



DIRECTOR'S REPORT

————— to the —————
National Advisory Council on Drug Abuse
————— September 2016 —————

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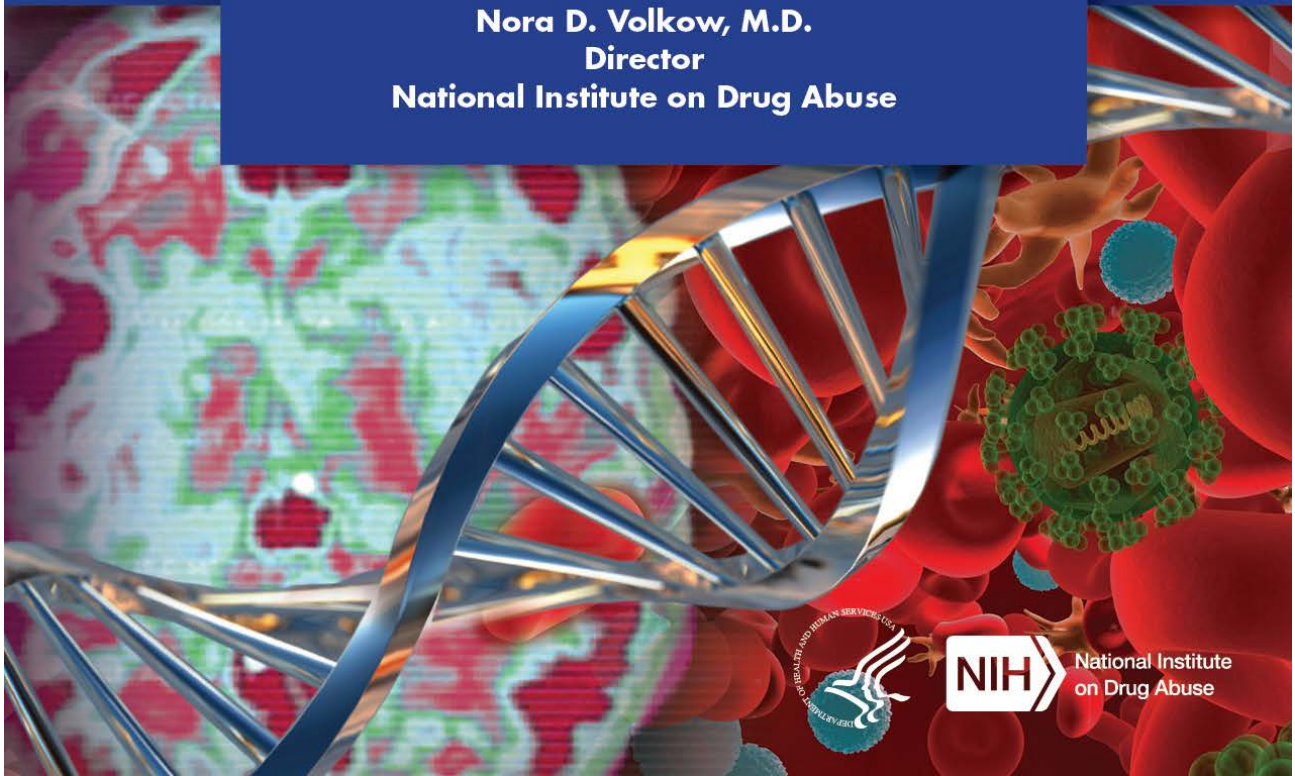


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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Endocannabinoid Modulation of Orbitostriatal Circuits Gates Habit Formation Gremel CM, Chancey JH, Atwood BK, Luo G, Neve R, Ramakrishnan C, Deisseroth K, Lovinger DM, Costa RM. *Neuron*. 2016 Jun 15;90(6):1312-24. doi: 10.1016/j.neuron.2016.04.043. Epub 2016 May 26. Everyday function demands efficient and flexible decision-making that allows for habitual and goal-directed action control. An inability to shift has been implicated in disorders with impaired decision-making, including obsessive-compulsive disorder and addiction. Despite this, our understanding of the specific molecular mechanisms and circuitry involved in shifting action control remains limited. Here the authors identify an endogenous molecular mechanism in a specific cortical-striatal pathway that mediates the transition between goal-directed and habitual action strategies. Deletion of cannabinoid type 1 (CB1) receptors from cortical projections originating in the orbital frontal cortex (OFC) prevents mice from shifting from goal-directed to habitual instrumental lever pressing. Activity of OFC neurons projecting to dorsal striatum (OFC-DS) and, specifically, activity of OFC-DS terminals is necessary for goal-directed action control. Lastly, CB1 deletion from OFC-DS neurons prevents the shift from goal-directed to habitual action control. These data suggest that the emergence of habits depends on endocannabinoid-mediated attenuation of a competing circuit controlling goal-directed behaviors.

Cocaine Cues Retain Silent Traces Of An Excitatory History After Conversion Into Conditioned Inhibitors: 'The Ghost In The Addict' Weiss SJ, Kearns DN. *Behav Pharmacol*. 2016; 27(2-3 Spec Issue): 293-300.

The present experiment investigated the extent to which the A+/AB- conditioned inhibition procedure could counteract an excitatory drug-related conditioning history. In two groups of rats, a light stimulus was established as a signal for the absence of cocaine. For the History group, the light had previously been a discriminative stimulus (S) that occasioned cocaine self-administration and could thus be classified as a cocaine excitor. In comparison, the No-History group first encountered the light during conditioned inhibition training. During conditioned inhibition training, both groups self-administered cocaine during tone as well as during click Ss, whereas drug seeking was eliminated in click-plus-light, wherein cocaine was not available (A+/AB-). Drug seeking was essentially eliminated in both groups. Nevertheless, on a summation test the light reduced cocaine seeking occasioned by the tone S by 95% in the No-History group, but by less than 50% in the History group. This summation test result showed that the effects of a drug-related history persisted even after the light was converted into an effective conditioned inhibitor on the training baseline through the powerful A+/AB- procedure. Future research should seek procedures that produce even stronger conditioned inhibition that eliminates such residual 'silent' drug excitation, the 'ghost in the addict'.

TRIBE: Hijacking An RNA-Editing Enzyme To Identify Cell-Specific Targets Of RNA-Binding Proteins McMahon AC, Rahman R, Jin H, Shen JL, Fieldsend A, Luo W, Rosbash M. *Cell*. 2016; 165(3): 742-753.

RNA transcripts are bound and regulated by RNA-binding proteins (RBPs). Current methods for identifying in vivo targets of an RBP are imperfect and not amenable to examining small numbers of cells. To address these issues, the authors developed TRIBE (targets of RNA-binding proteins identified by editing), a technique that couples an RBP to the catalytic domain of the *Drosophila*

RNA-editing enzyme ADAR and expresses the fusion protein in vivo. RBP targets are marked with novel RNA editing events and identified by sequencing RNA. The authors have used TRIBE to identify the targets of three RBPs (Hrp48, dFMR1, and NonA). TRIBE compares favorably to other methods, including CLIP, and they have identified RBP targets from as little as 150 specific fly neurons. TRIBE can be performed without an antibody and in small numbers of specific cells.

Excision Of HIV-1 DNA By Gene Editing: A Proof-of-concept In Vivo Study Kaminski R, Bella R, Yin C, Otte J, Ferrante P, Gendelman HE, Li H, Booze R, Gordon J, Hu W, Khalili K. *Gene Ther.* 2016.

A CRISPR/Cas9 gene editing strategy has been remarkable in excising segments of integrated HIV-1 DNA sequences from the genome of latently infected human cell lines and by introducing InDel mutations, suppressing HIV-1 replication in patient-derived CD4⁺ T-cells, ex vivo. Here, the authors employed a short version of the Cas9 endonuclease, saCas9, together with a multiplex of guide RNAs (gRNAs) for targeting the viral DNA sequences within the 5'-LTR and the Gag gene for removing critically important segments of the viral DNA in transgenic mice and rats encompassing the HIV-1 genome. Tail-vein injection of transgenic mice with a recombinant Adeno-associated virus 9 (rAAV9) vector expressing saCas9 and the gRNAs, rAAV:saCas9/gRNA, resulted in the cleavage of integrated HIV-1 DNA and excision of a 978 bp DNA fragment spanning between the LTR and Gag gene in the spleen, liver, heart, lung and kidney as well as in the circulating lymphocytes. Retro-orbital inoculation of rAAV9:saCas9/gRNA in transgenic rats eliminated a targeted segment of viral DNA and substantially decreased the level of viral gene expression in circulating blood lymphocytes. The results from the proof-of-concept studies, for the first time, demonstrate the in vivo eradication of HIV-1 DNA by CRISPR/Cas9 on delivery by an rAAV9 vector in a range of cells and tissues that harbor integrated copies of viral DNA. *Gene Therapy* advance online publication, 19 May 2016; doi:10.1038/gt.2016.41.

ML314: A Biased Neurotensin Receptor Ligand For Methamphetamine Abuse Barak LS, Bai Y, Peterson S, Evron T, Urs NM, Peddibhotla S, Hedrick MP, Hershberger P, Maloney PR, Chung TDY, Rodriguiz RM, Wetsel WC, Thomas JB, Hanson GR, Pinkerton AB, Caron MG. *ACS Chem Biol.* 2016; 11(7): 1880-1890.

Pharmacological treatment for methamphetamine addiction will provide important societal benefits. Neurotensin receptor NTR1 and dopamine receptor distributions coincide in brain areas regulating methamphetamine-associated reward, and neurotensin peptides produce behaviors opposing psychostimulants. Therefore, undesirable methamphetamine-associated activities should be treatable with druggable NTR1 agonists, but no such FDA-approved therapeutics exist. The authors address this limitation with proof-of-concept data for ML314, a small-molecule, brain penetrant, β -arrestin biased, NTR1 agonist. ML314 attenuates amphetamine-like hyperlocomotion in dopamine transporter knockout mice, and in C57BL/6J mice it attenuates methamphetamine-induced hyperlocomotion, potentiates the psychostimulant inhibitory effects of a ghrelin antagonist, and reduces methamphetamine-associated conditioned place preference. In rats, ML314 blocks methamphetamine self-administration. ML314 acts as an allosteric enhancer of endogenous neurotensin, unmasking stoichiometric numbers of hidden NTR1 binding sites in transfected-cell membranes or mouse striatal membranes, while additionally supporting NTR1 endocytosis in cells in the absence of NT peptide. These results indicate ML314 is a viable, preclinical lead for methamphetamine abuse treatment and support an allosteric model of G protein-coupled receptor signaling.

EPIDEMIOLOGY RESEARCH

Predictors Of Transition To Heroin Use Among Initially Non-opioid Dependent Illicit Pharmaceutical Opioid Users: A Natural History Study

Carlson RG, Nahhas RW, Martins SS, Daniulaityte R. Drug Alcohol Depend. 2016; 160(3): 127-134.

Increases in illicit pharmaceutical opioid (PO) use have been associated with risk for transition to heroin use. The authors identify predictors of transition to heroin use among young, illicit PO users with no history of opioid dependence or heroin use at baseline. Respondent-driven sampling recruited 383 participants; 362 returned for at least one biannual structured interview over 36 months. Cox regression was used to test for associations between lagged predictors and hazard of transition to heroin use. Potential predictors were based on those suggested in the literature. The authors also computed population attributable risk (PAR) and the rate of heroin transition. Over 36 months, 27 (7.5%) participants initiated heroin use; all were white, and the rate of heroin initiation was 2.8% per year (95% CI=1.9%-4.1%). Mean length of PO at first reported heroin use was 6.2 years (SD=1.9). Lifetime PO dependence (AHR=2.39, 95% CI=1.07-5.48; PAR=32%, 95% CI=2% to 64%), early age of PO initiation (AHR=3.08, 95% CI=1.26-7.47; PAR=30%, 95% CI=2%-59%), using illicit POs to get high but not to self-medicate a health problem (AHR=4.83, 95% CI=2.11-11.0; PAR=38%, 95% CI=12%-65%), and ever using PO non-orally most often (AHR=6.57, 95% CI=2.81-17.2; PAR=63%, 95% CI=31%-86%) were significant predictors. This is one of the first prospective studies to test observations from previous cross-sectional and retrospective research on the relationship between illicit PO use and heroin initiation among young, initially non-opioid dependent PO users. The results provide insights into targets for the design of urgently needed prevention interventions.

