprenorphine prescribers twice, posing as uninsured or Medicaid-covered patients seeking buprenorphine treatment. Measurements: Rates of new appointments offered, whether buprenorphine prescription was possible at the first visit, and wait times. Results: Among 1092 contacts with 546 clinicians, schedulers were reached for 849 calls (78% response rate). Clinicians offered new appointments to 54% of Medicaid contacts and 62% of uninsured-self-pay contacts, whereas 27% of Medicaid and 41% of uninsured-self-pay contacts were offered an appointment with the possibility of buprenorphine prescription at the first visit. The median wait time to the first appointment was 6 days (interquartile range [IQR], 2 to 10 days) for Medicaid contacts and 5 days (IQR, 1 to 9 days) for uninsured-self-pay contacts. These wait times were similar regardless of clinician type or payer status. The median wait time from first contact to possible buprenorphine induction was 8 days (IQR, 4 to 15 days) for Medicaid and 7 days (IQR, 3 to 14 days) for uninsured-self-pay contacts. Limitation: The survey sample included only publicly listed buprenorphine prescribers. Conclusion: Many buprenorphine prescribers did not offer new appointments or rapid buprenorphine access to callers reporting active heroin use, particularly those with Medicaid coverage. Nevertheless, wait times were not long, implying that opportunities may exist to increase access by using the existing prescriber workforce.

Stigma And Drug Use Settings As Correlates Of Self-Reported, Non-Fatal Overdose Among People Who Use Drugs In Baltimore, Maryland Latkin CA, Gicquelais RE, Clyde C, Dayton L, Davey-Rothwell M, German D, Falade-Nwulia S, Saleem H, Fingerhood M, Tobin K. Int J Drug Policy. 2019; 68: 86-92.

Fatalities from opioid overdose quadrupled during the last 15 years as illicit opioid use increased. This study assesses how stigma and drug use settings are associated with non-fatal overdose to identify targets for overdose risk reduction interventions and inform overdose education and naloxone distribution programs. We surveyed 444 people who used drugs in Baltimore, Maryland, USA, from 2009 to 2013 as part of a randomized clinical trial of a harm reduction intervention. Participants reported demographic characteristics, drug use, overdose history, use of a local syringe services program, involvement in the local drug economy, and whether they experienced discrimination from others (i.e., enacted stigma) or stigmatized themselves (i.e., internalized stigma) related to their drug use. We used multinomial logistic regression models to identify correlates of experiencing a non-fatal overdose within the past year or >1 year ago relative to participants who never experienced an overdose. Stigma was positively associated with experiencing a non-fatal overdose in the past year (adjusted Odds Ratio [aOR]: 1.7, 95% Confidence Interval [CI]: 1.1-2.7) and >1 year ago (aOR [95% CI]: 1.5 [1.1-2.0]) after adjustment for demographic and substance use characteristics. The association of stigma with overdose was stronger for enacted versus internalized stigma. The number of public settings (shooting gallery, crack house, abandoned building, public bathroom, outside) where participants used drugs was also positively associated with experiencing an overdose. Stigma related to drug use and using drugs in more settings may increase overdose risk. The effectiveness of overdose prevention and naloxone training may be improved by reducing discrimination against people who use drugs in community and medical settings and diversifying the settings in which overdose prevention trainings are delivered. These efforts may be enhanced by use of peer outreach approaches in which people who use drugs diffuse prevention messages through their social networks and within settings of drug consumption outside the medical setting.

TREATMENT RESEARCH

A Recombinant Humanized Anticocaine Monoclonal Antibody Alters The Urinary Clearance Of Cocaine And Its Metabolites In Rats Marckel JA, Wetzel HN, Amlal S, Amlal H, Norman AB. Drug Metab Dispos. 2019; 47(3): 184-188.
A recombinant humanized anticocaine monoclonal antibody, h2E2, has shown potential in the preclinical phases for the treatment of cocaine abuse. The standard tests for cocaine usage are the detection of benzoylecgonine (BE) and cocaine in the urine. This includes workplace drug screens as well as in clinical trials for potential treatments of cocaine abuse. By sequestering cocaine into the plasma compartment, h2E2 prevents cocaine from entering the brain. Due to the altered disposition of cocaine in the presence of h2E2, we investigated the effects of h2E2 on cocaine and metabolite levels in the urine of rats to clarify the use of BE as an endpoint measurement for effectiveness in future clinical trials. The urine concentrations of cocaine and metabolites were considerably altered in the presence of h2E2. After a single injection of h2E2 (120 mg/kg) and cocaine hydrochloride (0.56 mg/kg), the concentration of cocaine and BE excreted into the urine of rats decreased by 92% and 91%, respectively, from vehicle controls. Due to the significant decrease in urinary excretion, BE is not an appropriate indicator of cocaine usage in the presence of h2E2. Another endpoint measurement must be selected for the measurement of cocaine usage in the upcoming clinical trials of h2E2. In contrast to the effects on cocaine and BE urinary excretion, there was a 3-fold increase in ecgonine methyl ester (EME) in the presence of h2E2. Therefore, we conclude that EME is a more appropriate measurement of cocaine intake in the presence of h2E2.

Integrated Cognitive Behavioral Therapy For Comorbid Cannabis Use And Anxiety Disorders: A Pilot Randomized Controlled Trial Buckner JD, Zvolensky MJ, Ecker AH, Schmidt NB, Lewis EM, Paulus DJ, Lopez-Gamundi P, Crapanzano KA, Bakhshaie J. Behav Res Ther. 2019; 115: 38-45.
Cannabis use disorder (CUD) is the most common illicit substance use disorder and individuals with CUD have high rates of comorbid anxiety disorders. Comorbidity between CUD and anxiety disorders is of public health relevance given that although motivation enhancement therapy (MET) combined with cognitive-behavioral therapy (CBT) is an efficacious intervention for CUD, outcomes are worse for patients with elevated anxiety. The current study tested the acceptability and efficacy of the integration of a transdiagnostic anxiety CBT (i.e., treatment of patients with any anxiety disorder) with MET-CBT (integrated cannabis and anxiety reduction treatment, or ICART) for CUD compared to MET-CBT alone. Treatment-seeking cannabis users (56.4% male, Mage = 23.2, 63.3% non-Hispanic White) with CUD and at least one comorbid anxiety disorder were randomly assigned to ICART (n = 27) or MET-CBT (n = 28). Patients in the ICART condition attended significantly more treatment sessions than those in the MET-CBT condition. Patients in the ICART condition were more likely to be abstinent post-treatment than those in MET-CBT. Further, treatment produced decreases in cannabis use and related problems. Notably, therapy type did not moderate the impact of treatment on frequency of use and related problems. Together, these data suggest that ICART may be at least as efficacious as a gold-standard psychosocial CUD treatment, MET-CBT, for a difficult-to-treat subpopulation of cannabis users.