The Potential That Electronic Nicotine Delivery Systems Can Be A Disruptive Technology: Results From A National Survey

Pechacek TF, Nayak P, Gregory KR, Weaver SR, Eriksen MP. Nicotine Tob Res. 2016; (5).

This study evaluates the reasons for use and acceptance of Electronic Nicotine Delivery Systems (ENDS) among current and former cigarette smokers to assess if ENDS may become a satisfying alternative to cigarettes. Data are from a national probability sample of 5717 US adults, surveyed June-November 2014. The survey contained questions on awareness, usage, and reasons for use of traditional and novel tobacco products. The analytic sample was current and former smokers who ever used ENDS (n = 729) and was divided into four mutually exclusive categories. Among the 585 current smokers, 337 were no longer using ENDS ("E-Cig Rejecters"), and 248 were continuing to use both ENDS and cigarettes ("E-Cig Dual Users"). Among 144 former cigarette smokers, 101 were non-recent users of ENDS ("Quit All Products"), and 43 were continuing to use ENDS exclusively ("Switchers"). Former smokers (the "Switchers") report finding ENDS a satisfying alternative to regular cigarettes, with only 15.8% (95% confidence interval [CI] 4.4-27.1) rating ENDS as less enjoyable than regular cigarettes. However, greater than fivefold more current smokers did not find them satisfying and stopped using them (77.3%; 95% CI 72.1-82.4 of "E-Cig Rejecters" rated ENDS as less enjoyable). Being less harmful was the most highly rated reason for continuing to use ENDS among "Switchers." Most (80.9%) "Switchers" reported that ENDS helped them quit cigarettes. Since many current smokers who have tried ENDS reject them as a satisfying alternative to regular cigarettes, ENDS will not replace regular cigarettes unless they improve. Since about one-half of recent former smokers are trying ENDS with about one-fourth continuing to use them, and many reporting that these products have helped them quit regular cigarettes, the potential impact of ENDS on population quit rates deserves continued surveillance. However, since most current smokers who have tried ENDS reject them as a satisfying alternative to regular cigarettes,

the potential of ENDS becoming a disruptive technology replacing regular cigarettes remains uncertain. ENDS need to improve as a satisfying alternative or the attractiveness and appeal of the regular cigarette must be degraded to increase the potential of ENDS replacing regular cigarettes.

[The Rearing Environment and Risk For Drug Abuse: A Swedish National High-risk Adopted and Not Adopted Co-sibling Control Study](#) Kendler KS, Ohlsson H, Sundquist K, Sundquist J. *Psychol Med.* 2016; 46(7): 1359-1366.

Although drug abuse (DA) is strongly familial, with important genetic influences, we need to know more about the role of rearing environment in the risk for DA. To address this question, the authors utilized a high-risk adopted and non-adopted co-sibling control design. High-risk offspring had one or more biological parents registered for DA, alcohol use disorders or criminal behavior. Using Swedish registries, the authors identified 1161 high-risk full-sibships and 3085 high-risk half-sibships containing at least one member who was adopted-away and one member who was not. Registration for DA was via national criminal, medical and pharmacy registers. In Sweden, adoptive families are screened to provide high-quality rearing environment for adoptees. Controlling for parental age at birth and gender (and, in half-siblings, high-risk status of the other parent), risk for DA was substantially lower in the full- and half-siblings who were adopted v. not adopted [hazard ratios and 95% confidence intervals: 0.55 (0.45-0.69) and 0.55 (95% CI 0.48-0.63), respectively]. The protective effect of adoption on risk for DA was significantly stronger in the full- and half-sibling pairs with very high familial liability (two high-risk parents) and significantly weaker when the adoptive family was broken by death or divorce, or contained a high-risk parent. In both full- and half-sibling pairs, we found replicated evidence that rearing environment strongly impacts on risk for DA. High-quality rearing environments can substantively reduce risk for DA in those at high genetic risk.

PREVENTION RESEARCH

[Preliminary Evidence Of the Impact Of Early Childhood Maltreatment and A Preventive Intervention On Neural Patterns Of Response Inhibition In Early Adolescence](#) Jankowski KF, Bruce J, Beauchamp KG, Roos LE, Moore 3rd, WE, Fisher PA. *Dev Sci.* 2016; (4)7.

Maltreated youths in foster care often experience negative developmental and psychological outcomes, which have been linked with poor response inhibition. Recent evidence suggests that childhood maltreatment is also associated with alterations in the neural circuitry underlying response inhibition. However, a burgeoning line of research has begun to explore the mitigating effects of preventive interventions on neural functioning. The current study used event-related functional magnetic resonance imaging to explore the impact of early childhood maltreatment and a preventive intervention on response inhibition in early adolescence. Thirty-six demographically similar adolescents (ages 9-14 years) completed a Go/NoGo task. The sample included nonmaltreated adolescents (n = 14) and maltreated adolescents who were in foster care as preschoolers and randomly assigned to receive services as usual (n = 11) or a preventive intervention, Multidimensional Treatment Foster Care for Preschoolers (n = 11). The groups demonstrated similar behavioral performance but significantly different neural patterns. The maltreated adolescents who received services as usual demonstrated subcortical hypoactivity during successful response inhibition and subcortical hyperactivity during unsuccessful response inhibition. In contrast, the nonmaltreated adolescents and maltreated adolescents who received the intervention exhibited strikingly similar neural patterns during successful response inhibition, but the maltreated adolescents who received the intervention demonstrated prefrontal hypoactivity during unsuccessful response inhibition. These findings offer preliminary evidence that early

childhood maltreatment alters the neural patterns underlying response inhibition in early adolescence and that participating in a preventive intervention could mitigate maltreatment-related effects on these neural systems.

[Exposure To Graphic Warning Labels On Cigarette Packages: Effects On Implicit and Explicit Attitudes Towards Smoking Among Young Adults](#) Macy JT, Chassin L, Presson CC, Yeung E. *Psychol Health*. 2016; 31(3): 349-363.

The aim of this study was to test the effect of exposure to the US Food and Drug Administration's proposed graphic images with text warning statements for cigarette packages on implicit and explicit attitudes towards smoking. A two-session web-based study was conducted with 2192 young adults 18-25-years-old. During session one, demographics, smoking behaviour, and baseline implicit and explicit attitudes were assessed. Session two, completed on average 18 days later, contained random assignment to viewing one of three sets of cigarette packages, graphic images with text warnings, text warnings only, or current US Surgeon Generals text warnings. Participants then completed post-exposure measures of implicit and explicit attitudes. ANCOVAs tested the effect of condition on the outcomes, controlling for baseline attitudes. Smokers who viewed packages with graphic images plus text warnings demonstrated more negative implicit attitudes compared to smokers in the other conditions ($p = .004$). For the entire sample, explicit attitudes were more negative for those who viewed graphic images plus text warnings compared to those who viewed current US Surgeon General's text warnings ($p = .014$), but there was no difference compared to those who viewed text-only warnings. Graphic health warnings on cigarette packages can influence young adult smokers'; implicit attitudes towards smoking.

[Cumulative Stress In Childhood Is Associated With Blunted Reward-related Brain Activity In Adulthood](#) Hanson JL, Albert D, Iselin A-MR, Carré JM, Dodge KA, Hariri AR. *Soc Cogn Affect Neurosci*. 2016; 11(3): 405-412.

Early life stress (ELS) is strongly associated with negative outcomes in adulthood, including reduced motivation and increased negative mood. The mechanisms mediating these relations, however, are poorly understood. The authors examined the relation between exposure to ELS and reward-related brain activity, which is known to predict motivation and mood, at age 26, in a sample followed since kindergarten with annual assessments. Using functional neuroimaging, they assayed individual differences in the activity of the ventral striatum (VS) during the processing of monetary rewards associated with a simple card-guessing task, in a sample of 72 male participants. They examined associations between a cumulative measure of ELS exposure and VS activity in adulthood. They found that greater levels of cumulative stress during childhood and adolescence predicted lower reward-related VS activity in adulthood. Extending this general developmental pattern, they found that exposure to stress early in development (between kindergarten and grade 3) was significantly associated with variability in adult VS activity. These results provide an important demonstration that cumulative life stress, especially during this childhood period, is associated with blunted reward-related VS activity in adulthood. These differences suggest neurobiological pathways through which a history of ELS may contribute to reduced motivation and increased negative mood.

[Antisocial Peer Affiliation and Externalizing Disorders In the Transition From Adolescence To Young Adulthood: Selection Versus Socialization Effects](#) Samek DR, Goodman RJ, Erath SA, McGue M, Iacono WG. *Dev Psychol*. 2016; 52(5): 813-823.

Prior research has demonstrated both socialization and selection effects for the relationship between antisocial peer affiliation and externalizing problems in adolescence. Less research has evaluated

such effects postadolescence. In this study, a cross-lagged panel analysis was used to evaluate the extent of socialization (i.e., the effect of antisocial peer affiliation on subsequent externalizing disorders) and selection (i.e., the effect of externalizing disorders on subsequent antisocial peer affiliation) in the prospective relationships between antisocial peer affiliation and externalizing disorders from adolescence through young adulthood. Data from a community sample of 2,769 individuals (52% female) with assessments at ages 17, 20, 24, and 29 were used. Analyses with a latent externalizing measure (estimated using clinical symptom counts of nicotine dependence, alcohol use disorder, illicit drug use disorder, and adult antisocial behavior) and self-reported antisocial peer affiliation revealed significantly stronger socialization effects from age 17 to 20, followed by significantly stronger selection effects from age 20 to 24 and 24 to 29. To better understand the impact of college experience, moderation by college status was evaluated at each developmental transition. Results were generally consistent for those who were in or were not in college. Results suggest selection effects are more important in later developmental periods than earlier periods, particularly in relation to an overall liability toward externalizing disorders, likely due to more freedom in peer selection postadolescence.

How Does The Fast Track Intervention Prevent Adverse Outcomes In Young Adulthood?

Sorensen LC, Dodge KA, Conduct Problems Prevention Research Group. *Child Dev.* 2016; 87(2): 429-445.

Numerous studies have shown that childhood interventions can foster improved outcomes in adulthood. Less well understood is precisely how—that is, through which developmental pathways—these interventions work. This study assesses mechanisms by which the Fast Track project (n = 891), a randomized intervention in the early 1990s for high-risk children in four communities (Durham, NC; Nashville, TN; rural PA; and Seattle, WA), reduced delinquency, arrests, and general and mental health service utilization in adolescence through young adulthood (ages 12-20). A decomposition of treatment effects indicates that about a third of Fast Track’s impact on later crime outcomes can be accounted for by improvements in social and self-regulation skills during childhood (ages 6-11), such as prosocial behavior, emotion regulation, and problem solving. These skills proved less valuable for the prevention of general and mental health problems.

TREATMENT RESEARCH

Cocaine Hydrolase Gene Transfer Demonstrates Cardiac Safety and Efficacy Against Cocaine-Induced QT Prolongation In Mice

Murthy V, Reyes S, Geng L, Gao Y, Brimijoin S. *J Pharmacol Exp Ther.* 2016; 356(3): 720-725.

Cocaine addiction is associated with devastating medical consequences, including cardiotoxicity and risk-conferring prolongation of the QT interval. Viral gene transfer of cocaine hydrolase engineered from butyrylcholinesterase offers therapeutic promise for treatment-seeking drug users. Although previous preclinical studies have demonstrated benefits of this strategy without signs of toxicity, the specific cardiac safety and efficacy of engineered butyrylcholinesterase viral delivery remains unknown. Here, telemetric recording of electrocardiograms from awake, unrestrained mice receiving a course of moderately large cocaine doses (30 mg/kg, twice daily for 3 weeks) revealed protection against a 2-fold prolongation of the QT interval conferred by pretreatment with cocaine hydrolase vector. By itself, this prophylactic treatment did not affect QT interval duration or cardiac structure, demonstrating that viral delivery of cocaine hydrolase has no intrinsic cardiac toxicity and, on the contrary, actively protects against cocaine-induced QT prolongation.

[Adverse Effects Of Synthetic Cannabinoids: Management Of Acute Toxicity and Withdrawal](#)

Cooper ZD. *Curr Psychiatry Rep.* 2016; 18(5): 52.

Although several chemical structural classes of synthetic cannabinoids (SCs) were recently classified as Schedule I substances, rates of use and cases of serious toxic effects remain high. While case reports and media bring attention to severe SC toxicity, daily SC use resulting in dependence and withdrawal is a significant concern that is often overlooked when discussing the risks of these drugs. There is a rich literature on evidence-based approaches to treating substance use disorders associated with most abused drugs, yet little has been published regarding how to best treat symptoms related to SC dependence given its recency as an emerging clinically significant issue. This review provides a background of the pharmacology of SCs, recent findings of adverse effects associated with both acute intoxication and withdrawal as a consequence of daily use, and treatment approaches that have been implemented to address these issues, with an emphasis on pharmacotherapies for managing detoxification. In order to determine prevalence of use in cannabis smokers, a population at high risk for SC use, the author obtained data on demographics of SC users, frequency of use, and adverse effects over a 3.5-year period (2012-2015) in the New York City metropolitan area, a region with a recent history of high SC use. While controlled studies on the physiological and behavioral effects of SCs are lacking, it is clear that risks associated with using these drugs pertain not only to the unpredictable and severe nature of acute intoxication but also to the effects of long-term, chronic use. Recent reports in the literature parallel findings from this survey, indicating that there is a subset of people who use SCs daily. Although withdrawal has not been systematically characterized and effective treatments have yet to be elucidated, some symptom relief has been reported with benzodiazepines and the atypical antipsychotic, quetiapine. Given the continued use and abuse of SCs, empirical studies characterizing (1) SCs acute effects, (2) withdrawal upon cessation of use, and (3) effective treatment strategies for SC use disorder are urgently needed.

[1,4-Diphenalkylpiperidines: A New Scaffold For the Design Of Potent Inhibitors Of the Vesicular Monoamine Transporter-2](#)

Nickell JR, Culver JP, Jangananati V, Zheng G, Dwoskin LP, Crooks PA. *Bioorg Med Chem Lett.* 2016; 26(13): 2997-3000.

A series of 1,4-diphenalkylpiperidine analogs were synthesized and evaluated for their affinity and inhibitory potency at the [(3)H]dihydrotrabenzazine (DTBZ) binding site and [(3)H]dopamine (DA) uptake site on the vesicular monoamine transporter-2 (VMAT2). Results revealed that translocation of the phenethyl side chains of lobelane from C2 and C6 to C1 and C4 around the central piperidine ring slightly reduces affinity and inhibitory potency at VMAT2 with respect to lobelane. However, methoxy and fluoro-substitution of either phenyl ring of these 1,4-diphenethyl analogs afforded VMAT2 inhibition comparable or higher (5-fold) affinity at the DTBZ binding and DA uptake sites relative to lobelane, whereas replacement of the 4-phenethyl moiety in these analogs with a 4-phenmethyl moiety markedly reduced affinity for the DTBZ binding and DA uptake sites by 3- and 5-fold, respectively. Among the twenty five 1,4-diphenethylpiperidine analogs evaluated, compounds containing a 4-(2-methoxyphenethyl) moiety exhibited the most potent inhibition of DTBZ binding and vesicular DA uptake. From this subgroup, analogs 8h, 8j and 8m exhibited K_i values of 9.3nM, 13nM and 13nM, respectively, for inhibition of [(3)H]DA uptake by VMAT2, and represent some of the most potent inhibitors of VMAT2 function reported thus far.

An Adaptation Of Motivational Interviewing Increases Quit Attempts In Smokers With Serious Mental Illness Steinberg ML, Williams JM, Stahl NF, Budsock PD, Cooperman NA. *Nicotine Tob Res.* 2016; 18(3): 243-250.

Smokers with serious mental illness (SMI) have a high smoking prevalence and a low quit rate. Motivational interviewing (MI) is an empirically supported approach for addressing substance use disorders and may motivate smokers with SMI to quit. The authors randomized smokers (N = 98) with SMI to receive a single 45-minute session of (1) MI with personalized feedback or (2) interactive education. They hypothesized that participants receiving the MI intervention would be more likely to follow-up on a referral for tobacco dependence treatment, to make a quit attempt, and to quit smoking than those receiving the interactive educational intervention. Smokers receiving an MI intervention were significantly more likely to make a quit attempt by the 1-month follow-up (34.7% vs. 14.3%; OR = 4.39 [95% CI = 1.44 to 13.34], P = .009); however, these quit attempts did not translate into abstinence. In addition, 32.7% of those receiving MI followed-up on a referral for tobacco dependence treatment (vs. 20.4% receiving interactive education; OR = 2.02 [95% CI = 0.76 to 3.55], P = .157). MI Treatment Integrity Code ratings indicated that the interventions were easily distinguishable from each other and that MI was delivered with proficiency. Despite the intervention's brevity, participants reported high levels of therapeutic alliance with their therapist. A brief adaptation of MI with personalized feedback appears to be a promising approach for increasing quit attempts in smokers with SMI, but future research is required to determine how to best help smokers with SMI to attain sustained abstinence.

Anhedonia, Depression, Anxiety, and Craving In Opiate Dependent Patients Stabilized On Oral Naltrexone Or An Extended Release Naltrexone Implant Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Wahlgren V, Tsoy-Podosenin M, Bushara N, Burakov A, Masalov D, Romanova T, Tyurina A, Palatkin V, Yaroslavtseva T, Pecoraro A, Woody G. *Am J Drug Alcohol Abuse.* 2016 Jul 19:1-7.

Naltrexone is a μ -opioid receptor antagonist that blocks opioid effects. Craving, depression, anxiety, and anhedonia are common among opioid dependent individuals and concerns have been raised that naltrexone increases them due to blocking endogenous opioids. Here, we present data that address these concerns. The objective of this study was to assess the relationship between affective responses and naltrexone treatment. Opioid dependent patients (N = 306) were enrolled in a three cell (102ss/cell) randomized, double blind, double dummy, placebo-controlled 6-month trial comparing extended release implantable naltrexone with oral naltrexone and placebo (oral and implant). Monthly assessments of affective responses used a Visual Analog Scale for opioid craving, the Beck Depression Inventory, Spielberger Anxiety Test, and the Ferguson and Chapman Anhedonia Scales. Between-group outcomes were analyzed using mixed model analysis of variance (Mixed ANOVA) and repeated measures and the Tukey test for those who remained and treatment and did not relapse, and between the last measure before dropout with the same measure for those remaining in treatment. Depression, anxiety, and anhedonia were elevated at baseline but reduced to normal within the first 1-2 months for patients who remained in treatment and did not relapse. Other than a slight increase in two anxiety measures at week two, there were no significant between-group differences prior to treatment dropout. These data do not support concerns that naltrexone treatment of opioid dependence increases craving, depression, anxiety or anhedonia.

Modafinil and Sleep Architecture In An Inpatient-outpatient Treatment Study Of Cocaine Dependence

Morgan PT, Angarita GA, Canavan S, Pittman B, Oberleitner L, Malison RT, Mohsenin V, Hodges S, Easton C, McKee S, Bessette A, Forselius E. Drug Alcohol Depend. 2016; 160: 49-56.

The aim of this study was to determine whether the increase in slow-wave sleep associated with modafinil treatment in chronic cocaine users mediates improved clinical outcomes. Fifty-seven cocaine dependent participants were randomized to receive modafinil 400mg or placebo daily during a period of inpatient treatment followed by six weeks of outpatient treatment. Participants underwent polysomnographic sleep recording during inpatient treatment prior to and after starting modafinil. Outpatient treatment consisted of weekly cognitive behavioral therapy. Contingency management was used to promote participation in treatment and research demands, including thrice weekly visits during the outpatient phase for urine toxicology screens and other assessments. The primary clinical outcome was the percent of urine toxicology screens that were negative for cocaine. Modafinil treatment was associated with a higher mean percentage (52% vs. 26%) of cocaine-free urine screens ($p=0.02$) and an increase in N3 sleep time ($p=0.002$). The change in N3 sleep time mediated the higher rate of cocaine-free urine screens. Modafinil treatment was also associated with more consecutive days abstinent during outpatient treatment, greater survival of abstinence, higher daily rates of abstinence, and less sleep degradation typically associated with abstinence from chronic cocaine use. Morning-dosed modafinil improves slow-wave sleep in abstinent cocaine users in the inpatient setting, and this effect is a statistical mediator of improved clinical outcomes associated with continued modafinil treatment. The high rates of abstinence achieved in this trial suggest that promoting healthy sleep physiology in an inpatient setting may be important in the effective treatment of cocaine dependence.

"I Kicked The Hard Way. I Got Incarcerated." Withdrawal From Methadone During Incarceration and Subsequent Aversion To Medication Assisted Treatments

Maradiaga JA, Nahvi S, Cunningham CO, Sanchez J, Fox AD. J Subst Abuse Treat. 2016; 62: 49-54.

Incarceration is a common experience for individuals with opioid use disorder, including those receiving medication assisted treatments (MAT), such as buprenorphine or methadone. In the United States, MAT is rarely available during incarceration. The authors were interested in whether challenges with methadone maintenance treatment during incarceration affected subsequent attitudes toward MAT following release. They conducted semi-structured interviews with 21 formerly incarcerated individuals with opioid use disorder in community substance abuse treatment settings. Interviews were audio recorded, transcribed, and analyzed using a grounded theory approach. Themes that emerged upon iterative readings of transcripts were discussed by the research team. The three main themes relating to methadone were: 1) rapid dose reduction during incarceration; 2) discontinuity of methadone during incarceration; and 3) post incarceration aversion to methadone. Participants who received methadone maintenance treatment prior to incarceration reported severe and prolonged withdrawal symptoms from rapid dose reductions or disruption of their methadone treatment during incarceration. The severe withdrawal during incarceration contributed to a subsequent aversion to methadone and adversely affected future decisions regarding reengagement in MAT. Though MAT is the most efficacious treatment for opioid use disorder, current penal policy, which typically requires cessation of MAT during incarceration, may dissuade individuals with opioid use disorder from considering and engaging in MAT after release from incarceration.