Concurrent Treatment Of Substance Use Disorders And PTSD, Using Prolonged Exposure: A Randomized Clinical Trial In Military Veterans Back SE, Killeen T, Badour C, Flanagan JC, Allan NP, Ana ES, Lozano B, Korte KJ, Foa EB, Brady KT. Addict Behav. 2019; 90: 369-377.
A substantial amount of individuals with substance use disorders (SUD) also meet criteria for posttraumatic stress disorder (PTSD). Prolonged Exposure (PE) is an effective, evidence-based

treatment for PTSD, but there is limited data on its use among individuals with current alcohol or drug use disorders. This study evaluated the efficacy of an integrated treatment that incorporates PE (Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure or COPE) among veterans. Military veterans (N = 81, 90.1% male) with current SUD and PTSD were randomized to 12 sessions of COPE or Relapse Prevention (RP). Primary outcomes included the Clinician Administered PTSD Scale (CAPS), PTSD Checklist-Military version (PCL-M), and the Timeline Follow-back (TLFB). On average, participants attended 8 out of 12 sessions and there were no group differences in retention. Intent-to-treat analyses revealed that COPE, in comparison to RP, resulted in significantly greater reductions in CAPS ($d = 1.4$, $p < .001$) and PCL-M scores ($d = 1.3$, $p = .01$), as well as higher rates of PTSD diagnostic remission (OR = 5.3, $p < .01$). Both groups evidenced significant and comparable reductions in SUD severity during treatment. At 6-months follow-up, participants in COPE evidenced significantly fewer drinks per drinking day than participants in RP ($p = .05$). This study is the first to report on the use of an integrated, exposure-based treatment for co-occurring SUD and PTSD in a veteran sample. The findings demonstrate that integrated, exposure-based treatments are feasible and effective for military veterans with SUD and PTSD. Implications for clinical practice are discussed.

Relationships Between Marijuana Use, Severity Of Marijuana-Related Problems, And Health-Related Quality Of Life Liao J-Y, Mooney LJ, Zhu Y, Valdez J, Yoo C, Hser Y-I. Psychiatry Res. 2019; 279:237-243.
Studies on the relationships between marijuana use and quality of life have reported mixed findings. Based on a survey of 123 marijuana users conducted in Los Angeles during 2017-2018, we investigated the relationships between marijuana use frequency, severity of marijuana-related problems, and health-related quality of life (HRQoL). Results indicated that (1) marijuana use frequency was positively related to severity of marijuana-related problems; (2) severity of marijuana-related problems was negatively related to mental domain of HRQoL but was not significantly related to physical domain of HRQoL; and (3) marijuana use frequency was positively associated with mental health symptoms and physical health conditions, and both in turn were negatively linked to mental and physical domains of HRQoL, respectively. Reduction of marijuana-related problems and mitigation of mental and physical health problems may improve HRQoL among marijuana users. The study findings may contribute to developing treatment interventions for marijuana use that simultaneously address marijuana-related problems and associated mental and physical issues.

Mechanisms Linking Mindfulness And Early Smoking Abstinence: An Ecological Momentary Assessment Study Spears CA, Li L, Wu C, Vinci C, Heppner WL, Hoover DS, Lam C, Wetter DW. Psychol Addict Behav. 2019; 33(3): 197-207.
Research has suggested that individuals with greater dispositional mindfulness (i.e., nonjudgmental, present-focused attention) are more likely to quit smoking, but the underlying mechanisms are unclear. This study investigated mechanisms linking mindfulness and early smoking abstinence using ecological momentary assessment (EMA). Participants were 355 smokers (33% Caucasian, 33% African American, 32% Latino; 55% female) receiving smoking cessation treatment. Mindfulness was assessed at baseline and on the quit date. For 4 days pre-quit and 1 week post-quit, participants completed up to 4 EMAs per day indicating levels of negative affect (NA), positive affect (PA), smoking urges, and affect regulation expectancies. Mean, slope, and volatility were calculated for each prequit and postquit EMA variable. Associations among mindfulness, EMA parameters, and abstinence on the quit day and 7 days postquit, as well as indirect effects of mindfulness on abstinence through EMA parameters,

were examined. Mindfulness predicted higher odds of abstinence in unadjusted but not covariate-adjusted models. Mindfulness predicted lower NA, higher PA, and lower affective volatility. Lower stress mediated the association between mindfulness and quit-day abstinence. Higher ratings of happy and relaxed, and lower ratings of bored, sad, and angry, mediated the association between mindfulness and postquit abstinence. Mindfulness appeared to weaken the association between craving and postquit abstinence. This study elucidates real-time, real-life mechanisms underlying dispositional mindfulness and smoking abstinence. During the early process of quitting smoking, more mindful individuals appeared to have more favorable emotional profiles, which predicted higher likelihood of achieving abstinence 1 week after the quit date.

Effectiveness Of Switching To Very Low Nicotine Content Cigarettes Plus Nicotine Patch Versus Reducing Daily Cigarette Consumption Plus Nicotine Patch To Decrease Dependence: An Exploratory Randomized Trial Klemperer EM, Hughes JR, Callas PW, Benner J, Morley NE. Addiction. 2019; 279:237-243.
The United States Food and Drug Administration has proposed regulation to require cigarettes contain very low nicotine content (VLNC). In contrast, reducing the number of cigarettes per day (CPD) is the most common current method to reduce nicotine. This trial aims to explore whether gradually transitioning to VLNC cigarettes plus nicotine patch or reducing CPD plus nicotine patch is more effective at decreasing nicotine dependence. A two-arm, individually randomized open label trial. Community setting, Vermont, USA PARTICIPANTS: 68 adult daily smokers (40% female) of ≥ 10 cigarettes/day who were not planning to quit in the next 30 days. All participants smoked study cigarettes with a nicotine yield similar to most commercial cigarettes ad lib for 1 week (baseline). Participants then gradually reduced to 70%, 35%, 15% and 3% of baseline nicotine over 4 weeks by either a) transitioning to lower nicotine content cigarettes (N=36) or b) reducing the number of full nicotine cigarettes (N=32). All participants received nicotine patches. The primary outcome was change in nicotine dependence assessed at baseline and weekly during the intervention with the Nicotine Dependence Syndrome Scale. Dependence declined over time for both VLNC and CPD participants but declined more for VLNC (mean decrease in z-score of 1.0) than CPD (mean decrease in z-score of 0.5) participants over time (interaction p=.018). Transitioning to very low nicotine content cigarettes reduced nicotine dependence over a 4-week period to a greater extent than reducing cigarettes per day when both conditions were aided by nicotine patch.

HIV/AIDS-RELATED RESEARCH

Sequential LASER ART And CRISPR Treatments Eliminate HIV-1 In A Subset Of Infected Humanized Mice Dash PK, Kaminski R, Bella R, Su H, Mathews S, Ahooyi TM, Chen C, Mancuso P, Sariyer R, Ferrante P, Donadoni M, Robinson JA, Sillman B, Lin Z, Hilaire JR, Banoub M, Elango M, Gautam N, Mosley RL, Poluektova LY, McMillan J, Bade AN, Gorantla S, Sariyer IK, Burdo TH, Young WB, Amini S, Gordon J, Jacobson JM, Edagwa B, Khalili K, Gendelman HE. Nat Commun. 2019 Jul 2; 10(1):2753.
Elimination of HIV-1 requires clearance and removal of integrated proviral DNA from infected cells and tissues. Here, sequential long-acting slow-effective release antiviral therapy (LASER ART) and CRISPR-Cas9 demonstrate viral clearance in latent infectious reservoirs in HIV-1 infected humanized mice. HIV-1 subgenomic DNA fragments, spanning the long terminal repeats and the Gag gene, are excised in vivo, resulting in elimination of integrated proviral DNA; virus is not detected in blood, lymphoid tissue, bone marrow and brain by nested and digital-droplet PCR

as well as RNAscope tests. No CRISPR-Cas9 mediated off-target effects are detected. Adoptive transfer of human immunocytes from dual treated, virus-free animals to uninfected humanized mice fails to produce infectious progeny virus. In contrast, HIV-1 is readily detected following sole LASER ART or CRISPR-Cas9 treatment. These data provide proof-of-concept that permanent viral elimination is possible.

Mitochondrial Biogenesis Is Altered In HIV+ Brains Exposed To ART: Implications For Therapeutic Targeting of Astroglia Swinton MK, Carson A, Telese F, Sanchez AB, Soontornniyomkij B, Rad L, Batki I, Quintanilla B, Pérez-Santiago J, Achim CL, Letendre S, Ellis RJ, Grant I, Murphy AN, Fields JA. Neurobiol Dis. 2019 Jun 22; 130: 104502. [Epub ahead of print].

The neuropathogenesis of HIV associated neurocognitive disorders (HAND) involves disruption of mitochondrial homeostasis and increased neuroinflammation. However, it is unknown if alterations in mitochondrial biogenesis in the brain underlie the neuropathogenesis of HAND. In this study, neuropathological and molecular analyses of mitochondrial biogenesis and inflammatory pathways were performed in brain specimens from a well-characterized cohort of HIV+ cases that were on antiretroviral regimens. In vitro investigations using primary human astroglia and neurons were used to probe the underlying mechanisms of mitochondrial alterations. In frontal cortices from HAND brains compared to cognitive normal brains, total levels of transcription factors that regulate mitochondrial biogenesis, peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) and transcription factor A, mitochondrial (TFAM) were decreased. Immunohisto-chemical analyses revealed that TFAM was decreased in neurons and increased in astroglia. These changes were accompanied by decreased total mitochondrial DNA per cell and increased levels of messenger RNA for the proinflammatory cytokine interleukin (IL)-1β. To determine how IL-1β affects astroglial bioenergetic processes and mitochondrial activity, human astroglial cultures were exposed to recombinant IL-1β. IL-1β induced mitochondrial activity within 30 min of treatment, altered mitochondrial related gene expression, altered mitochondrial morphology, enhanced adenoside triphosphate (ATP) utilization and increased the expression of inflammatory cytokines. WIN55,212-2 (WIN), an aminoalkylindole derivative and cannabinoid receptor agonist, blocked IL-1β-induced bioenergetic fluctuations and inflammatory gene expression in astroglia independent of cannabinoid receptor (CB)1 and peroxisome proliferator-activated receptor (PPAR) γ. A PPARα antagonist reversed the anti-inflammatory effects of WIN in human astroglia. These results show that mitochondrial biogenesis is differentially regulated in neurons and astroglia in HAND brains and that targeting astroglial bioenergetic processes may be a strategy to modulate neuroinflammation.

Implementing An Updated "Break the Cycle" Intervention To Reduce Initiating Persons Into Injecting Drug Use In An Eastern European And A U.S. "Opioid Epidemic" Setting Des Jarlais D, Uuskula A, Talu A, Barnes DM, Raag M, Arasteh K, Org G, Demarest D, Feelemyer J, Berg H, Tross S. AIDS Behav. 2019. [Epub ahead of print].

We tested the hypothesis that an updated "Break the Cycle" (BtC) intervention, based in social cognitive theory and motivational interviewing, would reduce the likelihood that current persons who inject drugs (PWID) would assist persons who do not inject drugs (non-PWID) with first injections in Tallinn, Estonia and Staten Island, New York City. 402 PWID were recruited, a baseline interview covering demographics, drug use, and assisting non-PWID with first drug injections was administered, followed by BtC intervention. 296 follow-up interviews were conducted 6 months post-intervention. Percentages assisting with first injections declined from 4.7 to 1.3% (73% reduction) in Tallinn ($p < 0.02$), and from 15 to 6% (60% reduction) in Staten Island

($p < 0.05$). Persons assisted with first injections declined from 11 to 3 in Tallinn ($p = 0.02$) and from 32 to 13 in Staten Island. ($p = 0.024$). Further implementation research on BtC interventions is urgently needed where injecting drug use is driving HIV/HCV epidemics and areas experiencing opioid epidemics.

Cost-Effectiveness Of Integrating Buprenorphine-Naloxone Treatment For Opioid Use Disorder Into Clinical Care For Persons With HIV/Hepatitis C Co-infection Who Inject Opioids Barocas JA, Morgan JR, Fiellin DA, Schackman BR, Eftekhari Yazdi G, Stein MD, Freedberg KA, Linas BP. Int J Drug Policy. 2019. [Epub ahead of print].
Untreated opioid use disorder (OUD) affects the care of HIV/HCV co-infected people who inject opioids. Despite active injection opioid use, there is evidence of increasing engagement in HIV care and adherence to HIV medications among HIV/HCV co-infected persons. However, less than one-half of this population is offered HCV treatment onsite. Treatment for OUD is also rare and largely occurs offsite. Integrating buprenorphine-naloxone (BUP-NX) into onsite care for HIV/HCV co-infected persons may improve outcomes, but the clinical impact and costs are unknown. We evaluated the clinical impact, costs, and cost-effectiveness of integrating (BUP-NX) into onsite HIV/HCV treatment compared with the status quo of offsite referral for medications for OUD. We used a Monte Carlo microsimulation of HCV to compare two strategies for people who inject opioids: 1) standard HIV care with onsite HCV treatment and referral to offsite OUD care (status quo) and 2) standard HIV care with onsite HCV and BUP-NX treatment (integrated care). Both strategies assume that all individuals are already in HIV care. Data from national databases, clinical trials, and cohorts informed model inputs. Outcomes included mortality, HCV reinfection, quality-adjusted life years (QALYs), costs (2017 US dollars), and incremental cost-effectiveness ratios. Integrated care reduced HCV reinfections by 7%, cases of cirrhosis by 1%, and liver-related deaths by 3%. Compared to the status quo, this strategy also resulted in an estimated 11/1,000 fewer non-liver attributable deaths at one year and 28/1,000 fewer of these deaths at five years, at a cost-effectiveness ratio of $57,100/QALY. Integrated care remained cost-effective in sensitivity analyses that varied the proportion of the population actively injecting opioids, availability of BUP-NX, and quality of life weights. Integrating BUP-NX for OUD into treatment for HIV/HCV co-infected adults who inject opioids increases life expectancy and is cost-effective at a $100,000/QALY threshold.