Intranasal Buprenorphine Alone and In Combination With Naloxone: Abuse Liability and Reinforcing Efficacy In Physically Dependent Opioid Abusers Walsh SL, Nuzzo PA, Babalonis S, Casselton V, Lofwall MR. *Drug Alcohol Depend.* 2016; 162: 190-198. Buprenorphine can be abused by the intranasal route. This study sought to examine the relative abuse liability and reinforcing efficacy of intranasal buprenorphine compared to intranasal buprenorphine/naloxone in opioid-dependent individuals. Eleven healthy male and female volunteers physically dependent on short-acting opioids resided as inpatients during participation in this double blind, within subject, placebo-controlled study. Participants were maintained on oxycodone (30mg/q.i.d., p.o.) throughout the 6-week study. Eight pairs of experimental sessions were conducted at ≥ 48 h intervals to examine the pharmacodynamic profile (Sample) and reinforcing efficacy (Self-administration the following day) of intranasal placebo, oxycodone (60mg), buprenorphine (2, 8 & 16mg) and buprenorphine/naloxone (2/0.5, 8/2 & 16/4mg). Subjective, observer-rated and physiological measures were collected to assess the magnitude of opioid agonist and antagonist effects. A progressive ratio self-administration procedure assessed choices for drug versus money. All active doses produced opioid agonist-like effects (e.g., increased ratings of "liking," and miosis) compared to placebo. The effects of buprenorphine and buprenorphine/naloxone were not reliably dose-dependent. Intranasal buprenorphine/naloxone elicited modest and transient opioid withdrawal-like effects in the first hour post-drug administration, while simultaneously blunting or blocking the early onset of agonist effects seen with buprenorphine alone. All active doses of buprenorphine were self-administered more than placebo, but buprenorphine/naloxone doses were not. These data confirm that intranasal buprenorphine/naloxone has deterrent properties related to transient withdrawal effects that likely decrease its desirability for misuse compared to buprenorphine in opioid-dependent individuals maintained on short-acting opioids.

Electronic Cigarette Nicotine Delivery Can Exceed That Of Combustible Cigarettes: A Preliminary Report Ramôa CP, Hiler MM, Spindle TR, Lopez AA, Karaoghlanian N, Lipato T, Breland AB, Shihadeh A, Eissenberg T. *Tob Control.* 2016; 25(e1): e6-9. Electronic cigarettes (ECIGs) aerosolize a liquid that usually contains propylene glycol and/or vegetable glycerine, flavourants and the dependence-producing drug, nicotine, in various concentrations. This laboratory study examined the relationship between liquid nicotine concentration and plasma nicotine concentration and puffing behaviour in experienced ECIG users. Sixteen ECIG-experienced participants used a 3.3-Volt ECIG battery attached to a 1.5-Ohm dual-coil 'cartomiser'; loaded with 1 mL of a flavoured propylene glycol/vegetable glycerine liquid to complete four sessions, at least 2 days apart, that differed by nicotine concentration (0, 8, 18 or 36 mg/mL). In each session, participants completed two 10-puff ECIG-use bouts (30 s puff interval) separated by 60 min. Venous blood was sampled to determine plasma nicotine concentration. Puff duration, volume and average flow rate were measured. Immediately after bout 1, mean plasma nicotine concentration was 5.5 ng/mL (SD=7.7) for 0 mg/mL liquid, with significantly ($p < 0.05$) higher mean concentrations observed for the 8 (mean=17.8 ng/mL, SD=14.6), 18 (mean=25.9 ng/mL, SD=17.5) and 36 mg/mL (mean=30.2 ng/mL; SD=20.0) concentrations; a similar pattern was observed for bout 2. For bout 1, at 36 mg/mL, the mean post- minus pre-bout difference was 24.1 ng/mL (SD=18.3). Puff topography data were consistent with previous results and revealed few reliable differences across conditions. This study demonstrates a relationship between ECIG liquid nicotine concentration and user plasma nicotine concentration in experienced ECIG users. Nicotine delivery from some ECIGs may exceed that of a combustible cigarette. The rationale for this higher level of nicotine delivery is uncertain.

Cue-induced Craving To Paraphernalia and Drug Images In Opioid Dependence McHugh RK, Fulciniti F, Mashhoon Y, Weiss RD. Am J Addict. 2016; 25(2): 105-109.

Stimuli that are repeatedly paired with substance use, such as drug paraphernalia, can themselves elicit drug craving. The aim of this study was to examine whether particular cue types elicit greater craving responses than others among individuals with opioid dependence. Participants seeking inpatient treatment for opioid dependence were recruited for a study of cue-induced craving. This sample (N = 50), included 25 primary heroin users, 20 primary prescription opioid users, and 5 users of heroin and prescription opioids equally. Participants completed a cue reactivity task, in which images of drug-related stimuli were presented on a computer screen, each followed by a question assessing state drug craving. Overall, participants reported higher craving following paraphernalia stimuli relative to drug stimuli. However, this was moderated by opioid type; there was significantly higher craving in response to images of paraphernalia cues in the heroin group, and higher craving in response to drug cues in the prescription opioid group. These findings highlight potential differences in cue reactivity to opioid paraphernalia and drug cues, which appear to be moderated by drug type. Cue-induced craving is an important factor in relapse. This study adds further to the literature on cue-induced craving in opioid dependence, suggesting that craving may vary based on both cue type and opioid type. Future studies designed to discriminate the impact of substance of abuse, route of administration, and cue type will help to further clarify cue-induced craving in this population.

Validation Of Criteria To Guide Prehospital Naloxone Administration For Drug-Related Altered Mental Status Friedman MS, Manini AF. J Med Toxicol. 2016.

The authors aimed to validate previously derived clinical criteria to predict successful prehospital response to naloxone in patients with altered mental status treated by EMS. They hypothesized that prehospital naloxone criteria would have high sensitivity for effective antidote response, but would be underutilized, in patients with drug-related altered mental status (DRAMS). This study was a secondary data analysis of a prospective cohort of acute DRAMS at an urban ED. Naloxone criteria (respiratory rate (RR) <12, miotic pupils, or drug paraphernalia) and mental status, graded by either AVPU (Alert, Verbal, Painful, Unresponsive) or Glasgow Coma Scales, were abstracted from prehospital care reports. Interventions were compared for effective antidote response (EAR), defined as immediate improvement in RR, AVPU, or GCS. EMS transported 249 DRAMS over 17 months (48 % males, mean age 41.5, ALS 33.7 %). Forty-three (17 %) patients met naloxone criteria, of whom 44.2 % received the antidote. Naloxone criteria significantly predicted EAR (OR 7.0, $p < 0.05$) with 83 % sensitivity (95 % CI, 55-95 %). Miotic pupils (OR 20.0, $p < 0.01$) outperformed RR (OR 2.3, $p = \text{NS}$) as the best single criterion with 91 % sensitivity (95 % CI, 62-98 %). This study validates prehospital criteria to guide naloxone administration. In addition, prehospital naloxone was underutilized for DRAMS. Further studies should address potential barriers to prehospital naloxone administration.

Effects Of Progesterone Stimulated Allopregnanolone On Craving and Stress Response In Cocaine Dependent Men and Women Milivojevic V, Fox HC, Sofuoglu M, Covault J, Sinha R. Psychoneuroendocrinology. 2016; 65: 44-53.

Fluctuations in progesterone levels during the menstrual cycle have been shown to affect physiological and subjective effects of cocaine. Furthermore, the authors' laboratory has demonstrated that following drug-cue exposure, cocaine dependent women with high levels of circulating progesterone display lower diastolic and systolic blood pressure responses and report lower levels of anxiety and drug craving compared to cocaine dependent women with low levels of progesterone. In the current study we examined the role of the progesterone derived neuroactive

steroid allopregnanolone (ALLO) on stress arousal, inhibitory control and drug craving in cocaine dependent subjects. Plasma levels of ALLO were measured using GC/MS in 46 treatment-seeking cocaine dependent men and women on day 5 of a 7-day treatment regimen of micronized progesterone (15M/8F) (400mg/day) or placebo (14M/9F) administered in a double blind, randomized manner. As a control, levels of the testosterone derived neurosteroid androstenediol (ADIOL) were also measured. All subjects participated in laboratory sessions on days 5-7 of progesterone/placebo administration in which they were exposed to a series of 5-min personalized guided imagery of either a stressful situation, cocaine use or of a neutral setting and dependent variables including subjective craving, mood, Stroop task as a measure of inhibitory control performance and plasma cortisol were assessed. Participants were grouped by high or low ALLO level and levels of dependent variables compared between ALLO groups. Progesterone relative to placebo significantly increased ALLO levels with no sex differences. There were no effects of micronized progesterone on the testosterone derived ADIOL. Individuals in the high versus the low ALLO group showed decreased levels of cortisol at baseline, and a higher cortisol response to stress; higher positive mood scores at baseline and improved Stroop performance in the drug-cue and stress conditions, and reduced cocaine craving across all imagery conditions. As expected, cocaine dependent individuals administered progesterone showed significantly higher ALLO plasma levels. High levels of ALLO appeared to normalize basal and stress response levels of cortisol, decrease cocaine craving and also contribute to improvements in positive emotion and Stroop performance in response to stress and drug-cue exposures. These findings suggest that the neuroactive steroid ALLO plays a significant role in mediating the positive effects of progesterone on stress arousal, cognitive performance and drug craving in cocaine dependence.

MEDICAL CONSEQUENCES OF DRUG ABUSE RESEARCH

[Engineered Bispecific Antibodies with Exquisite HIV-1-Neutralizing Activity](#) Huang Y, Yu J, Lanzi A, Yao X, Andrews CD, Tsai L, Gajjar MR, Sun M, Seaman MS, Padte NN, Ho DD. Cell 165, 1621–1631, June 16, 2016.

While the search for an efficacious HIV-1 vaccine remains elusive, emergence of a new generation of virus-neutralizing monoclonal antibodies (mAbs) has re-ignited the field of passive immunization for HIV-1 prevention. However, the plasticity of HIV-1 demands additional improvements to these mAbs to better ensure their clinical utility. Here, the authors report engineered bispecific antibodies that are the most potent and broad HIV-neutralizing antibodies to date. One bispecific antibody, 10E8V2.0/iMab, neutralized 118 HIV-1 pseudotyped viruses tested with a mean 50% inhibitory concentration (IC₅₀) of 0.002 mg/mL. 10E8V2.0/iMab also potently neutralized 99% of viruses in a second panel of 200 HIV-1 isolates belonging to clade C, the dominant subtype accounting for ~50% of new infections worldwide. Importantly, 10E8V2.0/iMab reduced virus load substantially in HIV-1-infected humanized mice and also provided complete protection when administered prior to virus challenge. These bispecific antibodies hold promise as novel prophylactic and/or therapeutic agents in the fight against HIV-1.

[Correlates and Longitudinal Renal and Cardiovascular Implications of FGF23 Levels in HIV-Positive Individuals](#) Atta MG, Estrella MM, Fine DM, Zook K, Trujillo JMM, Stein JH, Lucas GM, PLOS ONE DOI:10.1371/journal.pone.0155312 May 13, 2016.

Fibroblast growth factor23 (FGF23), an early marker of kidney dysfunction, is associated with cardiovascular death. Its role in HIV-positive individuals is unknown. The authors measured FGF23 in 100 HIV-negative and 191 HIV-positive nondiabetic adults with normal baseline estimated glomerular filtration rate (GFR). They measured GFR by iohexol annually, albumin

creatinine ratio (ACR) every 6 months, as well as pulse wave velocity, carotid plaque, and carotid intima media thickness (IMT) at baseline and 2 years. Progressive albuminuria was defined as follow-up ACR ≥ 2 -fold than baseline and ≥ 30 mg/g. Regression models assessed associations of FGF23 with baseline factors and longitudinal changes in disease markers. FGF23 levels were similar in HIV serostatus. Among HIV-positive persons, factors independently associated with higher baseline FGF23 levels included female (adjusted ratio of geometric means [95% CI], 1.46 [1.21, 1.76]), serum phosphorus (1.20 [1.03, 1.40]), HCV (1.31 [1.10, 1.56]) and non-suppressed HIV RNA (1.27 [1.01, 1.76]). At baseline, FGF23 was not associated with GFR, albuminuria, carotid plaque, or carotid IMT in cross-sectionally adjusted analysis of HIV-positive individuals. However, higher baseline FGF23 was associated with progressive albuminuria (odds ratio 1.48 [95% CI]: 1.05, 2.08) and a more rapid increase in IMT (13 $\mu\text{m}/\text{year}$, 95% CI, 3, 24). These findings suggest a role for FGF23 in HIV-positive populations in identifying patients at greater risk for cardiovascular and kidney disease.