Cost Effectiveness Of Text Messages To Reduce Methamphetamine Use And HIV Sexual Risk Behaviors Among Men Who Have Sex With Men Reback CJ, Fletcher JB, Leibowitz AA. J Subst Abuse Treat. 2019; 100: 59-63.
Methamphetamine use is highly prevalent among gay, bisexual, and other men who have sex with men (MSM) in the United States and has been associated with condomless anal intercourse (CAI), a common route of HIV infection. Text messaging is a very low-cost method of delivery for intervention content. This paper presents a cost-effectiveness analysis of a randomized controlled trial testing three nested methods of text message delivery designed to reduce methamphetamine use and HIV sexual risk behaviors among MSM (Project Tech Support2). From March 2014 to January 2016, 286 non-treatment seeking methamphetamine-using MSM were randomized into one of three study arms: 1) Interactive text message conversations with Peer Health Educators, plus five daily automated, unidirectional theory-based messages, plus a weekly self-monitoring text message assessment (TXT-PHE; $n = 94$); or, 2) Five daily automated, unidirectional theory-based messages plus a weekly self-monitoring text message assessment (TXT-Auto; $n = 99$); or, 3) The weekly self-monitoring text message assessment only (AO; $n = 93$). Methamphetamine use at nine months post-enrollment was lower than at baseline in all three arms. The addition of Peer Health Educators

and/or theory-based text messages did not produce cost-effective reductions in methamphetamine use over the weekly AO text messages. However, both intervention arms outperformed the AO arm in reducing HIV risk behaviors, but the TXT-Auto arm dominated the TXT-PHE arm in achieving greater reductions in days of methamphetamine use and CAI at lower cost. The TXT-Auto arm achieved greater reductions in CAI than the attentional control at a cost in the base case of ~$37.50 per episode of CAI reduced per month. Sensitivity analyses showed that results were robust to a number of changes in assumptions. Interventions seeking to reduce methamphetamine use among non-treatment-seeking MSM may seek to add minimal attentional control-style text messages to their routines querying about recent methamphetamine use and/or high-risk sex. Interventions seeking to additionally reduce HIV sexual risk behaviors among non-treatment-seeking MSM, specifically engagement in CAI, may seek to additionally apply theory-based text messages.

Barriers And Facilitators Of Hepatitis C Treatment Uptake Among People Who Inject Drugs Enrolled In Opioid Treatment Programs In Baltimore Falade-Nwulia O, Irvin R, Merkow A, Sulkowski M, Niculescu A, Olsen Y, Stoller K, Thomas DL, Latkin C, Mehta SH. J Subst Abuse Treat. 2019; 100: 45-51.

Hepatitis C virus (HCV) infection is a major public health issue among people who inject drugs (PWID) with prevalence of 50-80% in the United States. Effective, simple, oral direct acting agents (DAA) of short duration with minimal side effects have been associated with cure rates > 95%. However, HCV treatment uptake among PWID remains low. We characterized the HCV care continuum, HCV treatment knowledge, as well as barriers and facilitators to HCV treatment uptake among PWID enrolled in two opioid treatment programs (OTPs) in Baltimore, Maryland, USA. Between July and November 2016, 124 HCV infected PWID were recruited from two opioid treatment programs in Baltimore through convenience sampling. Participants completed a 50-item questionnaire to assess HCV treatment knowledge, attitudes, and practices. Progress through the HCV care continuum was assessed based on a series of questions assessing evaluation for HCV treatment, recommendation for HCV treatment by a provider, and HCV treatment initiation. HCV status was assessed based on participant self-report. The median age was 52 years (IQR 44-58), 56% were male, the majority were African American (69%), and 19% reported HIV coinfection. Participants had been tested for HCV at their primary care provider' (PCP's) office (34%), drug treatment center (20%), emergency room (11%), or prison (9%), and most (60%) had been diagnosed with HCV over 5 years prior. The majority reported that HCV was a major health concern for them (91%), were aware there were new treatments for HCV (89%), and that the new treatments cure most people (69%). More than half (60%) had seen a health professional who could treat HCV, 40% had HCV therapy recommended by their HCV specialist, and 20% had started or completed treatment. In univariable analysis, PWID were significantly more likely to have been treated if they were HIV co-infected (OR 3.4 (95% CI 1.3-9.2)) or had a partner or friend concerned about their HCV (OR 3.4 (95% CI 1.2-9.7)), and were significantly less likely to have been treated if they had used any illicit drugs in the preceding 6 months (OR 0.4 (95% CI 0.2-0.99). In multivariable analysis, having a friend or partner concerned about their HCV remained significantly associated with HCV treatment (OR 5.0 (95% CI 1.4-17.7)). When questioned about what would facilitate HCV treatment, the majority (85%) reported that a friend telling them that HCV treatment had helped them and having HCV treatment provided at their opioid treatment program would make them more likely to engage in HCV treatment. Despite a high prevalence of HCV among opioid treatment program patients and the availability of effective treatments, uptake remains low. We identified several key barriers and facilitators that can affect HCV treatment uptake.

Differences In The Rate Of Nicotine Metabolism Among Smokers With And Without HIV Ashare RL, Thompson M, Leone F, Metzger D, Gross R, Mounzer K, Tyndale RF, Lerman C, Mahoney MC, Cinciripini P, George TP, Collman RG, Schnoll R. AIDS. 2019; 33(6): 1083-1088.
HIV-infected smokers lose more life years to tobacco use than to HIV infection. The nicotine metabolite ratio (NMR), a biomarker of CYP2A6, represents individual variation in the rate at which nicotine is metabolized and is associated with response to smoking cessation treatments. We evaluated whether HIV-infected smokers metabolize nicotine faster than HIV-uninfected smokers, which may contribute to the disproportionate smoking burden and may have important treatment implications. We analysed baseline data from two clinical trials (NCT01710137; NCT01314001) to compare the NMR in HIV-infected smokers (N=131) to HIV-uninfected smokers (N=199). Propensity scores were used to match the groups 2:1 on characteristics that influence NMR: sex, race, BMI and smoking rate. Nicotine metabolites were assessed via liquid chromatography-tandem mass spectrometry methods and the ratio of 3-hydroxycotinine:cotinine was used to compute the NMR.HIV-infected smokers had significantly higher NMR (mean=0.47, SEM=0.02) and were more likely to be in the highest NMR quartile compared with HIV-uninfected smokers (mean=0.34, SEM=0.02; Ps<0.001).The higher NMR observed among HIV-infected smokers may partially explain higher smoking rates and lower response to transdermal nicotine therapy. Understanding the mechanisms by which HIV and/or ART contribute to faster nicotine metabolism may guide the use of the NMR to personalize tobacco cessation strategies in this underserved population.

CLINICAL TRIALS NETWORK RESEARCH

Correlates Of Opioid Abstinence In A 42-Month Posttreatment Naturalistic Follow-Up Study Of Prescription Opioid Dependence Weiss RD, Griffin ML, Marcovitz DE, Hilton BT, Fitzmaurice GM, McHugh RK, Carroll KM. J Clin Psychiatry. 2019 Mar 26;80(2).
OBJECTIVE: The natural course of prescription opioid use disorder has not been examined in longitudinal studies. The current study examined correlates of opioid abstinence over time after completion of a treatment trial for prescription opioid dependence.
METHODS: The multisite Prescription Opioid Addiction Treatment Study examined different durations of buprenorphine-naloxone treatment and different intensities of counseling to treat prescription opioid dependence, as assessed by DSM-IV; following the clinical trial, a longitudinal study was conducted from March 2009-January 2013. At 18, 30, and 42 months after treatment entry, telephone interviews were conducted (N = 375). In this exploratory, naturalistic study, logistic regression analyses examined the association between treatment modality (including formal treatment and mutual help) and opioid abstinence rates at the follow-up assessments.
RESULTS: At the 3 follow-up assessments, approximately half of the participants reported engaging in current substance use disorder treatment (47%-50%). The most common treatments were buprenorphine maintenance (27%-35%) and mutual-help group attendance (27%-30%), followed by outpatient counseling (18%-23%) and methadone maintenance (4%). In adjusted analyses, current opioid agonist treatment showed the strongest association with current opioid abstinence (odds ratios [ORs] = 5.4, 4.6, and 2.8 at the 3 assessments), followed by current mutual-help attendance (ORs = 2.2, 2.7, and 1.9); current outpatient counseling was not significantly associated with abstinence in the adjusted models.
CONCLUSIONS: While opioid agonist treatment was most strongly associated with opioid abstinence among patients with prescription opioid dependence over time, mutual-help group

attendance was independently associated with opioid abstinence. Clinicians should consider recommending both of these interventions to patients with opioid use disorder.

Escalating Opioid Dose Is Associated With Mortality: A Comparison Of Patients With And Without Opioid Use Disorder Hser Y-I, Saxon AJ, Mooney LJ, Miotto K, Zhu Y, Yoo CK, Liang D, Huang D, Bell DS. J Addict Med. 2019 Jan/Feb; 13(1):41-46.
OBJECTIVE: Prescription Drug Monitoring Programs (PDMPs) are intended to help reduce prescription drug misuse and opioid overdose, yet little is known about the longitudinal patterns of opioid prescribing that may be associated with mortality. This study investigated longitudinal opioid prescribing patterns among patients with opioid use disorder (OUD) and without OUD in relation to mortality using PDMP data.
METHODS: Growth modeling was used to examine opioid prescription data from the California PDMP for a 4-year period before death or a comparable period ending in 2014 for those remaining from a sample of 7728 patients (2576 with OUD, and 5152 matched non-OUD controls) treated in a large healthcare system.
RESULTS: Compared to controls, individuals with OUD (alive and deceased) had received significantly more opioid prescriptions, greater number of days' supply, and steeper increases of opioid dosages over time. For morphine equivalents (ME, in grams), the interaction of OUD and mortality was significant at both intercept (β=10.4, SE=4.4, P<0.05) and slope (β=6.0, SE=1.1, P<0.001); deceased OUD patients demonstrated the sharpest increase (i.e., an average yearly increment of 7.84 grams over alive patients without OUD) and ended with the highest level of opioids prescribed before they died (i.e., 20.2 grams higher). Older age, public health insurance, cancer, and chronic pain were associated with higher number and dose of opioid prescriptions.
CONCLUSIONS: Besides the amount of prescriptions, clinicians must be alert to patterns of opioid prescription such as escalating dosage as critical warning signals for heightened mortality risks, particularly among patients with OUD.

Acute and long-term cannabis use among stimulant users: Results from CTN-0037 Stimulant Reduction Intervention using Dosed Exercise (STRIDE) Randomized Control Trial. Vidot DC, Rethorst CD, Carmody TJ, Stoutenberg M, Walker R, Greer TL, Trivedi MH. Drug Alcohol Depend. 2019 Jul 1;200: 139-144.
AIMS: The aim of this study was to examine the impact of vigorous intensity, high dose exercise (DEI) on cannabis use among stimulant users compared to a health education intervention (HEI) using data from the Stimulant Reduction Intervention using Dosed Exercise, National Institute of Drug Abuse National Drug Treatment Clinical Trials Network Protocol Number 0037 (STRIDE).
METHODS: Adults (N = 302) enrolled in the STRIDE randomized clinical trial were randomized to either the DEI or the HEI. Interventions included supervised sessions three times a week during the Acute phase (12 weeks) and once a week during the Follow-up phase (6 months). Cannabis use was measured at each assessment via Timeline Follow Back and urine drug screens. Cannabis use was compared between the groups during the Acute and Follow-up phases using both the intent-to-treat sample and a complier average causal effects (CACE) analysis.
FINDINGS: Approximately 43% of the sample reported cannabis use at baseline. The difference in cannabis use between the DEI and HEI groups during the Acute phase was not significant. During the Follow-up phase, the days of cannabis use was significantly lower among those in the DEI group (1.20 days) compared to the HEI group (2.15 days; p = 0.04).
CONCLUSIONS: For those who adhered to the exercise intervention, vigorous intensity, high dose exercise resulted in less cannabis use. Results suggest that there were no significant short-term

differences in cannabis use between the groups. Further study on the long-term impact of exercise as a treatment to reduce cannabis use should be considered.