[Using HIV Sequence and Epidemiologic Data to Assess the Effect of Self-referral Testing for Acute HIV Infection on Incident Diagnoses in San Diego, California](#)

Mehta SR, Murrell B, Anderson CM, Pond SLK, Wertheim JO, Young JA, Freitas L, Richman DD, Mathews WC, Scheffler K, Little SJ, Smith DM. *Clinical Infectious Diseases*® 2016;63(1):101–107.

Because recently infected individuals disproportionately contribute to the spread of human immunodeficiency virus (HIV), the authors evaluated the impact of a primary HIV screening program (the Early Test) implemented in San Diego. The Early Test program used combined nucleic acid and serology testing to screen for primary infection targeting local high-risk individuals. Epidemiologic, HIV sequence, and geographic data were obtained from the San Diego County Department of Public Health and the Early Test program. Poisson regression analysis was performed to determine whether the Early Test program was temporally and geographically associated with changes in incident HIV diagnoses. Transmission chains were inferred by phylogenetic analysis of sequence data. Over time, a decrease in incident HIV diagnoses was observed proportional to the number primary HIV infections diagnosed in each San Diego region ($P < .001$). Molecular network analyses also showed that transmission chains were more likely to terminate in regions where the program was marketed ($P = .002$). Although, individuals in these zip codes had infection diagnosed earlier ($P = .08$), they were not treated earlier ($P = .83$). These findings suggest that early HIV diagnoses by this primary infection screening program probably contributed to the observed decrease in new HIV diagnoses in San Diego, and they support the expansion and evaluation of similar programs.

[Preexposure Prophylaxis Awareness and Use in a Population-Based Sample of Young Black Men Who Have Sex With Men](#)

Khanna AS, Michaels S, Skaathun B, Morgan E, Green K, Young L, Schneider JA, for the uConnect Study Team. *JAMA Internal Medicine* January 2016: 176(1).

In the United States, reducing new human immunodeficiency virus (HIV) infections will require a determined focus on primary HIV prevention among young black men who have sex with men (YBMSM), the only group in the United States where HIV incidence has increased over the past decade. Through 2011, effective clinic-based HIV prevention interventions that target YBMSM have been virtually nonexistent. In 2012, the US Food and Drug Administration approved a preexposure prophylaxis (PrEP) consisting of daily oral tenofovir disoproxil fumarate and emtricitabine. This PrEP has an estimated effectiveness of over 90% and, therefore, an HIV prevention effect potential for several domestic HIV epicenters.

The Population Impact Of Eliminating Homelessness On HIV Viral Suppression Among People Who Use Drugs Marshall BDL, Elston B, Dobrer S, Parashar S, Hogg RS, Montaner JSG, Kerr T, Wood E, Milloy M-J. AIDS 2016; 30:933–941.

The authors sought to estimate the change in viral suppression prevalence if homelessness were eliminated from a population of HIV-infected people who use drugs. This was a community-recruited prospective cohort of HIV-infected people who use drugs in Vancouver, Canada. Behavioural information was collected at baseline and linked to a province-wide HIV/AIDS treatment database. The primary outcome was viral suppression (<50 copies/ml) measured during subsequent routine clinical care. The authors employed an imputation-based marginal modelling approach. First, they used modified Poisson regression to estimate the relationship between homelessness and viral suppression (adjusting for sociodemographics, substance use, addiction treatment, and other confounders). Then, they imputed an outcome probability for each individual while manipulating the exposure (homelessness). Population viral suppression prevalence under realized and ‘housed’ scenarios were obtained by averaging these probabilities across the study population. Bootstrapping was conducted to calculate 95% confidence limits. Of 706 individuals interviewed between January 2005 and December 2013, the majority were men (66.0%), of white race/ethnicity (55.1%), and had a history of injection drug use (93.6%). At first study visit, 223 (31.6%) reported recent homelessness, and 37.8% were subsequently identified as virally suppressed. Adjusted marginal models estimated a 15.1% relative increase [95% confidence interval (CI) 9.0–21.7%) in viral suppression in the entire population – to 43.5% (95% CI 39.4–48.2%) – if all homeless individuals were housed. Among those homeless, eliminating this exposure would increase viral suppression from 22.0 to 40.1% (95% CI 35.1–46.1%), an 82.3% relative increase. The authors conclude that interventions to house homeless, HIV-positive individuals who use drugs could significantly increase population viral suppression. Such interventions should be implemented as a part of renewed HIV/AIDS prevention and treatment efforts.

HIV Infection Itself May Not Be Associated With Subclinical Coronary Artery Disease Among African Americans Without Cardiovascular Symptoms Lai H, Moore R, Celentano DD, Gerstenblith G, Treisman G, Keruly JC, Kickler T, Li J, Chen S, Lai S, Fishman EK. J Am Heart Assoc. 2016; 4(3): e002529.

The key objectives of this study were to examine whether HIV infection itself is associated with subclinical coronary atherosclerosis and the potential contributions of cocaine use and antiretroviral therapies (ARTs) to subclinical coronary artery disease (CAD) in HIV-infected persons. Between June 2004 and February 2015, 1429 African American (AA) adults with/without HIV infection in Baltimore, Maryland, were enrolled in an observational study of the effects of HIV infection, exposure to ART, and cocaine use on subclinical CAD. The prevalence of subclinical coronary atherosclerosis was 30.0% in HIV-uninfected and 33.7% in HIV-infected (P=0.17). Stratified analyses revealed that compared to HIV-uninfected, HIV-infected ART naïve were at significantly lower risk for subclinical coronary atherosclerosis, whereas HIV-infected long-term ART users (≥36 months) were at significantly higher risk. Thus, an overall nonsignificant association between subclinical coronary atherosclerosis and HIV was found. Furthermore, compared to those who were ART naïve, long-term ART users (≥36 months) were at significantly higher risk for subclinical coronary atherosclerosis in chronic cocaine users, but not in those who never used cocaine. Cocaine use was independently associated with subclinical coronary atherosclerosis. Overall, HIV infection, per se, was not associated with subclinical coronary atherosclerosis in this population. Cocaine use was prevalent in both HIV-infected and -uninfected individuals and itself was associated with subclinical disease. In addition, cocaine significantly elevated the risk for ART-associated

subclinical coronary atherosclerosis. Treating cocaine addiction must be a high priority for managing HIV disease and preventing HIV/ART-associated subclinical and clinical CAD in individuals with HIV infection.

SERVICES RESEARCH

Hepatitis C Virus Testing and Treatment Among Persons Receiving Buprenorphine In An Office-Based Program For Opioid Use Disorders Carey KJ, Huang W, Linas BP, Tsui JI. *J Subst Abuse Treat.* 2016; (7)66: 54-59.

In the United States, hepatitis C virus (HCV) infection is primarily spread through injection drug use. There is an urgent need to improve access to care for HCV among persons with opioid use disorders who inject drugs. The purpose of this study was to determine the prevalence of HCV, patient characteristics, and receipt of appropriate care in a sample of patients treated with buprenorphine for their opioid use disorders in a primary care setting. This study used retrospective clinical data from the electronic medical record. The study population included patients receiving buprenorphine in the Office Based Opioid Treatment (OBOT) clinic within the adult primary medicine clinic at Boston Medical Center between October 2003 and August 2013 who received a conclusive HCV antibody (Ab) test within a year of clinic entry. The authors compared characteristics by HCV serostatus using Pearson's chi-square and provided numbers/percentages receiving appropriate care. The sample comprised 700 patients. Slightly less than half of all patients (n=334, 47.7%) were HCV Ab positive, and were significantly more likely to be older, Hispanic or African American, have diagnoses of post-traumatic stress disorder (PTSD) or bipolar disorder, have prior heroin or cocaine use, and be HIV-infected. Among the 334 HCV Ab positive patients, 226 (67.7%) had detectable HCV ribonucleic acid (RNA) indicating chronic HCV infection; only 5 patients (2.21%) with chronic HCV infection ever initiated treatment. Nearly half of patients (47.7%) receiving office-based treatment with buprenorphine for their opioid use disorder had a positive hepatitis C virus antibody screening test although initiation of HCV treatment was nearly non-existent (2.21%).

Eighteen- To 30-year-olds More Likely To Link To Hepatitis C Virus Care: An Opportunity To Decrease Transmission Young KL, Huang W, Horsburgh CR, Linas BP, Assoumou SA. *J Viral Hepat.* 2016; 23(4): 274-281.

Hepatitis C virus (HCV) infection incidence among 18- to 30-year-olds is increasing and guidelines recommend treatment of active injection drug users to limit transmission. The authors aimed to: measure linkage to HCV care among 18- to 30-year-olds and identify factors associated with linkage; compare linkage among 18- to 30-year-olds to that of patients >30 years. They used the electronic medical record at an urban safety net hospital to create a retrospective cohort with reactive HCV antibody between 2005 and 2010. The authors report seroprevalence and demographics of seropositive patients, and used multivariable logistic regression to identify factors associated with linkage to HCV care. They defined linkage as having evidence of HCV RNA testing after reactive antibody. Thirty two thousand four hundred and eighteen individuals were tested, including 8873 between 18 and 30 years. The seropositivity rate among those ages 18-30 was 10%. In multivariate analysis, among those 18-30, diagnosis location (Outpatient vs Inpatient/ED) (OR 1.78, 95% CI 1.28-2.49) and number of visits after diagnosis (OR 5.30, 95% CI 3.91-7.19) were associated with higher odds of linking to care. When the authors compared linkage in patients ages 18-30 to that among those older than 30, patients in the 18-30 years age group were more likely to link to HCV care than those in the older cohort even when controlling for gender, ethnicity, socioeconomic status, birthplace, diagnosis location and duration of follow-up. Eighteen-

to 30-year-olds are more likely to link to HCV care than their older counterparts. During the interferon-free treatment era, there is an opportunity to prevent further HCV transmission in this population.

Brief Intervention For Daily Marijuana Users Identified By Screening In Primary Care: A Subgroup Analysis Of The ASPIRE Randomized Clinical Trial Fuster D, Cheng DM, Wang N, Bernstein JA, Palfai TP, Alford DP, Samet JH, Saitz R. *Subst Abus.* 2016; 37(2): 336-342.

The use of brief intervention for decreasing frequent marijuana use holds potential, but its efficacy in primary care is not known. The aim of this study was to assess the impact of 2 brief interventions on marijuana use among daily/or almost daily marijuana users. Subgroup analysis of a 3-arm randomized clinical trial of 2 brief counseling interventions compared with no brief intervention on daily marijuana use in a primary care setting (ASPIRE). ASPIRE study participants who both reported 21-30 days of marijuana use during the past month and identified marijuana as their drug of most concern. (1) brief negotiated interview (BNI), a 10-15-minute structured interview, and (2) an adaptation of motivational interviewing (MOTIV), a 30-45-minute intervention. Control group participants received only a list of substance use treatment resources. The primary outcome was number of days of marijuana use in the past 30 days at the 6-month follow-up. Secondary outcomes were (1) number of days of marijuana use at 6-week follow-up and (2) drug problems (Short Inventory of Problems-Drugs, SIP-D) at 6-week and 6-month follow-ups. Differences between intervention groups were analyzed using negative binomial regression models. Among the 167 eligible participants, the authors did not find any significant impact of either of the 2 interventions on past 30 days of marijuana use at 6 months (adjusted incidence rate ratio [aIRR]: 0.95, 95% confidence interval [CI]: 0.75-1.15, $P = .82$ for BNI vs. control; aIRR: 1.02, 95% CI: 0.85-1.23, $P = .82$ for MOTIV vs. control). There was no significant impact on drug-related problems at 6-month follow-up (aIRR: 1.12, 95% CI: 0.69-1.82, $P = .66$ and aIRR: 1.46, 95% CI: 0.89-2.38, $P = .27$ for BNI vs. control and MOTIV vs. control, respectively). Results were similar at 6 weeks. Brief intervention has no apparent impact on marijuana use or drug-related problems among primary care patients with frequent marijuana use identified by screening.