A Systematic Scoping Review Of Research On Black Participants In The National Drug Abuse Treatment Clinical Trials Network Montgomery L, Burlew AK, Haeny AM, Jones CA. Psychol Addict Behav. 2019 Jun 27. [Epub ahead of print].
Black individuals experience a disproportionate burden of substance-related disabilities and premature death relative to other racial/ethnic groups, highlighting the need for additional research. The National Drug Abuse Treatment Clinical Trials Network (CTN), a research platform for multisite behavioral, pharmacological, and integrated trials designed to evaluate the effectiveness of substance use treatments in community settings with diversified patient populations, provides a wealth of research knowledge on substance use. Although CTN trials have enrolled over 5,000 Black individuals since its inception in 2000, there has been no synthesis of the findings, discussion of the implications, or suggestions for future research for Black individuals. Members of the Minority Interest Group of the CTN conducted a scoping review of published research on Black participants in CTN trials. Studies were included if the sample was more than 75% Black and/or specific findings pertaining to Black participants were reported. The review yielded 50 articles, with studies that mostly focused on baseline characteristics, followed by substance use treatment outcomes, HIV/risky sex behaviors, retention, comorbid conditions and measurement issues. This review highlighted the importance of several issues that are critical to understanding and treating substance misuse among Black people, such as the characteristics of Black people entering treatment, measurement equivalence, and engaging/retaining adolescents and young adults in treatment. There is still a continued need to identify the most effective treatments for Black individuals who use substances. The CTN offers several untapped opportunities to further advance research on Black individuals who use substances (e.g., secondary analyses of publicly available data).

Interpretation And Integration Of The Federal Substance Use Privacy Protection Rule In Integrated Health Systems: A Qualitative Analysis Campbell ANC, McCarty D, Rieckmann T, McNeely J, Rotrosen J, Wu LT, Bart G. J Subst Abuse Treat. 2019 Feb; 97: 41-46.
BACKGROUND: Federal regulations (42 CFR Part 2) provide special privacy protections for persons seeking treatment for substance use disorders. Primary care providers, hospitals, and health care organizations have struggled to balance best practices for medical care with adherence to 42 CFR Part 2, but little formal research has examined this issue. The aim of this study was to explore institutional variability in the interpretation and implementation of 42 CFR Part 2 regulations related to health systems data privacy practices, policies, and information technology architecture.
METHODS: This was a cross-sectional qualitative study using purposive sampling to conduct interviews with privacy/legal officers (n = 17) and information technology specialists (n = 10) from 15 integrated healthcare organizations affiliated with three research nodes of the National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN). Trained staff completed a short survey and digitally recorded semi-structured qualitative interview with each participant. Interviews were transcribed and coded within Atlas.ti. Framework analysis was used to identify and organize key themes across selected codes.
RESULTS: Participants voiced concern over balancing patient safety with 42 CFR Part 2 privacy protections. Although similar standards of protection regarding release of information outside of the health system was described, numerous workarounds were used to manage intra-institutional communication and care coordination. To align 42 CFR Part 2 restrictions with electronic health

records, health systems used sensitive note designation, "break the glass" technology, limited role-based access for providers, and ad hoc solutions (e.g., provider messaging).
CONCLUSIONS: In contemporary integrated care systems, substance-related EHR records (e.g., patient visit history, medication logs) are often accessible internally without specific consent for sharing despite the intent of 42 CFR Part 2. Recent amendments to 42 CFR Part 2 have not addressed information sharing needs within integrated care settings.

INTRAMURAL RESEARCH

Synaptic Plasticity Section
Cellular Neurobiology Research Branch

High-Frequency Activation Of Nucleus Accumbens D1-MSNs Drives Excitatory Potentiation On D2-MSNs Francis TC, Yano H, Demarest TG, Shen H, Bonci A. Neuron 2019 Jun 7; 103:1–13.
Subtypes of nucleus accumbens medium spiny neurons (MSNs) promote dichotomous outcomes in motivated behaviors. However, recent reports indicate enhancing activity of either nucleus accumbens (NAc) core MSN subtype augments reward, suggesting coincident MSN activity may underlie this outcome. Here, we report a collateral excitation mechanism in which high-frequency, NAc core dopamine 1 (D1)-MSN activation causes long-lasting potentiation of excitatory transmission (LLP) on dopamine receptor 2 (D2)-MSNs. Our mechanistic investigation demonstrates that this form of plasticity requires release of the excitatory peptide substance P from D1-MSNs and robust cholinergic interneuron activation through neurokinin receptor stimulation. We also reveal that D2-MSN LLP requires muscarinic 1 receptor activation, intracellular calcium signaling, and GluR2-lacking AMPAR insertion. This study uncovers a mechanism for shaping NAc core activity through the transfer of excitatory information from D1-MSNs to D2-MSNs and may provide a means for altering goal-directed behavior through coordinated MSN activity.

Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section
NIAAA/NIDA IRP

Heroin Addiction Engages Negative Emotional Learning Brain Circuits In Rats Carmack SA, Keeley RJ, Vendruscolo JCM, Lowery-Gionta EG, Lu H, Koob GF, Stein EA, Vendruscolo LF. J Clin Invest. 2019 Mar 26; 130:2480-2484.
Opioid use disorder (OUD) is associated with the emergence of persistent negative emotional states during drug abstinence that drive compulsive drug taking and seeking. Functional magnetic resonance imaging (fMRI) in rats identified neurocircuits that were activated by stimuli that were previously paired with heroin withdrawal. The activation of amygdala and hypothalamic circuits was related to the degree of heroin dependence, supporting the significance of conditioned negative affect in sustaining compulsive-like heroin seeking and taking and providing neurobiological insights into the drivers of the current opioid crisis.

Neuroimaging Research Branch

Intrinsic Insular-Frontal Networks Predict Future Nicotine Dependence Severity Hsu L-M, Keeley RJ, Liang X, Brynildsen JK, Lu H, Yang Y, Stein, EA. Journal of Neuroscience 2019; 39: 5028-5037.
Although 60% of the US population have tried smoking cigarettes, only 16% smoke regularly. Identifying this susceptible subset of the population before the onset of nicotine dependence may encourage targeted early interventions to prevent regular smoking and/or minimize severity. While prospective neuroimaging in human populations can be challenging, preclinical neuroimaging models before chronic nicotine administration can help to develop translational biomarkers of disease risk. Chronic, intermittent nicotine (0, 1.2, or 4.8 mg/kg/d; N10 –11/group) was administered to male Sprague Dawley rats for 14 d; dependence severity was quantified using precipitated withdrawal behaviors collected before, during, and following forced nicotine abstinence. Resting-state fMRI functional connectivity (FC) before drug administration was subjected to a graph theory analytical framework to form a predictive model of subsequent individual differences in nicotine dependence. Whole-brain modularity analysis identified five modules in the rat brain. A metric of intermodule connectivity, participation coefficient, of an identified insular–frontal cortical module predicted subsequent dependence severity, independent of nicotine dose. To better spatially isolate this effect, this module was subjected to a secondary exploratory modularity analysis, which segregated it into three submodules (frontal-motor, insular, and sensory). Higher FC among these three submodules and three of the five originally identified modules (striatal, frontal-executive, and sensory association) also predicted dependence severity. These data suggest that predispositional, intrinsic differences in circuit strength between insular-frontal-based brain networks before drug exposure may identify those at highest risk for the development of nicotine dependence.