Long-term Outcomes After Randomization To Buprenorphine/naloxone Versus Methadone In A Multi-site Trial Hser Y-I, Evans E, Huang D, Weiss R, Saxon A, Carroll KM, Woody G, Liu D, Wakim P, Matthews AG, Hatch-Maillette M, Jelstrom E, Wiest K, McLaughlin P, Ling W. *Addiction.* 2016; 111(4): 695-705.

The aim of this study was to compare long-term outcomes among participants randomized to buprenorphine or methadone. Follow-up was conducted in 2011-14 of 1080 opioid-dependent participants entering seven opioid treatment programs in the United States between 2006 and 2009 and randomized (within each program) to receive open-label buprenorphine/naloxone or methadone for up to 24 weeks; 795 participants completed in-person interviews (~74% follow-up interview rate) covering on average 4.5 years. Outcomes were indicated by mortality and opioid use. Covariates included demographics, site, cocaine use and treatment experiences. Mortality was not different between the two randomized conditions, with 23 (3.6%) of 630 participants randomized to buprenorphine having died versus 26 (5.8%) of 450 participants randomized to methadone. Opioid use at follow-up was higher among participants randomized to buprenorphine relative to methadone [42.8 versus 31.7% positive opioid urine specimens, $P < 0.01$, effect size (h) = 0.23 (0.09, 0.38); 5.8 days versus 4.4 days of past 30-day heroin use, $P < 0.05$, effect size (d) = 0.14 (0.00, 0.28)]. Opioid use during the follow-up period by randomization condition was also significant ($F(7,39\ 600) = 3.16$; $P < 0.001$) due mainly to less treatment participation among participants randomized to buprenorphine than methadone. Less opioid use was associated with both

buprenorphine and methadone treatment (relative to no treatment); no difference was found between the two treatments. Individuals who are white or used cocaine at baseline responded better to methadone than to buprenorphine. There are few differences in long-term outcomes between buprenorphine and methadone treatment for opioid dependence, and treatment with each medication is associated with a strong reduction in opioid use.

Effects of Global Payment and Accountable Care on Tobacco Cessation Service Use: An Observational Study

Huskamp HA, Greenfield SF, Stuart EA, Donohue JA, Duckworth K, Kouri EM, Song Z, Chernew ME, Barry CL. J Gen Intern Med. Published online: 2016, (4)13.

Tobacco use is a leading cause of preventable death and disability. New payment and delivery system models including global payment and accountable care have the potential to increase use of cost-effective tobacco cessation services. The objective of this study was to examine how the Alternative Quality Contract (AQC) established in 2009 by Blue Cross Blue Shield of Massachusetts (BCBSMA) has affected tobacco cessation service use. The authors used 2006–2011 BCBSMA claims and enrollment data to compare adults 18–64 years in AQC provider organizations to adults in non-AQC provider organizations. They examined the AQC's effects on all enrollees; a subset at high risk of tobacco-related complications due to certain medical conditions; and behavioral health service users. The authors examined use of: (1) any cessation treatment (pharmacotherapy or counseling); (2) varenicline or bupropion; (3) nicotine replacement therapies (NRTs); (4) cessation counseling; and (4) combination therapy (pharmacotherapy plus counseling). They also examined duration of pharmacotherapy use and number of counseling visits among users. Rates of tobacco cessation treatment use were higher following implementation of the AQC relative to the comparison group overall (2.02 vs. 1.87 %, $p < 0.0001$), among enrollees at risk for tobacco-related complications (4.97 vs. 4.66 %, $p < 0.0001$), and among behavioral health service users (3.67 vs. 3.25 %, $p < 0.0001$). Statistically significant increases were found for use of varenicline or bupropion alone, counseling alone, and combination therapy, but not for NRT use, pharmacotherapy duration, or number of counseling visits among users. The authors conclude that in its initial three years, the AQC was associated with increases in use of tobacco cessation services.

CTN-RELATED RESEARCH

Predictors of 12-Step Attendance and Participation for Individuals With Stimulant Use Disorders

Hatch-Maillette M, Wells EA, Doyle SR, Brigham GS, Daley D, DiCenzo J, Donovan D, Garrett S, Horigian VE, Jenkins L, Killeen T, Owens M, Perl HI. J Subst Abuse Treat. 2016 Sep;68:74-82. Epub 2016 Jun 16.

Few studies have examined the effectiveness of 12-step peer recovery support programs with drug use disorders, especially stimulant use, and it is difficult to know how outcomes related to 12-step attendance and participation generalize to individuals with non-alcohol substance use disorders (SUDs). A clinical trial of 12-step facilitation (N=471) focusing on individuals with cocaine or methamphetamine use disorders allowed examination of four questions: Q1) To what extent do treatment-seeking stimulant users use 12-step programs and, which ones? Q2) Do factors previously found to predict 12-step participation among those with alcohol use disorders also predict participation among stimulant users? Q3) What specific baseline "12-step readiness" factors predict subsequent 12-step participation and attendance? And Q4) Does stimulant drug of choice differentially predict 12-step participation and attendance? The four outcomes variables, attendance, speaking, duties at 12-step meetings, and other peer recovery support activities, were not related to baseline demographic or substance problem history or severity. Drug of choice was associated with differential days of Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) attendance

among those who reported attending, and cocaine users reported more days of attending AA or NA at 1-, 3- and 6-month follow-ups than did methamphetamine users. Pre-randomization measures of perceived benefit of 12-step groups predicted 12-step attendance at 3- and 6-month follow-ups. Pre-randomization 12-step attendance significantly predicted number of other self-help activities at end-of-treatment, 3- and 6-month follow-ups. Pre-randomization perceived benefit and problem severity both predicted number of self-help activities at end-of-treatment and 3-month follow-up. Pre-randomization perceived barriers to 12-step groups were negatively associated with self-help activities at end-of-treatment and 3-month follow-up. Whether or not one participated in any duties was predicted at all time points by pre-randomization involvement in self-help activities. The primary finding of this study is one of continuity: prior attendance and active involvement with 12-step programs were the main signs pointing to future involvement. Limitations and recommendations are discussed.

Effect of Patient Navigation With or Without Financial Incentives on Viral Suppression Among Hospitalized Patients With HIV Infection and Substance Use: A Randomized Clinical Trial

Metsch LR, Feaster DJ, Gooden L, Matheson T, Stitzer M, Das M, Jain MK, Rodriguez AE, Armstrong WS, Lucas GM, Nijhawan AE, Drainoni ML, Herrera P, Vergara-Rodriguez P, Jacobson JM, Mugavero MJ, Sullivan M, Daar ES, McMahon DK, Ferris DC, Lindblad R, VanVeldhuisen P, Oden N, Castellón PC, Tross S, Haynes LF, Douaihy A, Sorensen JL, Metzger DS, Mandler RN, Colfax GN, del Rio C. JAMA. 2016 Jul 12;316(2):156-170.

Substance use is a major driver of the HIV epidemic and is associated with poor HIV care outcomes. Patient navigation (care coordination with case management) and the use of financial incentives for achieving predetermined outcomes are interventions increasingly promoted to engage patients in substance use disorders treatment and HIV care, but there is little evidence for their efficacy in improving HIV-1 viral suppression rates. The objective of this study was to assess the effect of a structured patient navigation intervention with or without financial incentives to improve HIV-1 viral suppression rates among patients with elevated HIV-1 viral loads and substance use recruited as hospital inpatients. From July 2012 through January 2014, 801 patients with HIV infection and substance use from 11 hospitals across the United States were randomly assigned to receive patient navigation alone (n = 266), patient navigation plus financial incentives (n = 271), or treatment as usual (n = 264). HIV-1 plasma viral load was measured at baseline and at 6 and 12 months. Patient navigation included up to 11 sessions of care coordination with case management and motivational interviewing techniques over 6 months. Financial incentives (up to \$1160) were provided for achieving targeted behaviors aimed at reducing substance use, increasing engagement in HIV care, and improving HIV outcomes. Treatment as usual was the standard practice at each hospital for linking hospitalized patients to outpatient HIV care and substance use disorders treatment. The primary outcome was HIV viral suppression (≤ 200 copies/mL) relative to viral nonsuppression or death at the 12-month follow-up. Of 801 patients randomized, 261 (32.6%) were women (mean [SD] age, 44.6 years [10.0 years]). There were no differences in rates of HIV viral suppression versus nonsuppression or death among the 3 groups at 12 months. Eighty-five of 249 patients (34.1%) in the usual-treatment group experienced treatment success compared with 89 of 249 patients (35.7%) in the navigation-only group for a treatment difference of 1.6% (95% CI, -6.8% to 10.0%; P = .80) and compared with 98 of 254 patients (38.6%) in the navigation-plus-incentives group for a treatment difference of 4.5% (95% CI -4.0% to 12.8%; P = .68). The treatment difference between the navigation-only and the navigation-plus-incentives group was -2.8% (95% CI, -11.3% to 5.6%; P = .68). The authors concluded that among hospitalized patients with HIV infection and substance use, patient navigation with or without financial incentives did

not have a beneficial effect on HIV viral suppression relative to nonsuppression or death at 12 months vs treatment as usual. These findings do not support these interventions in this setting. TRIAL REGISTRATION: clinicaltrials.gov Identifier: [NCT01612169](https://clinicaltrials.gov/ct2/show/study/NCT01612169).

Utilizing a Two-stage Design to Investigate the Safety and Potential Efficacy of Monthly Naltrexone Plus Once-daily Bupropion as a Treatment for Methamphetamine Use Disorder

Mooney LJ, Hillhouse MP, Thomas C, Ang A, Sharma G, Terry G, Chang L, Walker R, Trivedi M, Croteau D, Sparenborg S, Ling W. J Addict Med. 2016 Jul 1. [Epub ahead of print].

This 2-stage open-label pilot study evaluated the safety and potential efficacy of naltrexone + bupropion as a pharmacotherapy for methamphetamine (MA) use disorder. The study was conducted in 2 stages of recruitment across 3 sites; 20 participants were enrolled in stage 1 and 29 participants were enrolled in stage 2. Eight weeks of open-label pharmacotherapy with a combination of extended-release injectable naltrexone (XR-NTX; Vivitrol) plus extended-release oral bupropion (BRP; Wellbutrin XL) were provided with a smartphone-assisted medication adherence platform. Participants met Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria for severe MA use disorder, self-reported ≥ 20 days of MA use in the 30 days prior to consent, and submitted 3 MA-positive urine drug screens (UDS) out of 4 collected during screening. Participants attended clinic twice weekly for observed BRP dosing, UDS testing, assessments, and medical management; XR-NTX was administered at weeks 1 and 5. A BRP taper and follow-up visit occurred in week 9. Analyses evaluated effects of XR-NTX+BRP to determine the number of "responders" according to a statistically predefined response criterion (6 of 8 MA-negative UDS during the last 4 weeks of medication). The 2-stage design required that stage 1 yield ≥ 3 responders to continue to stage 2; 11 of the 49 participants met responder criteria across both stages (5 in stage 1, 6 in stage 2). Under the statistical analysis plan, study "success" required ≥ 9 responders. With 11 responders, the study demonstrated sufficient potential of naltrexone plus bupropion as a combination pharmacotherapy for MA use disorder. The authors compared baseline differences and treatment outcomes between African American and Caucasian participants. A select few baseline differences were found (i.e., African Americans reported higher levels of spirituality than Caucasians; African American participants indicated more perceived benefits of 12-step involvement; Caucasians were more likely to endorse future involvement in 12-step). There were no outcome differences (e.g., substance use outcomes, 12-step meeting attendance). The tested intervention produced similar outcomes for both groups, indicating that it may be useful across racial categories.