Treatment Section
Clinical Pharmacology and Therapeutics Research Branch

End-Of-Day Reports Of Daily Hassles And Stress In Men And Women With Opioid-Use Disorder: Relationship To Momentary Reports Of Drug Use And Stress Preston KL, Kowalczyk WJ, Phillips KA, Jobes ML, Dwyer M, Vahabzadeh M, Lin J-L, Mezghanni M, Epstein DH. Drug and Alcohol Dependence 2018; 193:21-28.
Stress can be validly assessed “live” or by a summary evaluation of the very recent past. Using smartphone-based ecological momentary assessment (EMA) combined with end-of-day (EOD) entries, our laboratory assessed the association between daily hassles, stressful events and use of opioids and cocaine, in 161 opioid- and cocaine-using men and women in opioid-agonist treatment. Using smartphones, participants reported stressful events and drug use and completed an EOD questionnaire to report hassles encountered throughout the day and rate current perceived stress. Urine drug screens were conducted thrice weekly. The most frequently reported hassles were “not enough money” and maintaining abstinence. Total EOD hassles showed small but statistically significant associations stressful events, drug use reports, and urine drug screens positive for opioids or cocaine. Daily hassles, reported at the end of the day, are associated with both same-day stressful events and drug use. Monitoring hassles and devising specific coping strategies might be useful therapeutic targets.

Neuronal Circuits and Behavior Unit
Cellular Neurobiology Research Branch

Activation Of A Lateral Hypothalamic-Ventral Tegmental Circuit Gates Motivation Schiffino FL, Siemian JN, Petrella M, Laing BT, Sarsfield S, Borja CB, Gajendiran A, Zuccoli ML, Aponte Y. PLoS One. 2019 Jul 10; 14(7): e0219522.

Across species, motivated states such as food-seeking and consumption are essential for survival. The lateral hypothalamus (LH) is known to play a fundamental role in regulating feeding and reward-related behaviors. However, the contributions of neuronal subpopulations in the LH have not been thoroughly identified. Here we examine how lateral hypothalamic leptin receptor-expressing (LHLEPR) neurons, a subset of GABAergic cells, regulate motivation in mice. We find that LHLEPR neuronal activation significantly increases progressive ratio (PR) performance, while inhibition decreases responding. Moreover, we mapped LHLEPR axonal projections and demonstrated that they target the ventral tegmental area (VTA), form functional inhibitory synapses with non-dopaminergic VTA neurons, and their activation promotes motivation for food. Finally, we find that LHLEPR neurons also regulate motivation to obtain water, suggesting that they may play a generalized role in motivation. Together, these results identify LHLEPR neurons as modulators within a hypothalamic-ventral tegmental circuit that gates motivation.

GRANTEE HONORS AND AWARDS

Richard F. Catalano, Jr., Ph.D., University of Washington, was accepted into the 2019 cohort of *Fellows* of the Society of Prevention Research. The status of *Fellow* is in recognition of a member's distinguished record of contributions in the field of prevention research, reflecting a substantial body of work that has had a broad and significant impact on prevention science.

Linda B. Cottler, Ph.D., M.P.H., University of Florida, received the Mentorship Award at the 2019 College on Problems of Drug Dependence Annual Meeting. Linda has been a Training Program Director on a NIDA-funded T32 for more than 20 years, first at the Washington University in St. Louis, and more recently at the University of Florida.

Daniel Max Crowley, Ph.D., The Pennsylvania State University, received the 2019 Society for Prevention Research *Public Service Award*, in recognition of his extensive and effective advocacy for prevention science and research-based programs.

Laura Hill, Ph.D., Washington State University, received the 2019 Society for Prevention Research *Friend of ECPN Award* for her support and encouragement of early career prevention scientists or issues.

Three Division of Neuroscience and Behavior grantees—**Amy Janes, Ph.D.**, Harvard Medical School; **Donna Calu, Ph.D.**, University of Maryland; and **Ian Maze, Ph.D.**, Mt. Sinai School of Medicine—were awarded the prestigious Presidential Early Career Award for Scientists and Engineers (PECASE). This is the highest honor given to scientists at the early career stage and recognizes outstanding leadership in science and innovation.

Hendrée Jones, Ph.D., University of North Carolina at Chapel Hill, received the 2019 Marian W. Fischman Lectureship Award at the 2019 College on Problems of Drug Dependence meeting. This award in memory of Marian W. Fischman, a respected leader in drug abuse research and an outstanding scientist, was established in 2001 to recognize the contributions of an outstanding woman scientist in drug abuse research.

Hendrée Jones, Ph.D., was invited to speak at the joint annual meeting of the National Association of Women Judges and the Congressional Caucus for Women's Issues on July 16, 2019, in the Rayburn House Office Building. The topic of the meeting was "The Opioid Crisis and Its Impact on Women and Children: The dilemma for judges."

Emily Jutkiewicz, Ph.D., University of Michigan, was awarded the Young Investigator Award from the International Narcotics Research Conference in New York in July 2019.

Stephen Kohut, Ph.D., McLean Hospital and Harvard University, was awarded the Joseph Cochin Young Investigator Award by the College on Problems of Drug Dependence at the Annual Meeting in June 2019 in San Antonio, TX.

Alexandros Makriyannis, Ph.D., Professor, George D. Behrakis Chair, Northeastern University, Boston, presented the "President's Lecture" at the 29th annual symposium of the International Cannabinoid Research Society (ICRS), Bethesda, MD, June 29–July 4, 2019.

Jacques D. Nguyen, Ph.D., University of California San Diego School of Medicine, was awarded the Stephen G. Holtzman Travel Award for Preclinical Investigators by the College on Problems of Drug Dependence at the Annual Meeting in June 2019 in San Antonio, TX.

Rob Pack, Ph.D., M.P.H., (PI - R24DA036409) and the East Tennessee State University Center were awarded the 2018 Public Health Excellence Interprofessional Collaboration Award from the national Interprofessional Education Collaborative (IPEC).

Roger Pertwee, D.Phil., D.Sc., Emeritus Professor, University of Aberdeen, Scotland, a former NIDA grantee, made a presentation entitled "Cannabinoid Pharmacology: My First Half Century" and received the ICRS Lifetime Achievement Award at the 29th annual symposium of the International Cannabinoid Research Society, Bethesda, MD, June 29–July 4, 2019.

Bryan Roth, M.D., Ph.D., Michael Hooker Distinguished Professor, Department of Pharmacology, UNC Chapel Hill, presented the Kang Tsou Memorial lecture at the 29th annual symposium of the International Cannabinoid Research Society, Bethesda, MD, June 29–July 4, 2019.

Solomon Snyder, M.D., D.Sc., D.Phil., Johns Hopkins University, was awarded the Founders Lecturer Award at the International Narcotics Research Conference in New York in July 2019.

STAFF HONORS AND AWARDS

STAFF HONORS

Olivier Berton, Ph.D., Division of Neuroscience and Behavior, was selected as a Co-lead of Team A-Cells and Circuits of the BRAIN Initiative.

NIH DIRECTOR'S AWARDS

Mentoring Awards
Amy Newman, Ph.D., for exemplary performance while demonstrating significant leadership, skill, and ability in serving as a mentor.

NIDA staff included in other NIH Institutes and Centers' Group Award Nominations
IMPACT ANALYSIS WORKING GROUP, nominated by *The Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), **David Bochner, Ph.D.**: In recognition of their outstanding work developing and implementing a framework to assess the impact of NICHD's large programs.

THE ANTI-HARASSMENT PROGRAM TEAM, nominated by the Office of the Director, **Joellen Austin, M.P.Aff., M.S.M.**: In recognition of exceptional efforts in development and deployment of the NIH Anti-Harassment Program.

THE NIH HELPING TO END ADDICTION LONG-TERM (HEAL) TEAM, nominated by the Office of the Director: In recognition of exceptional contributions in the publication of funding opportunities announcements (FOAs) for The NIH Helping to End Addiction Long-term (HEAL) initiative.

- Carlos Blanco, M.D., Ph.D.
- David Bochner, Ph.D.
- Redonna Chandler, Ph.D.
- Ronald Dobbins, M.B.A.
- Gaya Dowling, Ph.D.
- Emily Einstein, Ph.D.
- Jennifer A. Hobin, Ph.D.
- Katia Howlett, Ph.D., M.P.P., M.B.A.
- Emily Jones, Ph.D.
- Elena Koustova, Ph.D., M.B.A.
- Jacqueline Lloyd, Ph.D.
- Ivan Montoya, M.D., M.P.H.
- Kurt Rasmussen, Ph.D.
- Jack Stein, Ph.D.
- Betty Tai, Ph.D.
- Jennifer Villani, Ph.D.
- Tracy Waldeck, Ph.D.
- Susan Weiss, Ph.D.
- Tisha Wiley, Ph.D.

OTHER STAFF AWARDS

The NIDA Intramural Research Program (IRP) **Animal Care Program** received a ranking of "full accreditation" from the AAALAC International Council following their site visit to the IRP.

Jeremiah Bertz, Ph.D., IRP, received a Fellows Award for Research Excellence (FARE award).

Alessandro Bonifazi, Ph.D., IRP, received the NIDA-IRP Post-doctoral Mentoring Award in May 2019.

Chloe Jordan, Ph.D., IRP, received a Center for Compulsive Behaviors Fellowship in May 2019.

Brenton Laing, Ph.D., IRP, received a 2019 NIDA Outstanding Poster Award.

Gerald McLaughlin, Ph.D., Chief of the Scientific Review Branch at NIDA, Division of Extramural Research, was elected to the Board of Directors of NIH's Foundation for Advanced Education in the Sciences (FAES). FAES conducts advanced educational programs and supporting activities to promote the productivity and attractiveness of professional life on the NIH campuses.

Daria Piacentino, M.D., Ph.D., M.Sc., IRP, received the American Society of Clinical Psychopharmacology (ASCP) New Investigator Award.

Sarah Sarsfield, M.S., IRP, received a 2019 KGS Distinguished Achievement Award for her experimental skills and outstanding contributions to all research projects in the lab.

Justin Siemian, Ph.D., IRP, received a 2019 NIDA Outstanding Poster Award and a Fellows Award for Research Excellence (FARE Award).

STAFF CHANGES

New Staff

Lori Ducharme, Ph.D., re-joined the staff of the Services Research Branch as a Health Scientist Administrator. Lori has been a program officer at NIH since 2008, having worked at both NIDA and NIAAA. She oversees a portfolio of research, small business, and training grants that explore ways to increase the adoption and sustained use of evidence-based treatments, enhance the integration of addiction treatment in general medical settings, improve service access and utilization, and build organizational linkages between the criminal justice and public health systems. While at NIAAA, she led the development of the Institute's Alcohol Treatment Navigator®, an online resource offering a strategy to help individuals find evidence-based alcohol treatment services. Prior to joining NIH, she worked in both academic and contract research settings, studying the evolution of the U.S. addiction treatment system in response to changes in financing, regulation, and the introduction of novel medications and behavioral therapies. Lori received her Ph.D. in sociology from the University of Georgia.

Yvonne Ferguson, Ph.D., M.P.H., joined the NIDA Scientific Review Branch in June 2019. Yvonne joins our review team with a great deal of experience, as she previously served as Scientific Review Officer for the Dissemination and Implementation Research in Health Study Section and other special emphasis panels at the Centers for Scientific Review. Her research interests include health disparities, dissemination and implementation science, HIV/AIDS, global health, women's health, health prevention, process and outcome evaluation, and community-engaged research. Yvonne was also a W.K. Kellogg Post-Doctoral Health Scholar at UNC Chapel Hill with an emphasis on HIV/AIDS research, and she was a Service Fellow with the HHS Office of Women's Health. Her master's and Ph.D. degrees are from UNC Chapel Hill in Health Behavior.

Lennin Greenwood joined the NIDA Grants Management Branch in June 2019 as a Senior Grants Management Specialist. Lennin brings approximately 12 years in grants management experience from NHLBI, NIGMS, and NIST. Lennin earned a Bachelor of Arts degree in English from the Stevenson University and a Master of Business Administration degree from the University of Scranton.

Staff Departures

After 13 years at NIDA, **Linda Moore** has accepted a new position with the U.S. Department of Health and Human Services, Food and Drug Administration, Office of Strategic Programs, Administrative Management Team in the Center for Drug Evaluation and research located in Silver Spring, MD, as an Administrative Officer. She will be managing the telework program, the Integrated Time and Attendance System, the credit card program, as well as staff travel, and other assigned duties.

In Memoriam

Ahmed Elkashef, M.D., former NIDA staff member, passed away on Monday, August 5, 2019. A psychiatrist by training, he served at NIDA from 1997–2010 as Chief of the Clinical Medical Branch. Prior to that, he was a senior staff fellow at NIMH, focusing on schizophrenia research. Ahmed contributed as an author to dozens of peer-reviewed journal articles and received a variety of medical and academic awards. He completed his residency in psychiatry at the W.S. Hall Psychiatric Institute at the University of South Carolina in Columbia, and at the University of Maryland Medical School in Baltimore. His teaching experience includes 10 years as an assistant clinical professor of psychiatry at George Washington University in Washington, DC.


NIH
National Institute
on Drug Abuse