Longitudinal Association Between Pain Severity and Subsequent Opioid Use In Prescription Opioid Dependent Patients With Chronic Pain

Griffin ML, McDermott KA, McHugh RK, Fitzmaurice GM, Jamison RN, Weiss RD. Drug Alcohol Depend. 2016 Jun 1;163:216-221. Epub 2016 Apr 25.

Patients with prescription opioid use disorder commonly report relief of chronic pain as the chief reason for first opioid use; indeed, the prevalence of chronic pain is high in this population. Understanding the association between pain severity and subsequent opioid use is crucial for understanding how to manage these conditions simultaneously and has not been examined in this population. The aim of this analysis was to examine the proximal effect of pain severity on opioid use during 12 weeks of buprenorphine-naloxone therapy for patients with chronic pain and prescription opioid use disorder. This study is a secondary analysis of a national, randomized, controlled trial of buprenorphine-naloxone plus counseling for prescription opioid dependent patients. The association between past-week pain severity and opioid use in the subsequent week was examined in 148 patients presenting with chronic pain at baseline.

Results from a multivariable logistic regression model showed that greater pain severity in a given week was significantly associated with increased odds of opioid use in the following week over the 12-week treatment, even after adjusting for covariates associated with opioid use (aOR=1.15, $p < 0.001$). Despite previous reports of no association between baseline pain and subsequent opioid use, our findings suggest that patients who experience flare-ups of pain during treatment are prone to relapse to opioid use. Future studies may identify those who are at risk to use opioids by carefully monitoring patterns of their pain intensity over time.

INTRAMURAL RESEARCH

Morphine Paradoxically Prolongs Neuropathic Pain In Rats By Amplifying Spinal NLRP3 Inflammasome Activation Grace PM, Strand KA, Galer EL, Urban DJ, Wang X, Baratta MV, Fabisiak TJ, Anderson ND, Cheng K, Greene LI, Berkelhammer D, Zhang Y, Ellis AL, Yin HH, Campeau S, Rice KC, Roth BL, Maier SF, Watkins LR. Proc Natl Acad Sci U S A 2016, epub May 31, 2016.

Opioid use for pain management has dramatically increased, with little assessment of potential pathophysiological consequences for the primary pain condition. Here, a short course of morphine, starting 10 d after injury in male rats, paradoxically and remarkably doubled the duration of chronic constriction injury (CCI)-allodynia, months after morphine ceased. No such effect of opioids on neuropathic pain has previously been reported. Using pharmacologic and genetic approaches, the authors discovered that the initiation and maintenance of this multimonth prolongation of neuropathic pain was mediated by a previously unidentified mechanism for spinal cord and pain—namely, morphine-induced spinal NOD-like receptor protein 3 (NLRP3) inflammasomes and associated release of interleukin-1 β (IL-1 β). As spinal dorsal horn microglia expressed this signaling platform, these cells were selectively inhibited *in vivo* after transfection with a novel Designer Receptor Exclusively Activated by Designer Drugs (DREADD). Multiday treatment with the DREADD-specific ligand clozapine-N-oxide prevented and enduringly reversed morphine-induced persistent sensitization for weeks to months after cessation of clozapine-N-oxide. These data demonstrate both the critical importance of microglia and that maintenance of chronic pain created by early exposure to opioids can be disrupted, resetting pain to normal. These data also provide strong support for the recent "two-hit hypothesis" of microglial priming, leading to exaggerated reactivity after the second challenge, documented here in the context of nerve injury followed by morphine. This study predicts that prolonged pain is an unrealized and clinically concerning consequence of the abundant use of opioids in chronic pain.

Blockade of Cocaine or σ Receptor Agonist Self Administration by Subtype-Selective σ Receptor Antagonists Katz JL, Hiranita T, Kopajtic TA, Rice KC, Mesangeau C, Narayanan S, Abdelazeem AH, McCurdy CR. J Pharmacol Exp Ther. 2016; 358(1): 109-124.

The identification of sigma receptor (σ R) subtypes has been based on radioligand binding and, despite progress with σ 1R cellular function, less is known about σ R subtype functions *in vivo*. Recent findings that cocaine self administration experience will trigger σ R agonist self administration was used in this study to assess the *in vivo* receptor subtype specificity of the agonists (+)-pentazocine, PRE-084 [2-(4-morpholinethyl) 1-phenylcyclohexanecarboxylate hydrochloride], and 1,3-di-*o*-tolylguanidine (DTG) and several novel putative σ R antagonists. Radioligand binding studies determined *in vitro* σ R selectivity of the novel compounds, which were subsequently studied for self administration and antagonism of cocaine, (+)-pentazocine, PRE-084, or DTG self administration. Across the dose ranges studied, none of the novel compounds were self administered, nor did they alter cocaine self administration. All compounds blocked DTG self

administration, with a subset also blocking (+)-pentazocine and PRE-084 self administration. The most selective of the compounds in binding σ 1Rs blocked cocaine self administration when combined with a dopamine transport inhibitor, either methylphenidate or nomifensine. These drug combinations did not decrease rates of responding maintained by food reinforcement. In contrast, the most selective of the compounds in binding σ 2Rs had no effect on cocaine self administration in combination with either dopamine transport inhibitor. Thus, these results identify subtype-specific *in vivo* antagonists, and the utility of σ R agonist substitution for cocaine self administration as an assay capable of distinguishing σ R subtype selectivity *in vivo*. These results further suggest that effectiveness of dual σ R antagonism and dopamine transport inhibition in blocking cocaine self administration is specific for σ 1Rs and further support this dual targeting approach to development of cocaine antagonists.

[Insula Demonstrates A Non-Linear Response To Varying Demands For Cognitive Control and Weaker Resting Connectivity With the Executive Control Network In Smokers](#) Fedota JR, Matous AL, Salmeron BJ, Gu H, Ross TJ, Stein, EA. *Neuropsychopharmacology* 2016 May 25. doi: 10.1038/npp.2016.62. [Epub ahead of print].

Deficits in cognitive control processes are a primary characteristic of nicotine addiction. However, while network-based connectivity measures of dysfunction have frequently been observed, empirical evidence of task-based dysfunction in these processes has been inconsistent. Here, in a sample of smokers (n=35) and non-smokers (n=21), a previously validated parametric flanker task is employed to characterize addiction-related alterations in responses to varying (ie, high, intermediate, and low) demands for cognitive control. This approach yields a demand-response curve that aims to characterize potential non-linear responses to increased demand for control, including insensitivities or lags in fully activating the cognitive control network. The authors further used task-based differences in activation between groups as seeds for resting-state analysis of network dysfunction in an effort to more closely link prior inconsistencies in task-related activation with evidence of impaired network connectivity in smokers. For both smokers and non-smokers, neuroimaging results showed similar increases in activation in brain areas associated with cognitive control. However, reduced activation in right insula was seen only in smokers and only when processing intermediate demand for cognitive control. Further, in smokers, this task-modulated right insula showed weaker functional connectivity with the superior frontal gyrus, a component of the task-positive executive control network. These results demonstrate that the neural instantiation of salience attribution in smokers is both more effortful to fully activate and has more difficulty communicating with the exogenous, task-positive, executive control network. Together, these findings further articulate the cognitive control dysfunction associated with smoking and illustrate a specific brain circuit potentially responsible.

[Role Of Ventral Subiculum In Context-Induced Relapse To Alcohol Seeking After Punishment-Imposed Abstinence](#) Marchant NJ, Campbell EJ, Harvey BK, Kaganovsky K, Adhikary S, Heins R, Whitaker LR, Hope BT, Prinszano TE, Vardy E, Bonci A, Bossert JM, Shaham Y. *The Journal of Neuroscience* 2016; 36:3281-3294

In many human alcoholics, abstinence is self-imposed because of the negative consequences of excessive alcohol use, and relapse is often triggered by exposure to environmental contexts associated with prior alcohol drinking. The authors recently developed a rat model of this human condition in which they train alcohol-preferring P-rats to self-administer alcohol in one context (A), punish the alcohol-reinforced responding in a different context (B), and then test for relapse to alcohol seeking in contexts A and B without alcohol or shock. Here, the authors studied the role of projections to nucleus accumbens (NAc) shell from ventral subiculum (vSub), basolateral

amygdala, paraventricular thalamus, and ventral medial prefrontal cortex in context-induced relapse after punishment-imposed abstinence. First, the authors measured double-labeling of the neuronal activity marker Fos with the retrograde tracer cholera toxin subunit B (CTb, injected in NAc shell) and demonstrated that context-induced relapse is associated with selective activation of the vSub→NAc shell projection. Next, they reversibly inactivated the vSub with GABA receptor agonists (muscimol+baclofen) before the context-induced relapse tests and provided evidence for a causal role of vSub in this relapse. Finally, the authors used a dual-virus approach to restrict expression of the inhibitory kappa opioid-receptor based DREADD (KORD) in vSub→NAc shell projection neurons. They found that systemic injections of the KORD agonist salvinorin B, which selectively inhibits KORD-expressing neurons, decreased context-induced relapse to alcohol seeking. These results demonstrate a critical role of vSub in context-induced relapse after punishment-imposed abstinence and further suggest a role of the vSub→NAc projection in this relapse.

[Midbrain Dopamine Neurons Compute Inferred and Cached Value Prediction Errors In A Common Framework](#) Sadacca BF, Jones JL, Schoenbaum G. eLIFE 2016 DOI: 10.7554/eLife.13665.001.

Midbrain dopamine neurons have been proposed to signal reward prediction errors as defined in temporal difference (TD) learning algorithms. While these models have been extremely powerful in interpreting dopamine activity, they typically do not use value derived through inference in computing errors. This is important because much real world behavior – and thus many opportunities for error-driven learning – is based on such predictions. Here, the authors show that error-signaling rat dopamine neurons respond to the inferred, model-based value of cues that have not been paired with reward and do so in the same framework as they track the putative cached value of cues previously paired with reward. This suggests that dopamine neurons access a wider variety of information than contemplated by standard TD models and that, while their firing conforms to predictions of TD models in some cases, they may not be restricted to signaling errors from TD predictions.

GRANTEE HONORS AND AWARDS

Dr. Joseph Ditre is one of 3 semi-finalists and the winner of the 2016 NIH Pain Consortium Mitchell Max Award, elected on May 31 by NIH staffs at the Pain Consortium Conference titled "Advances in Pain Research". He is also an invited speaker, presented at the conference "Nicotine Deprivation Increases Pain Sensitivity, Neurogenic Inflammation, and Secondary Hyperalgesia among Daily Tobacco Smokers".

Dr. Diana Fishbein, The Pennsylvania State University, received the 2016 Society for Prevention Research Translational Science Award in recognition of her contributions to the field of prevention science in the area of Type 1 translational research.

Dr. Kevin Haggerty, University of Washington, received the 2016 Society for Prevention Research Prevention Science Award for his work developing and testing prevention intervention strategies.

Dr. J. David Hawkins, University of Washington, received the 2016 Society for Prevention Research Friend of ECPN (Early Career Preventionist Network) award for his support and encouragement of early career prevention scientists.

Dr. Nicholas Ialongo, Johns Hopkins University, received the 2016 Society for Prevention Research Presidential Award for his major lifetime contribution to prevention science.

Dr. Brian Mustanski, Northwestern University, received the 2016 Society for Prevention Research Advances in Culture and Diversity in Prevention Science Award for his contributions to prevention research in the area of community and culture.

Ms. Cassie Overstreet, a predoctoral student in clinical psychology at the Virginia Commonwealth University, and the recipient of a predoctoral fellowship award from NIDA (F31DA038912) on Prescription Drug Misuse and Traumatic Stress, was awarded the Virginia Commonwealth University Deborah Braffman Schroeder Scholarship for her research endeavors in April, 2016.

Dr. Guillermo “Willy” Prado, University of Miami, and his team, received the 2016 Society for Prevention Research International Collaborative Prevention Research award for his contributions to collaborative international research.

Dr. Steven Schinke, Columbia University, was selected into the 2016 cohort of Fellows of the Society for Prevention Research, for his particularly distinguished record of contributions in the field of prevention research.

Dr. Jasmin Vassileva was an invited guest speaker in a TV Show in Bulgaria. At the press appearance, Dr. Vassileva, increased public awareness about the opiate and stimulant epidemics in Bulgaria that she has been studying in past 7 years, as reflecting maladaptive coping strategies for dealing with the stress and ‘unhappiness’ associated with the multiple recent transitional periods in Bulgarian history, from communism to democracy, from state-run to free economy, etc. Based upon what was learned from the R01 study carried out in Bulgarian, she spoke about the specific personality and neurocognitive profiles that increase risk for opiate vs. stimulant addiction, and how they seem to reflect substance-specific motivational pathways to addiction that need to be targeted distinct multidisciplinary therapeutic approaches.

STAFF HONORS AND AWARDS

2016 NIH DIRECTOR'S AWARDS

Dr. Susan Weiss, DER, received the *NIH Director's Award* in recognition of extraordinary leadership, vision, and hard work in facilitating collaborative research on addiction at NIH.

Drs. Maureen Boyle and **Michele Rankin**, OSPC, along with the other members of the NIH-Wide *Strategic Plan Working Group, (Scientific/Medical Category)* received the *NIH Director's Award* for significant contributions toward developing an NIH-wide Strategic Plan.

Dr. Roger Little, DNB, received the *NIH Director's Award* as a member of the *GTEX Implementation Team (Common Fund Leadership Category)* in recognition of outstanding leadership in developing and guiding the National Institutes of Health Common Fund GTEX project.

Dr. Roger Little, DNB, received the *NIH Director's Award* as a member of the *Single Cell Analysis Challenge Team (Administrative Category)* for extraordinary work developing and implementing the "Follow That Cell" Challenge awarding prizes to recognize innovative advances in single cell analysis.

Dr. Roger Little, DNB, received the *NIH Director's Award* as a member of the *NIH NeuroBioBank Team (Administrative Category)* for invaluable contributions of the NIH NeuroBioBank team to accelerating brain research through increased access to high quality tissue.

Dr. John Satterlee, DNB, received the *NIH Director's Award (Common Fund Leadership Category)* for remarkable scientific leadership and performance in developing, managing, and promoting multiple Common Fund initiatives.

Dr. Roger Sorensen, DNB, received the *NIH Director's Award*, as a member of the *Stimulating Peripheral Activity to Relieve Conditions (SPARC) Working Group (Common Fund Leadership Category)* in recognition of outstanding leadership, creativity and collaboration to launch the Stimulating Peripheral Activity to Relieve Conditions (SPARC) program.

Dr. Geetha Subramaniam, CCTN, received the *NIH Director's Award* as a member of the *NCS Redirection/ECHO Working Group*, nominated by the Office of the Director.

Dr. Marisela Morales, IRP, received the *NIH Director Award (Individual Scientific/Medical Category)* for discoveries that have challenged 2 dogmas prevailing over 50 years, "The signaling of one neurotransmitter per neuron", and "Dorsal raphe nucleus signaling by serotonergic neurotransmission".

The Medications Development Naloxone Team, Division of Therapeutics and Medical Consequences received the *NIH Director's Award* for leading the development of an intranasal naloxone product for the treatment of opioid overdose. Members include Dr. Nora Chiang, Dr. David McCann, Dr. Shwe Gyaw, Robert Walsh, Dr. Moo Park, and Dr. Phil Krieter.

Dr. Cora Lee Wetherington, DNB, received the Outstanding Contributions to Advancing the Understanding of Addictions Award for 2016 from Division 50: Society of Addiction Psychology

of the American Psychological Association (APA) at the annual convention in Denver, CO, August 4-7, 2016.

Dr. Mehdi Farokhnia, IRP, (postdoctoral fellow in Dr. Leggio's CPN lab) received a 2016 Early Career Investigator Travel Award from the Society of Biological Psychiatry (SOBP), Atlanta, GA.

Dr. Mehdi Farokhnia, IRP, (postdoctoral fellow in Dr. Leggio's CPN lab) received a 2016 Travel Award for Early Career Investigators from the College of Problems on Drug Dependence (CPDD), Palms Spring, CA.

Dr. Lorenzo Leggio, IRP, was presented with the Research Society on Alcoholism (RSA) Early Career Investigator Award during the RSA meeting in New Orleans. As the 2016 awardee, he will also be a plenary speaker at the 2017 RSA meeting.

Ms. Breanne Hobden, Ph.D. Candidate (Graduate Student at the Health Behaviour Research Group, School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia) received the 2016 Adam J Berry Memorial Fund Award. The awardee (1 per year) is selected by an NIH committee from a group of semifinalists selected by the Australian Academy of Sciences and forwarded to the NIH Foundation. This awardee allows Ms. Hobden to spend this summer as a Visiting Pre-Doc Student in the NIAAA/NIDA section led by Dr. Lorenzo Leggio.

On May 18, 2016, the NIDA IRP Office of Education and Career Development hosted the NIDA Poster Day and Mentoring Awards Ceremony. IRP postdocs, grad students, and postbacs presented 46 posters. Mentoring Awards were presented to **Drs. William Kowalczyk, Brandon Harvey, Yavin Shaham, and Zheng-Xiong**. Additionally, seven Program Officers from NIDA attended the event to view posters and meet with postdocs about grant submissions.

STAFF CHANGES

New Appointments/Employees

Mark Fleming was appointed Branch Chief for the newly established Digital Communications Branch within NIDA's Office of Science Policy and Communications (OSPC). Mark comes to this position with extensive experience and history with NIDA where he has worked both as a contractor and an employee for over 30 years. For the past 16 years, Mark has been responsible for overseeing our multiple websites.

Dr. Lorenzo Leggio, IRP, was named Associate Director for Clinical Research of the Medications Development Program.

Dr. Thomas Stalnaker, IRP, was promoted to Staff Scientist.

Dr. Shang-Yi [Anne] Tsai, IRP, NIDA, completed a 6 month detail in the Division of Neuroscience and Behavior on 1 July, and has returned to her position as staff scientist within the Cellular Pathology Section, Integrative Neuroscience Research Branch, led by Tsung-Ping Su. Dr. Tsai's research interests are in understanding the neurobiological actions and biochemical characterizations of sigma receptors as ligand-regulated molecular chaperone proteins. During her detail, Dr. Tsai took the lead in writing the Funding Opportunity Announcements; PA-16-144 (R01) and PA-16-145 (R21), Role of Astrocytes and Astrocytic Networks in Drug Abuse. She also managed an extramural grant portfolio encompassing basic research on the neurobiological actions of drugs of abuse. It was a pleasure having Anne work at NIDA HQ. We wish her the best. Dr. Shang-Yi Tsai was on detail to the NIDA HQs from January 2-July 4th, 2016. She worked in the Division of Neuroscience under Dr. Joni Rutter and then Dr. Roger Little on how to develop program announcements to the extramural researchers. Dr. Tsai also was invited to give a talk on June 17, 2016 to the Division.

Dr. Amy C. Lossie joined the Genetics, Epigenetics, and Developmental Neuroscience Branch in the Division of Neuroscience and Behavior in June 2016 as a Health Scientist Administrator. As a Program Director, she will focus on developing a portfolio on genetic and genomic elements of drug abuse, focusing on bioinformatics, somatic mutations, transposable elements, non-coding RNAs and alternative splicing. Dr. Lossie has expertise in genetics, epigenetics, developmental biology, with a focus on alcoholism and peri-implantation development in humans and model organisms. Prior to joining GEDN, Amy spent almost two years in the Office of the Director, as a Health Scientist Administrator in the Office of Disease Prevention (ODP) and a Health Scientist and American Association for the Advancement of Science (AAAS) Science and Technology Fellow at the NIH Office of Behavioral and Social Sciences Research (OBSSR). In the OD, she lead efforts to identify gaps in prevention research, increased awareness and understanding of biomedical and psychosocial aspects of differences/disorders of sex development (i.e., intersex conditions), and created initiatives to address gene x environment interactions in behavioral sciences. Dr. Lossie received her B.S. in Cellular and Molecular Biology from the University of Michigan, Ann Arbor and her Ph.D. in the Molecular Genetics of Angelman Syndrome from the University of Florida College of Medicine. She completed her postdoctoral training with Dr. Monica J. Justice at Baylor College of Medicine. As a faculty member at Purdue University, she developed next generation tools to assess epigenetic marks in multiple single cell models, organized career development workshops and increased genetics literacy among high school teachers through the Geneticist --

Educator Network of Alliances (GENA) Project. Dr. Lossie published 31 peer-reviewed manuscripts and received grants from the NIH, NASA, the W. M. Keck Foundation and other private foundations.

Petra Jacobs, M.D., returned to join NIDA CCTN as a Health Science Administrator in July 2016. She will be working on opioid use disorder projects and HIV studies.

Pamela Daugherty-Smith joined NIDA's Office of Management, Office of Acquisitions' Station Support Branch as a Contract Specialist on May 1, 2016. Pamela comes to NIDA from the Private Sector.

Clark Tung joined DESPR's Office of the Director as a Program Support Assistant on May 29, 2016. Clark comes to NIDA from NINDS.

Danielle Brown joined NIDA's Office of Management, Office of Acquisitions' Station Support Branch as a Contract Specialist on June 12, 2016.

Shun Yiu (Leon) Wong joined NIDA's Office of Management, Office of Acquisitions' Station Support Branch as a Contract Specialist on July 10, 2016.

Rachelle Trice joined NIDA's Office of Management, Office of Acquisitions' Station Support Branch as a Supervisory Contract Specialist on July 24, 2016. Rachelle comes to NIDA from a position with the Small Business Administration (SBA).

Richard Clinkscales joined NIDA's Office of Management, Office of Acquisitions' Station Support Branch as a Contract Specialist on July 24, 2016.

Joshua Lazarus joined NIDA's Office of Management, Office of Acquisitions', NIDA R&D Branch as a Contract Specialist on August 21, 2016.

Susan Li joined NIDA's Office of Management, Office of Acquisitions' NIDA R&D Branch as a Contract Specialist on August 21, 2016.

Sneha Patel joined NIDA's Office of Management, Office of Acquisitions' Station Support Branch as a Contract Specialist on August 21, 2016.

Departures

Matthew Finger, a Supervisory Program Analyst in DESPR's Office of the Director, left NIDA on May 14, 2016 for a position with NCATS.

Kara Anderson, a Contract Specialist in NIDA's Office of Management, Office of Acquisitions' NIDA R&D Branch, left NIDA on June 11, 2016.

Philip DeCastro, a Contract Specialist in NIDA's Office of Management, Office of Acquisitions' NIDA R&D Branch, left NIDA on June 11, 2016.

Kathleen Hamill, a Program Support Clerk in DESPR's Office of the Director, left NIDA on June 24, 2016.

Jennifer Burns, a Contract Specialist in NIDA's Office of Management, Office of Acquisitions' Station Support Branch, left NIDA on July 22, 2016.

Gary Berkson, a Contract Specialist in NIDA's Office of Management, Office of Acquisitions' NIDA R&D Branch left NIDA on July 23, 2016.

Andriani Buck, a Contract Specialist in NIDA's Office of Management, Office of Acquisitions' Station Support Branch, left NIDA on July 23, 2016.

Retirements

Marc Brodsky, a Statistician (Health) in DESPR's Office of the Director, retired from Federal Service on June 30, 2016.

Anita LoMonico, an IT Specialist in NIDA's Office of Management, Information and Resource Management Branch, retired from Federal Service on July 2, 2016.

Dr. Steve Sparenborg retired from NIDA/CCTN and Federal Government Service in May 2016.

Dale Weiss, a Program Analyst in NIDA's International Program, Office of the Director, retired from Federal Service on June 30, 2016.



National Institute
on Drug Abuse